Effects of General Anesthesia Using Remifentanyl on Hemodynamics during Oral Surgery

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Abstract

Opioids are used to achieve analgesia during general anesthesia. Due to excellent adjustability, remifentanyl, a strong opioid analgesic, is widely used during general anesthesia while performing oral surgery. However, caution is advised since remifentanyl lowers blood pressure and heart rate. This study examined the effect of remifentanyl on circulatory fluctuations while performing oral surgery under general anesthesia.

The subjects were cases of general anesthesia performed in the hospital affiliated with our university between 2014 and 2017. Information was obtained from medical records and anesthesia minutes, regarding patient characteristics, surgical procedure, remifentanyl use, drugs used to induce and maintain anesthesia, circulatory fluctuations during surgery, and management of hemodynamic events.

Among the 1,474 cases in this study, remifentanyl was used in 795 cases during general anesthesia (R group). Within R group, circulatory fluctuations appeared in 46 cases, the most common being bradycardia (22 cases) and hypotension (11 cases). A treatment for circulatory fluctuations (bradycardia [2.8%] and hypotension [1.5%]) was administered in 54 cases (6.8%). Hypotension was often seen in the elderly and in patients who had taken hypotensive medicine prior to the surgery. Bradycardia often occurred during corrective surgery, open reduction, and internal fixation. Circulatory inhibition under general anesthesia occurs easily with remifentanyl use, which has a parasympathetic nerve stimulation effect, during maxillofacial surgery and cervical procedures where vagal reflexes such as trigeminal nerve stimulation and carotid sinus compression are likely to occur.

Keywords :

remifentanyl, general anesthesia, circulatory fluctuation, maxillofacial surgery

Introduction

The main purposes of general anesthesia are to achieve loss of consciousness and pain relief during surgery and prevent myotonia. Balanced general anesthesia is most commonly conducted through the appropriate use of three general anesthetic factors, namely anesthetics, analgesics, and muscle relaxants. In Japan, opioid drugs such as morphine and fentanyl have traditionally been used for

analgesia during surgery. Since 2007, the use of remifentanyl has become possible in Japan and has become an important analgesic during general anesthesia.

Remifentanyl, a selective μ -opioid receptor agonist, is widely used in oral surgery as a potent narcotic anesthetic with excellent adjustability. However, caution must be taken during its use due to post-operative effects, such as nausea, vomiting (1,2), shivering (3,4), and pain sensitivity (5-7). Moreover, remifentanyl lowers blood pressure and heart rate and has other circulation inhibiting effects during administration (8-13). Therefore, extra caution is advised in patients with complicating condi-

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Table 1. Background information of the study subjects

	R Group (n=795)	NR Group (n=679)
Age (y.o)	35.5±19.6	33.8±23.6
Height (cm)	161.2±11.6	152.8±19.9
Weight (kg)	57.8±15.2	50.8±19.5
Sex ratio (m/f)	343/452	385/294
P.S (I, II, III)	550/239/6	418/256/5
Surgery time (min)	133.4±117.6	72.3±44.9
Anesthesia time (min)	200.3±127.8	132.6±49.3
Urine volume/hour of anesthesia (ml/h)	116.2±77.7 ^{#1}	100.1±63.0 ^{#2}
Infusion volume/hour of anesthesia (ml/h)	362.5.±118.9	344.4±127.2

Urine volume/hour of anesthesia is only applicable to cases in which urine volume was measured by catheter.

#1: n=388, #2: n=652

tions, such as old age, ASA-P.S III-IV, hypertension, and arrhythmia, as detailed in the package insert(14). Multiple cases of sudden cardiac arrest(15,16) have been reported, thus necessitating a thorough examination of remifentanil use.

In this study, the effects of remifentanil administration on circulatory fluctuations under general anesthesia while performing oral surgery were retrospectively investigated using medical records and anesthesia minutes.

Subjects and Methods

The subjects were cases of general anesthesia performed in the hospital affiliated with Nihon University School of Dentistry at Matsudo between 2014 and 2017. Information on the investigation was obtained from medical records and anesthesia minutes, including patient background, drugs used to induce and maintain anesthesia, remifentanil use for maintaining general anesthesia, circulatory fluctuations during surgery and drugs administered in response to circulatory fluctuations, preoperative complications and medications, anesthesia times and infusion volumes, urinary volumes, time of the appearance of circulatory fluctuations, subject's age, and surgery method. The dose of remifentanil was decided in consideration of vital signs and anesthetic depth. Student's t-test and χ^2 tests were conducted, and results with $P<0.05$ were considered statistically significant. This

study was conducted with the permission of the Nihon University School of Dentistry at Matsudo Ethics Committee(EC No. 18-025).

