

High-Dose Remifentanil Anesthesia With Minimal Sedation in Neonates: A Single-Center Retrospective Study

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Koshi Suwa¹, Kyosuke Takahashi², Yusuke Iizuka¹, Alan K. Lefor³

1. Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, JPN 2. Department of Anesthesiology, Tokyo Medical and Dental University, Tokyo, JPN 3. Department of Surgery, Jichi Medical University, Shimotsuke, JPN

Corresponding author: Koshi Suwa, koshisuwa@icloud.com

Abstract

Introduction

Remifentanil is an opioid with rapid onset and elimination. Theoretically, reducing sedation using high-dose remifentanil may contribute to early emergence and prevention of postanesthetic complications related to residual anesthesia. However, there have been few reports of high-dose remifentanil anesthesia in neonatal surgery. This study aims to describe the techniques of high-dose remifentanil anesthesia in neonates and their safety outcomes.

Methods

This is a single-center, retrospective observational study from January 2016 to February 2022. Medical records from neonatal surgical procedures performed using high-dose remifentanil anesthesia were reviewed. "High dose" was defined as 0.5 mcg/kg/min or more. Patient profiles, anesthetic drugs used, and intra- and post-operative adverse events, including cardiopulmonary complications, were abstracted.

Results

There were 15 neonatal abdominal operations performed under high-dose (>0.5 mcg/kg/min) remifentanil anesthesia during the study period. The average remifentanil infusion rate was 1.9 (0.68-3.1) mcg/kg/min. Hypotension occurred in two patients (13%). Bradycardia was not observed in any patients. The mean time for tracheal extubation was 16 minutes. Five patients (33%) received naloxone administration before extubation, and two patients (13%) experienced hypoxemia immediately after extubation. No patient had cardiorespiratory complications after leaving the operating room.

Conclusions

High-dose remifentanil can be used without impairing hemodynamic stability in neonatal surgery, although there is concern about respiratory depression. Further research is needed on its potential impact on long-term outcomes.

Categories: Pediatric Surgery, Anesthesiology

Keywords: pediatric-anesthesia, remifentanil, neonate, general pediatric surgery, opioid

Introduction

Anesthesia for neonates requires specific considerations due to organ immaturity. Sensitivity to opioids in neonates is increased compared to older infants and adults, due to the limited development of the blood-brain barrier [1]. Hemodynamic instability and respiratory complications during and after anesthesia are common among neonates and necessitate careful titration of analgesics and sedatives. Remifentanil is an opioid with rapid onset and fast elimination, regardless of liver and kidney function; its half-time is 3.2 minutes, even after three hours of continuous infusion [2]. This pharmacological profile is preferable because the low accumulation of the drug could facilitate early emergence from anesthesia and prevent postanesthetic respiratory depression. Remifentanil also has sedative effects and is often used for procedural sedation in Intensive Care Unit settings [3,4].

Theoretically, reducing sedatives by using high-dose remifentanil has some possible advantages. First, we could expect fast recovery from anesthesia due to the characteristic of remifentanil's fast elimination, even in neonates. Sedatives and opioids, other than remifentanil, are metabolized by the liver and kidneys, making residual effects variable depending on organ function, particularly in newborns. Second, reducing sedatives may prevent potentially harmful effects on neurological development, such as apoptosis of neural cells in the immature rat brain, which some previous animal studies have shown [5].

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Some reports regarding the use of remifentanyl in neonates have demonstrated the utility of this drug for neonatal anesthesia [6-9]. Remifentanyl is often used in combination with sedatives, and the dose of remifentanyl varies across studies. Generally, remifentanyl exhibits dose-dependent hemodynamic depression, with major adverse events being hypotension and bradycardia during general anesthesia [10]. There have been few reports on the use of high-dose remifentanyl in neonatal surgery. Thus, the effects of high-dose remifentanyl on hemodynamics and respiratory recovery remain unknown.

