

ANALGESIA WITH REMIFENTANIL IN GENERAL ANESTHESIA IN LARGE OPERATION

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ABSTRACT

The study aimed at identifying the effect of Remifentanil on its effect on major surgical operations performed at Karkh Hospital in Iraq. These operations ranged from general surgery, urinary, chest, nose, ear, throat, etc. The study was applied to 75 patients who underwent major surgery. The study concluded that Remifentanil is very effective in major surgical operations and significantly reduces the side effects of other drugs.

KEYWORD: Remifentanil, Anesthesia, Large operation.

INTRODUCTION

Remifentanil, a new ultra-short-acting effective μ -opioid receptor agonist, is currently used for postoperative analgesia. However, its adverse effects such as severe respiratory depression call people's concern.^[1] Considerable evidence is available to support ketamine as an adjuvant to opioid for postoperative analgesia.^[2] A small clinical study reported that low-dose ketamine combined with remifentanil target controlled infusion might enhance the analgesic effect and reduce respiratory depression.^[3] However, there are few reports on the combination therapy of remifentanil for postoperative analgesia.

The aim of this review is to provide updated knowledge on the relationship between the use of remifentanil in clinical practice and the development of opioid-induced hyperalgesia (OIH).

Although remifentanil offers several advantages from clinical perspectives during both the intraoperative and the immediate postoperative period, its pharmacokinetic and

pharmacodynamics unique characteristics have been linked with the development of OIH. The occurrence of hyperalgesia may slow patient's recovery after surgery, preventing a timely discharge and also causing discomfort not only through higher pain scores, but also with the greater amount of analgesics and side effects related to their administration.

A recent meta-analysis including 27 studies and almost 1500 patients found that high intraoperative doses of remifentanyl are associated with small but significant increases in acute pain at 4 and 24 hours after surgery, and also with higher morphine requirements after the first postoperative day.^[4]

OIH is described as a phenomenon occurring in patients treated with opioids, causing a subsequent paradoxical increase in sensitivity to painful stimuli. Such an occurrence could be described as hyperalgesia, allodynia, or both. A dilemma faced by a clinician is to distinguish OIH from other phenomena such as acute opioid tolerance (AOT) or opioid withdrawal. More importantly, research has often investigated surrogate markers of OIH such as increased pain intensity scores and opioid consumption at variable time-points, rather than clearly distinguishing OIH from the other phenomena linked to the need for opioids. This has also contributed to difficulties in comparing available data and in heterogeneous literature.

Remifentanyl holds unique pharmacological properties, making it the ideal opioid for total intravenous anesthesia. However, opioids are associated with induction of hyperalgesia with sensitization of pronociceptive mechanisms even after a single dose^[5] and an association between remifentanyl and opioid-induced hyperalgesia has been shown both in human volunteers^[6], and in clinical studies.^[7] The clinical impact of remifentanyl-induced hyperalgesia (RIH) has been probably underestimated until a recent meta-analysis demonstrated that anesthesia conducted with remifentanyl is associated with higher pain scores and morphine consumption in the first 24 postoperative hours.^[8]

Despite advances in pain management, many patients still experience moderate to severe postoperative pain.^[9]

Regional, national, and continental surveys have documented that hospitalized patients receive suboptimal pain treatment, and a US survey found 50%-70% of patients reporting moderate to severe postoperative pain.^[10] Patient-reported outcomes (PROs) research is growing.

Objective: There are many benefits that can be obtained with the use of remifentanil, especially in large, time consuming surgical procedures. It does not accumulate in the body after repeated administration or after prolonged infusion, as is the case with other central analgesics. The elderly, patients with arterial hypertension and patients with renal insufficiency and hepatic insufficiency. Postoperative pain relief is reported by intravenous infusion in the Intensive Care Division and under the supervision of an anesthesiologist.

The aim of the study: The goal of the research is to seek the good absorption of patients during surgery, especially elderly patients and patients with hypertension and patients with renal insufficiency and hepatic insufficiency without complications during surgery and during the period of awakening.