Results

Comparison of the use of remifentanil to maintain general anesthesia

Among 1,474 subject cases investigated, remifentanil was used to maintain general anesthesia in 795 cases(R group), but not in the remaining 679 cases(NR group). Patient characteristics are summarized in Table 1.

1) Circulatory fluctuations while maintaining anesthesia

Circulatory fluctuations while maintaining anesthesia in the R and NR groups are summarized in Table 2. In the R group, there were 46 cases of circulatory fluctuations while maintaining anesthesia, the most common being bradycardia(22 cases, 2.8%), and hypotension(11 cases, 1.5%). The NR group had 38 cases, the most common being arrhythmia(14 cases, 2.1%), and hypertension(10 cases, 1.5%). No difference was observed between the two groups in terms of the total number of cases in which circulatory fluctuations were admitted, but the occurrence of bradycardia was significantly higher($p<0.05$) in the R versus NR group(22 and 7 cases, respectively).

In the comparison by the method of anesthesia, circulatory fluctuations were only admitted in the R Group for

Table 2. Circulatory fluctuations while maintaining anesthesia.

		R Group (n=795)	NR Group (n=679)	P value
Number of cases with event occurrence		46	38	0.876
Event types (including duplicates)		49 # ³	39 # ⁴	
	Bradycardia	22	7	< 0.05
	Tachycardia	1	0	0.355
	Arrhythmia	9	14	0.151
	Hypotension	11	4	0.130
	Hypertension	4	10	0.056
	ECG abnormality	2	4	0.310
Anesthesia method	AOP	19	0	< 0.05
	AOS	7	2	0.150
	GOP	8	3	0.097
	GOS	15	34	< 0.05
Induction drug	Propofol	45	26	0.844
	Midazolam	1	2	0.585
	Sevoflurane	2	9	0.466
	Others	0	2	0.243
Drug used to aid induction	Remifentanyl	48	0	0.344
	Fentanyl	1	34	0.543
	None	0	5	0.440

#³:Bradycardia + ECG abnormality 1 case, bradycardia + hypotension 1 case, high blood pressure + low blood pressure 1 case

#⁴:Hypotension + arrhythmia 1 case

AOP: Air + oxygen + propofol

GOP: Nitrous oxide + oxygen + propofol

AOS: Air + oxygen + sevoflurane

GOS: Nitrous oxide + oxygen + sevoflurane

AOP anesthesia, whereas they were significantly more frequent in the NR group for GOS anesthesia. No difference was observed due to the drugs used to induce general anesthesia and aid in the induction of general anesthesia.

2) Treatment of circulatory fluctuations

Measures taken in response to circulatory fluctuations in the R and NR groups are summarized in Table 3. Atropine sulfate was administered for treating bradycardia in 19 and 6 cases in the R and NR groups, respectively, and either drug administration or remifentanyl discontinu-

Table 3. Measures taken in response to circulatory fluctuations

Circulatory event	Response	R Group	NR Group
Bradycardia	Atropine sulfate administration	19	6
	Discontinuation of remifentanyl administration	3	1
Tachycardia	Inderal administration	1	—
Arrhythmia	Antiarrhythmic agent administration	1	0
	Medical observation	8	14
Hypotension	Ephedrine administration	11	3
	Discontinuation of anesthetic administration	0	1
Hypertension	Hypotensive drug administration	2	4
	Medical observation	2	6
Electrocardiogram abnormality	Antiarrhythmic agent administration	0	1
	Medical observation	2	3

ation was taken as a response in all cases. In response to hypotension, ephedrine was administered in all and 3 cases in the R and NR groups, respectively, and either drug administration or remifentanyl discontinuation was taken as a response in all cases. In response to arrhythmia, only medical observation was performed for 8 and all cases in the R and NR groups, respectively. No proactive measures were taken for most cases, such as changes in drug administration.

Study of the R Group

1) Patient background

Background information of the R-Group patients in the Event and Non-event groups are summarized in Table 4. Circulatory fluctuations were observed in 46 cases while maintaining anesthesia (the Event group). However, no significant difference was observed when compared with cases with no circulatory fluctuations (the Non-event group) in height, weight, sex, infusion amount per hour of anesthesia, or the rate of remifentanyl use while inducing anesthesia. Significant differences in age, surgery duration, anesthesia duration, and urine volume were observed between the two groups. Furthermore, the Event group had a significantly higher proportion of cases with

ASA physical status (ASA-PS) II than the Non-event-group.