The present study conducted a retrospective analysis of neonatal surgical procedures performed using high-dose remifentanyl anesthesia. This study aims to describe the anesthetic techniques and adverse events related to anesthesia.

Materials And Methods

This is a single-center, retrospective observational study. The Institutional Review Board of Jichi Medical University Saitama Medical Center approved the study design (Certification No. S22-047). The need for informed consent was waived due to the nature of this retrospective study. The authors obtained consent for publication by opt-out. Our study report adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [11]. Medical records were reviewed for neonatal operations performed between January 2016 and February 2022. Data from patients treated with high-dose remifentanyl were abstracted. "High dose" was defined as 0.5 mcg/kg/min or more. The dosage of remifentanyl for neonates varies significantly across studies [6-9,12]; therefore, the choice of 0.5 mcg/kg/min was based on our clinical experience.

Patient characteristics and intraoperative data were obtained from hospital electronic medical records and anesthesia records. Patient characteristics abstracted included age, post-conceptual age, weight, gender, underlying disease, diagnosis, and surgical procedure performed. Intraoperative data included duration of anesthesia, operating time, time to tracheal extubation, anesthesia agents used, and vital signs during anesthesia. The time to tracheal extubation was defined as the time from the end of remifentanyl infusion to tracheal extubation. Extracted vital sign data included minimum and average heart rate (HR) and blood pressure (BP) during surgery. BP was measured every two and a half to five minutes, and HR was recorded every minute. The following adverse events were collected: bradycardia (HR < 100/min), desaturation (SpO₂ < 90%) [4], hypotension (mean BP < 30 mmHg) [13], laryngospasm, and use of naloxone.

The average infusion rate of remifentanyl was calculated from the total remifentanyl dose per kilogram during surgery, divided by the duration of surgery. Data are expressed as mean ± standard deviation (SD), or median with range, or number (percentage).

Results

Patient profile

During the study period, 15 neonates underwent surgery under general anesthesia with high-dose remifentanyl. A summary of patient characteristics is shown in Table 1. The mean age of the patients was seven days, and the mean weight was 2.9 kg. Three patients were late preterm infants, and two patients were low birth weight infants. Of these, one was a very low birth weight infant who had trisomy 18 with multiple organ abnormalities. Eleven patients had gastrointestinal surgery; of these, 10 patients underwent open laparotomy. Three patients had anal surgery, and one patient underwent an endoscopic procedure.

Patient profile	Data
Age (days)	7 (1-30)
Post-conception age (weeks)	40 weeks, 6 days (35 weeks, 4 days-43 weeks, 1 day)
Weight (kg)	2.9 (1.4-3.8)
Gender (male)	10 (67%)
<i>Surgical procedure</i>	
Laparotomy (gastrointestinal surgery)	10 (67%)
Laparoscopic surgery	1 (6.7%)
Endoscopic surgery	1 (6.7%)
Others	3 (20%)
Operating time (min)	105 ± 38
Duration of anesthesia (min)	186 ± 52
Remifentanyl infusion rate (mcg/kg/min)	1.9 (0.68-3.1)
Mean heart rate (/min)	171 (155-194)
Minimum heart rate (/min)	151 (130-167)
Mean blood pressure (mmHg)	48 (36-64)
Minimum blood pressure (mmHg)	36 (25-52)
Time to extubation (min)	16 (8-32)

TABLE 1: Patient profile summary

Data are expressed as mean ± standard deviation, median (range), or number (percentage). Remifentanyl infusion rate, heart rate, blood pressure, and time to extubation are expressed as median (minimum-maximum value). The time to extubation is the duration between the end of remifentanyl infusion and extubation.

Anesthetic management

Table 2 describes details of anesthesia and outcomes. All patients underwent tracheal intubation and mechanical ventilation during anesthesia. For 14 patients (93%), anesthesia was induced in the operating room and one patient had been intubated in the Neonatal Intensive Care Unit before being transferred to the operating room.