Back ground: Remifentanil is not recommended for use as the sole agent in general anesthesia because the loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity and tachycardia. Continuous infusions of remifentanil should be administered only by an infusion device. I.V. bolus administration should only be used in intubated patients during the maintenance of general anesthesia. For induction of anesthesia in nonintubated patients, a single dose of remifentanil, not exceeding 1 µg/kg, may be administered over 30 to 60 seconds. Interruption of an infusion of remifentanil will result in a rapid offset of effect. Rapid clearance and lack of drug accumulation result in rapid dissipation of respiratory depressant and analgesic effects upon discontinuation of remifentanil at recommended doses.^[11]

However, delayed respiratory depression may occur in some patients up to 30 minutes after termination of remifentanil infusions due to residual effects of concomitant anesthetics. Discontinuation of an infusion of remifentanil should be preceded by the establishment of adequate postoperative analgesia.^[12]

Injections of remifentanil should be made into i.v. tubing at or close to the venous cannula. Upon discontinuation of remifentanil, the i.v. tubing should be removed or cleared to prevent the inadvertent administration of remifentanil at a later point in time. Failure to adequately clear the i.v. tubing to remove residual remifentanil has been associated with the appearance of respiratory depression, apnea and muscle rigidity upon the administration of additional fluids or medications through the same i.v. tubing.^[13]

Use of remifentanyl is associated with apnea and respiratory depression. Remifentanyl should be administered only in a setting fully equipped for the monitoring and support of the respiratory and cardiovascular function. Resuscitative and intubation equipment, oxygen and an opioid antagonist must be readily available. Remifentanyl should be administered only by persons specifically trained in the use of anesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation of patients in the age-group being treated. Such training must include the establishment and maintenance of a patent airway and assisted ventilation. Skeletal muscle rigidity can be caused by remifentanyl and is related to the dose and speed of administration. Remifentanyl may cause chest wall rigidity (inability to ventilate) after single doses $> 1 \mu\text{g}/\text{kg}$ administered over 30 to 60 seconds, or after infusion rates $> 0.1 \mu\text{g}/\text{kg}/\text{min}$. Single doses $< 1 \mu\text{g}/\text{kg}$ may cause chest wall rigidity when given concurrently with a continuous infusion of remifentanyl.^[14]

Muscle rigidity induced by remifentanyl should be managed in the context of the patient's clinical condition. Muscle rigidity occurring during the induction of anesthesia should be treated by the administration of a neuromuscular blocking agent and the concurrent induction medications. Remifentanyl should not be administered into the same i.v. tubing with blood/serum/plasma due to potential inactivation by nonspecific esterases in blood products. Vital signs and oxygenation must be continually monitored during the administration of remifentanyl. Intraoperative awareness has been reported in patients under 55 years of age when remifentanyl has been administered with propofol infusion rates of $\leq 75 \mu\text{g}/\text{kg}/\text{min}$. Therefore, propofol rates $< 100 \mu\text{g}/\text{kg}/\text{min}$ are not recommended for use with remifentanyl for total intravenous anesthesia in patients < 55 years of age.^[15]

Remifentanyl was negative in the *in vivo* micronucleus test and the liver unscheduled DNA synthesis assay. Remifentanyl was found to be genotoxic in mammalian cells *in vitro* in the mouse lymphoma assay. Remifentanyl concentrations over 4000 times greater than those seen with clinical use ($50 \text{ ng}/\text{mL}$) were mutagenic only in the presence of metabolic activation.^[16]

Cardiovascular

Hypotension has been reported with remifentanyl and is responsive to decreases in the administration of remifentanyl or to i.v. fluids or catecholamine (ephedrine, epinephrine, norepinephrine, etc.) administration.^[17]

Dependence/Tolerance

As with other opioids, remifentanyl can produce drug dependence of the morphine type and therefore has the potential of being abused.

Hepatic/Biliary/Pancreatic

Remifentanyl pharmacokinetic/pharmacodynamics profile is not changed in patients with severe hepatic impairment. However, these patients may be slightly more sensitive to respiratory depressant effects of remifentanyl. Therefore, these patients should be closely monitored and the dose of remifentanyl titrated to individual patient need.^[18]

Pharmacodynamics Hemodynamics

In premeditated patients undergoing anesthesia, 1-minute infusions of $< 2 \mu\text{g}/\text{kg}$ of remifentanyl caused dose-dependent hypotension and bradycardia. While additional doses $> 2 \mu\text{g}/\text{kg}$ (up to $30 \mu\text{g}/\text{kg}$) do not produce any further decreases in heart rate or blood pressure, the duration of the hemodynamic change is increased in proportion to the blood concentrations achieved.^[19]