Age (days)	Weight (kg)	Induction medications			Maintenance medications		Duration of anesthesia (min)	Time to extubation (min)	Desaturation in the operation room	Use of naloxone	Hypotension vasopressor
		Sedatives	Analgesics	Muscle relaxants	Infusion rate of remifentanyl (mcg/kg/min)	Sedatives					
10	3.2	PRP 1.6 mg/kg	FNT 7.8 mcg/kg	ROC 2.8 mg/kg	2.3	-	186	32	-	-	-
22	3.7	PRP 1.6 mg/kg	-	ROC 1.1 mg/kg	2.5	SEV	254	8	-	-	-
29	3.0	PRP 2.0 mg/kg	-	ROC 1.0 mg/kg	1.0	-	174	13	-	0.01 mg	-
30	3.7	-	FNT 1.4 mcg/kg	ROC 1.0 mg/kg	2.6	SEV	285	Not extubated	-	-	-
2	2.8	-	FNT 3.6 mcg/kg	ROC 1.1 mg/kg	1.5	-	172	27	Yes	0.03 mg	-
27	2.8	PRP 2.1 mg/kg	FNT 3.6 mcg/kg	ROC 0.4 mg/kg	1.9	-	274	11	Yes	-	+nothing
7	2.7	-	RMF 3.8 mcg/kg	ROC 1.1 mg/kg	2.7	-	106	13	-	0.02 mg	-CaGlu
7	3.6	MDZ 0.1 mg/kg	FNT 4.2 mcg/kg	ROC 1.0 mg/kg	1.5	-	190	21	-	-	-
7	3.1	MDZ 0.2 mg/kg	FNT 3.2 mcg/kg	ROC 1.0 mg/kg	0.7	MDZ	176	16	-	-	-
1	3.8	-	FNT 3.9 mcg/kg	ROC 1.1 mg/kg	1.0	-	112	Not extubated	-	-	-CaGlu
13	1.4	-	FNT 7.1 mcg/kg	ROC 1.1 mg/kg	0.9	-	157	Not extubated	-	-	-DOA+DOB
3	2.7	PRP 1.1 mg/kg	-	ROC 1.9 mg/kg	2.5	-	195	8	-	0.01 mg	-CaGlu
1	2.8	-	-	ROC 1.1 mg/kg	3.1	-	124	Not extubated	-	-	+PHE+CaGlu
7	2.2	MDZ 0.2 mg/kg	FNT 4.7 mcg/kg	ROC 0.9 mg/kg	1.5	-	215	20	-	0.02 mg	-
3	2.9	-	FNT 1.7 mcg/kg	ROC 1.4 mg/kg	2.8	-	173	19	-	-	-EPH

TABLE 2: Details of anesthetic drugs and outcomes

FNT: Fentanyl; RMF: Remifentanyl; PRP: Propofol; ROC: Rocuronium; MDZ: Midazolam; SEV: Sevoflurane; PHE: Phenylephrine; CaGlu: Calcium gluconate hydrate; EPH: Ephedrine

The time to extubation is the duration between the end of remifentanyl infusion and extubation. Desaturation is defined as an oxygen saturation of less than 90%.

Induction medications included propofol, midazolam, fentanyl, remifentanyl, and rocuronium. For induction, rocuronium was administered to all patients. In five patients (33%), propofol was given for induction; three patients (20%) received midazolam for induction; whereas seven patients (47%) were induced without sedation. As analgesics, fentanyl was used in 10 patients (67%), and a bolus infusion of remifentanyl was used in one patient (7%). The other four patients (26%) received a continuous infusion of high-dose remifentanyl for anesthesia induction, without a bolus infusion of any drugs.

During the maintenance of anesthesia, the average remifentanyl infusion rate was 1.9 (0.68-3.1) mcg/kg/min. Sevoflurane and midazolam were used for two (13%) patients and one (7%) patient, respectively. In the other 12 patients, anesthesia was maintained with high-dose remifentanyl only, without sedatives. Eleven patients (73%) were extubated in the operating room, and sugammadex was used for all extubated patients.

Adverse events

Hypotension was observed in two patients (13%), and bradycardia did not occur. During the operation, a few doses of vasopressors, such as phenylephrine, ephedrine, and calcium gluconate hydrate, were administered to five patients (33%). One patient required a continuous infusion of dopamine and dobutamine, which had started in the Neonatal Intensive Care Unit before being transferred to the operating room. Two patients (13%) had desaturation immediately after extubation. One patient recovered using continuous positive airway pressure delivered by a face mask, while one patient had laryngospasm, which required propofol administration to restore airway patency. Naloxone was administered to five patients (33%) before extubation. All patients were hemodynamically stable, without respiratory complications, after leaving the operating room.

Discussion

The present study describes administering anesthesia using high-dose remifentanyl with no or minimal sedation during 15 neonatal surgical procedures. Two patients experienced hypotension, but no bradycardia was observed in any patients. Two patients developed temporary hypoxemia after tracheal extubation.

Our results suggest that remifentanyl itself may not necessarily induce hemodynamic instability. Since remifentanyl is commonly used in conjunction with sedation, hypotension may be primarily caused by sedatives. A retrospective study described the use of remifentanyl in 46 neonates undergoing non-cardiac surgery. The average infusion rate was 0.14 $\mu\text{g}/\text{kg}/\text{min}$, and most patients also received sevoflurane or other sedatives [8]. Another study focused on neonatal abdominal surgery found that an infusion rate of 0.25 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl, combined with sevoflurane, was effective and well-tolerated in neonates [9]. Despite the modest doses of remifentanyl used in previous studies, hypotension and bradycardia were reported as common complications [8,9,14]. In contrast, in the present study, hypotension and bradycardia were not frequent, and hemodynamic instability was not observed except in one patient, who required continuous infusion of catecholamines in the Neonatal Intensive Care Unit before remifentanyl administration.

Hemodynamic instability during anesthesia using remifentanyl, as described in previous reports, can be partially attributed to the use of sedation. One study reported hemodynamic changes after a bolus infusion of remifentanyl, with stable BP and HR in early infant patients [15]. Additionally, two case reports described the anesthetic management of laparotomies for necrotizing enterocolitis in premature and very low birth weight newborns. The doses of remifentanyl were high (Case 1: maximum dose 7.2 $\mu\text{g}/\text{kg}/\text{min}$; Case 2: maximum dose 3 $\mu\text{g}/\text{kg}/\text{min}$), along with a single bolus of midazolam, and bradycardia was not observed [12]. Considering that these cases did not experience hemodynamic compromise despite high-dose remifentanyl infusion, the adverse effects on circulation could be induced by the concomitant use of sedation rather than by remifentanyl itself.

Respiratory depression is one of the major side effects of opioid administration. Remifentanyl is known to accumulate less than other opioids, due to its short context-sensitive half-time [16]. However, even though the half-life of remifentanyl in early infants is approximately five minutes [16], postoperative apnea and hypoxemia after anesthesia using remifentanyl have been reported [7,17]. A few patients in this study also developed hypoxemia after tracheal extubation, and 5 out of 11 extubated patients required the administration of naloxone before extubation. Although the use of naloxone may depend on the preferences of anesthesiologists, the percentage of naloxone use was quite high. Therefore, it should be noted that prolonged respiratory depression could occur after continuous infusion of high-dose remifentanyl. Further investigations will be required to determine the dose relationships between remifentanyl and the incidence of respiratory depression.