Peak hemodynamic effects occur within 3 to 5 minutes of a single dose of remifentanyl or an infusion rate increase. Glycopyrrolate, atropine, and vagolytic neuromuscular blocking agents attenuate the hemodynamic effects associated with remifentanyl. When appropriate, bradycardia and hypotension can be reversed by reduction of the rate of infusion of remifentanyl, or the dose of concurrent anesthetics, or by the administration of fluids or vasopressors.^[20]

Respiration Remifentanyl depresses respiration in a dose-related fashion. Unlike other fentanyl analogs, the duration of action of remifentanyl at a given dose does not increase with increasing duration of administration, due to lack of drug accumulation. When remifentanyl and alfentanil were dosed to equal levels of respiratory depression, recovery of the respiratory drive after 3-hour infusions was more rapid and less variable with remifentanyl.^[21]

Muscle Rigidity

Skeletal muscle rigidity can be caused by remifentanyl and is related to the dose and speed of administration. Remifentanyl may cause chest wall rigidity (inability to ventilate) after single doses of $> 1 \mu\text{g}/\text{kg}$ administered over 30 to 60 seconds or infusion rates $> 0.1 \mu\text{g}/\text{kg}/\text{min}$; peripheral muscle rigidity may occur at lower doses.^[22]

Administration of doses $< 1 \mu\text{g}/\text{kg}$ may cause chest wall rigidity when given concurrently with a continuous infusion of remifentanyl. Prior or concurrent administration of a hypnotic (propofol or thiopental) or a neuromuscular blocking agent may attenuate the development of muscle rigidity.

Excessive muscle rigidity can be treated by decreasing the rate or discontinuing the infusion of remifentanyl or by administering a neuromuscular blocking agent. Histamine Release Assays of histamine in patients and normal volunteers have shown no elevation in plasma histamine levels after administration of remifentanyl in doses up to $30 \mu\text{g}/\text{kg}$ over 60 seconds.^[23]

Anesthesia Remifentanyl is synergistic with the activity of hypnotics (propofol and thiopental), inhaled anesthetics, and benzodiazepines.

Gender

No differences have been shown in the pharmacodynamics activity (as measured by the EEG) of remifentanyl between men and women.

Pharmacokinetics Absorption

After i.v. doses administered over 60 seconds, the pharmacokinetics of remifentanyl fit a three-compartment model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes. Since the terminal elimination component contributes less than 10% of the overall area under the concentration versus time curve (AUC), the effective biological half-life of remifentanyl is 3 to 10 minutes.^[24]

This is similar to the 3- to 10-minute half-life measured after termination of prolonged infusions and correlates with recovery times observed in the clinical setting after infusions up to 12 hours. Concentrations of remifentanyl are proportional to the dose administered throughout the recommended dose range. The pharmacokinetics of remifentanyl are unaffected by the presence of renal or hepatic impairment.

Distribution

The initial volume of distribution (V_d) of remifentanyl is approximately $100 \text{ mL}/\text{kg}$ and represents distribution throughout the blood and rapidly perfused tissues. Remifentanyl subsequently distributes into peripheral tissues with a steady-state volume of distribution of

approximately 350 mL/kg. These two distribution volumes generally correlate with total body weight (except in severely obese patients when they correlate better with ideal body weight [IBW]). Remifentanyl is approximately 70% bound to plasma proteins of which two-thirds is binding to alpha-1-acid-glycoprotein.^[25]

Excretion

The clearance of remifentanyl in young, healthy adults is approximately 40 mL/min/kg. Clearance generally correlates with total body weight (except in severely obese patients when it correlates better with ideal body weight). The high clearance of remifentanyl combined with a relatively small volume of distribution produces a short elimination half-life of approximately 3 to 10 minutes. This value is consistent with the time taken for blood or effect site concentrations to fall by 50% (context-sensitive half-times), which is approximately 3 to 6 minutes. Unlike other fentanyl analogs, the duration of action does not increase with prolonged administration.^[26]

Methods

The research sample consisted of 75 patients aged between 20 and 80 who underwent major surgical operations of various types in Karkh Hospital in Iraq. There were 30 women with 40% and 45 men with 60%.

Hardware and materials used

- ECG monitor, pulse, arterial pressure and oxygen.
- Electric pump for infusion of Remifentanyl in doses.
- Serengets of different sizes, monotherapy and anesthetics.

General anesthesia method

Prepare and give the patient 0,5 Mg atropine and a 2 Mg medazolam intravenous dose.

Induction

- Remifentanyl dose of 1 mg / kg given in 30-60 seconds, then start with a dose of 0,4 mg/kg/d.
- A 2 mg Cisatracurium in vein.
- Provol venous 1-1,5 mg / kg.
- Start positive ventilation.
- Give Saxenilkoline with a dose of 1,5 mg / kg

- Perform the tracheal spasm after about 30 seconds of giving scaxylcoline Continuity give Cisatracurium.

Maintenance: Cisatracurium with a dose of 0.15 mg / kg with positive ventilation of nitrous oxide oxygen by 50% each, and after skin segmentation, the dose of remifentanil is reduced to 0,3 kg / kg / d. We then adjust the infusion dose during surgery to achieve the patient's hemodynamic stability.

Postoperative pain analgesia: The patient should be sufficiently accommodated prior to fasting, with 0,1-0,15mg / kg morphine or 1 to 1m,5 mg /kg betidine 15-20 minutes before the expected end of surgery.

Awakening: The infusion of remifentanil is stopped before 15 minutes from the expected end of the surgical operation, and then the nitrous oxide is stopped at the end of the surgical operation. Thus, the patient's inflorescence when the nasal respiration returns well, and the awakening of a long process is 4 hours or more. Rapid removal of remifentanil effect within 5-10 minutes of stopping infusion.

RESULT

The following table shows the distribution of patients by age variable

Table 1: The distribution of patients by age variable.

Age	20-40	41-60	61-80
Number of patients	32	21	22
%	42,66%	28%	29,33%

The following table shows the distribution of patients by type of surgical operation

Table 2: The distribution of patients by type of surgical operation.

type of surgical operation	General Surgery	Orthopedics	Thoracic surgery	Urinary surgery	Ear nose surgery
Number of patients	30	21	12	10	2
%	40%	28%	16%	13,33%	2,66%

Observation and Conflicts

- No recurrence was observed for the tracheal swelling (sweating, tears, open eyes, movement of the patient, increased heart rate for more than 90 strokes).
- There were 15 cases with a slow heart rate after the remifentanil was given and the pulse was less than 40 beats per minute, and those cases were older than 60 years.

- In 10 elderly patients, there was a ventricular ejaculation caused by hypoxia caused by respiratory inhibition immediately after administration of the remifentanyl or pain to the adequacy of the remifentanyl dose, ventricular ejaculation was removed after hypoxia and the dose of remifentanyl was increased slightly, and 11 cases of lower myocardial infarction from 40 beats per minute.
- There are cases in which hypoxia decreased by less than 90 due to delayed respiratory inhibition during remission dose and difficulty of applying the face mask well. The oxygenation was improved by applying the face mask and providing the patient with oxygen well.
- As for muscle stiffness, no condition was observed because all patients were medically prepared with medazolam, barbovol dose and muscle relaxant with remifentanyl.
- For respiratory inhibition, 30 cases of inhibition were observed immediately after remission of the remifentanyl.
- Systolic pressure and the number of heart beats were lower than the initial value in all patients, which decreased by 10-40% in 16 patients and were suffering from uncontrolled hypertension.

The following table shows the observed complications during direct anesthesia and after direct detection

Table. 3: observed complications during direct anesthesia and after direct detection.

Observed complications	Reaction reaction	Heartbeat is less than 40 beats	Alveolar contraction of the ventricle	Decreased systolic pressure by 10-40	Hypoxia	Respiratory inhibition	Muscle stiffness
Number of patients	0	15	10	16	4	0	30
%	0%	20%	13,3%	21,33%	5,33%	0%	40%

Interactions during the period of awakening

There were a number of complications, the most prominent of which were

- High arterial tension
- Decreased arterial tension.
- Accelerate the heart of my pocket
- Inhibition of respiratory
- Nausea
- Vomiting

Table. 4: The most prominent.

the most prominent	High arterial tension	Decreased arterial tension.	Accelerate the heart of my pocket	Inhibition of respiratory	Nausea	Vomiting
Number	4	5	10	13	2	1

DISCUSSION

The present study has shown that there are many effects related to remifentanyl. These results were consistent with the results of a study of Paolo, 2004 that used remifentanyl at doses very close to the doses used in the present study. The study found similar results for the current study regarding complications during initiation, surgery and the period of awakening.