We hypothesized that high-dose remifentanyl anesthesia would lead to a short time for tracheal extubation due to its rapid elimination. However, our results did not support the hypothesis. In this study, the time to tracheal extubation was 16 minutes, compared to 13 minutes in the previous study [8]. Additionally, interpreting the time to extubation in our study is complicated, as several influencing factors existed aside from remifentanyl administration. First, the doses of fentanyl used in induction (4.1 mcg/kg) were higher than the typical dose (1-2 mcg/kg), which could have extended the time to tracheal extubation. Secondly, since naloxone was used in five cases, the time to tracheal extubation could have been significantly longer if it had not been used. Therefore, the effects of high-dose remifentanyl anesthesia on time to extubation should be examined in prospective trials without these biases.

There are some concerns about high-dose remifentanyl anesthesia. First, the combination of low-dose sedatives and high-dose remifentanyl may predispose patients to intraoperative awareness. However, using high-dose remifentanyl without additional sedatives may be justified, because remifentanyl itself has a sedative effect. A previous study showed a dose-dependent decrease in values of the bispectral index (BIS) [13], suggesting that higher doses of remifentanyl may provide sufficient depth of anesthesia for amnesia. Moreover, concerns about intraoperative awareness could be less critical in neonates than in older populations. According to cohort studies that estimated the incidence of accidental awareness during general anesthesia in children, the youngest patient was three years old [18]. However, we were unable to

evaluate the sedative status in this study due to the lack of electroencephalographic monitoring during anesthesia.

Second, the effects of high-dose remifentanyl on neurological development are controversial. An animal study has demonstrated that relatively high-dose remifentanyl (80 mcg/kg/hr \times 1.3 mcg/kg/min) didn't increase apoptosis caused by isoflurane in immature brains [19]. Based on these findings, remifentanyl-centered anesthesia may not induce neurotoxicity in immature brains. However, there has been no research on the long-term effects of high-dose remifentanyl in human neonates.

Finally, high-dose remifentanyl may induce hyperalgesia. Some previous research showed that relatively high-dose remifentanyl (0.6-0.9 mcg/kg/min) induced hyperalgesia in a dose-dependent manner [13]. On the other hand, a prospective randomized clinical trial reported the opposite phenomenon: high-dose remifentanyl (1.2 mcg/kg/min) resulted in reduced postoperative visual analog scale (VAS) scores and morphine consumption compared to low-dose remifentanyl (0.2 mcg/kg/min). It was also suggested that remifentanyl, when administered beyond a certain dose, may paradoxically become less likely to induce hyperalgesia [20]. In this study, we used more remifentanyl than in the previous studies and did not evaluate postoperative pain, so the incidence of hyperalgesia remains unknown.

To summarize, there is not enough evidence regarding the effects of high-dose remifentanyl on intraoperative awareness, neurological development, and hyperalgesia in neonates. Further research on these topics is needed.

To the best of our knowledge, this is the largest case series to date demonstrating the feasibility of administering anesthesia using high-dose remifentanyl with minimal sedation in neonatal patients. The present study does have acknowledged limitations. First, there is no comparison group because this is a retrospective descriptive study. Therefore, the superiority of clinical practice cannot be assured for safety and adverse events compared to conventional anesthesia. Second, the sample size was small, and the doses of remifentanyl were highly varied because they were decided according to each anesthesiologist's preference. Consequently, the findings of this study may lack sufficient replicability.

Conclusions

In conclusion, high-dose remifentanyl can be used without impairing hemodynamic stability in neonatal surgery. However, this technique raises concerns about respiratory complications. Further research is warranted to determine the effects of high-dose remifentanyl on neonatal neurological development and hyperalgesia.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Koshi Suwa, Kyosuke Takahashi

Acquisition, analysis, or interpretation of data: Koshi Suwa, Yusuke Iizuka, Alan K. Lefor

Drafting of the manuscript: Koshi Suwa

Critical review of the manuscript for important intellectual content: Kyosuke Takahashi, Yusuke Iizuka, Alan K. Lefor

Supervision: Yusuke Iizuka, Alan K. Lefor

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Review Board of Jichi Medical University Saitama Medical Center issued approval S22-047. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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