Unlike other synthetic opioids which are hepatically metabolized, remifentanyl has an ester linkage which undergoes rapid hydrolysis by non-specific tissue and plasma esterases. This means that accumulation does not occur with remifentanyl and its context-sensitive half-life remains at 4 minutes after a 4-hour infusion.

Remifentanyl is metabolized to a compound (remifentanyl acid) which has 1/4600th the potency of the parent compound.^[27]

Due to its quick metabolism and short effects, remifentanyl has opened up new possibilities in anesthesia. When remifentanyl is used together with a hypnotic (i.e. one that produces sleep) it can be used in relatively high doses. This is because remifentanyl will be rapidly eliminated from the blood plasma on termination of the remifentanyl infusion, hence the effects of the drug will quickly dissipate even after very long infusions. Owing to synergism between remifentanyl and hypnotic drugs (such as propofol) the dose of the hypnotic can be substantially reduced.^[28] This leads often to more hemodynamic stability during surgery and quicker post-operative recovery time.

Remifentanyl is a specific μ -receptor agonist.^[29] Hence, it causes a reduction in sympathetic nervous system tone, respiratory depression and analgesia. The drug's effects include a dose-dependent decrease in heart rate and arterial pressure and respiratory rate and tidal volume. Muscle rigidity is sometimes noted.

The most common side effects reported by patients receiving this medication are a sense of extreme "dizziness" (often short lived, a common side effect of other fast-acting synthetic phenylpiperidine narcotics such as fentanyl and alfentanil) and intense itching (pruritus),

often around the face. These side effects are often controlled by either altering the administered dose (decreasing or in some cases, increasing the dose) or by administering other sedatives that allow the patient to tolerate or lose awareness of the side effect.

Because pruritus is due to excessive serum histamine levels, antihistamines such as diphenhydramine (Benadryl) are often co-administered. This is done with care, however, as excessive sedation may occur.

Nausea can occur as a side effect of remifentanil; however, it is usually transient in nature due to the drug's short half-life which rapidly removes it from the patient's circulation once the infusion is terminated.

Remifentanil, being a μ -receptor agonist, functions like other μ -receptor agonists, such as morphine and codeine, and can cause euphoria and has the potential for abuse.^[30] However, due to its rapid metabolism and short-acting half-life the likelihood of becoming abused is quite low. Nevertheless, there have been some documentations of remifentanil abuse.^[31]

In Hong Kong, remifentanil is regulated under Schedule 1 of Hong Kong's Chapter 134 Dangerous Drugs Ordinance. It can only be used legally by health professionals and for university research purposes. The substance can be given by pharmacists under a prescription. Anyone who supplies the substance without prescription can be fined \$10000 (HKD). The penalty for trafficking or manufacturing the substance is a \$5,000,000 (HKD) fine and life imprisonment. Possession of the substance for consumption without license from the Department of Health is illegal with a \$1,000,000 (HKD) fine and/or 7 years of jail time. Remifentanil is a Schedule II narcotic controlled substance in the United States with a DEA ACSCN of 9739 and a 2013 annual aggregate manufacturing quota of 3750 grams.^[32]

CONCLUSION

We can therefore be concluded that remifentanil is characterized by:

- Minimizes the need for the use of nanoxone after surgery.
- Is fast and full of energy compared to other opiates due to its rapid metabolism through blood and tissue.
- It is safe in patients with renal insufficiency, which is used without altering the dose because it is metabolized in the blood and tissues without kidney intervention.

- Provides cardiac stability during surgery.
- remifentanil ensures good analgesia during surgery and immobilizer prior to the end of surgery to ensure calmness.
- Because of the features and properties of remifentanil should be used in patients with high risk and patients with renal insufficiency and in large and long surgical operations.
- One of the disadvantages of remifentanil is its relatively high cost. In order to anesthetize a patient who weighs a 70 kilogram for a 90 minute, we need about one mg of it at a very high cost.

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