2) Appearance of circulatory fluctuations due to anesthesia method

Rate of circulatory events in the R Group by anesthesia method are summarized in Table 5. The appearance of circulatory fluctuations did not significantly differ by the anesthesia method used (AOP, GOP, AOS, or GOS).

3) Circulatory fluctuations compared with preoperative circulatory complications and medicines taken internally

Preoperative circulatory complications and medicine dosages in the Event group are shown in Table 6. Of the 26 P.S. II and III cases with circulatory fluctuations, 11 were complicated by hypertension. Furthermore, three of the seven cases in which hypotensive drugs were used as preoperative cardiovascular drugs, antithrombotic drugs were also administered. Cardiovascular drugs were administered in 5 of the 11 cases in which hypotension occurred. No significant relationship was observed between preoperative cardiovascular complications and types of circulatory fluctuations.

Table 4. Background information of R-Group patients

Background factors	Event group (n=46)	Non-event group (n=749)	P value (Ref.)
Age (y.o)	48.6±19.3	37.1±18.5	< 0.05
Height (cm)	162.4±7.3	162.6±9.2	0.290
Weight (kg)	59.3±8.2	58.4±12.3	0.294
Sex ratio (m/f)	19/27	324/425	0.795
P.S (I, II, III)	22/23/1	528/216/5	< 0.05
Surgery time (min)	225.2±217.4	126.6±97.4	< 0.05
Anesthesia time (min)	301.3±229.1	182.6±107.2	< 0.05
Urine volume/hour of anesthesia (ml/h)	128.4±83.6	95.1±80.3	< 0.05
Infusion volume/hour of anesthesia (ml/h)	345.7±117.5	371.1±119.4	0.325
Cases of the use of remifentanil when inducing anesthesia	45	699	0.226

Table 5. Rate of circulatory events in the R Group by anesthesia method

Anesthesia method	AOP	AOS	GOP	GOS	P value
Bradycardia	9	2	7	4	0.296
Tachycardia	0	1	0	0	0.079
Arrhythmia	4	2	1	2	0.775
Hypotension	4	1	1	5	0.085
Hypertension	2	1	0	1	0.725
ECG abnormality	0	0	0	1	0.176

AOP: Air + oxygen + propofol

GOP: Nitrous oxide + oxygen + propofol

AOS: Air + oxygen + sevoflurane

GOS: Nitrous oxide + oxygen + sevoflurane

4) Appearance of circulatory fluctuations by age and sex

The ratios of the appearance of each circulatory event by age group are shown in Fig. 1. Circulatory fluctuations were more frequently observed with increasing age. Compared to the other age groups, bradycardia was more common in the 20s, 30s, or 60s, whereas hypotension was more common in the 50s to 70s age groups.

No age-specific trend was observed for arrhythmia and hypertension occurrence. No significant difference was observed by sex (19 male and 27 female cases, $p=0.795$).

5) Period of the appearance of circulatory fluctuations

The time until the appearance of circulatory fluctuations after the administration of remifentanil are shown in Fig. 2. After the initial administration of remifentanil, bradycardia occurred within 15 minutes in most ($n=11$) cases, whereas hypotension often occurred within 60 minutes. All cases of tachycardia and hypertension appeared during the patient revival, when the administration of remifentanil was already complete.

6) Circulatory fluctuations and oral surgery procedures

Table 6. Preoperative circulatory complications and internally administered medicines for circulatory event group (duplicates included)

Circulatory event	P.S			Preoperative cardiovascular complications (Duplicates included)	Contents and administration of cardiovascular drugs		
	I	II	III				
Bradycardia (n=22)	13	9	0	High blood pressure 2	2	ARB	2
Tachycardia (n=1)	1	0	0	WPW syndrome 1	0	—	—
Arrhythmia (n=9)	5	4	0	High blood pressure 2 Ischemic heart disease 1	3	Ca blocker 1 Antithrombotic drugs 2	—
Hypotension (n=11)	2	9	0	High blood pressure 4	5	Ca blocker 2 ARB 1 PG formulation 1 Antithrombotic 1	—
Hypertension (n=4)	0	3	1	High blood pressure 3	1	Ca blocker 1	—
Electrocardiogram abnormality (n=2)	2	0	0	—	0	—	—

ARB: Angiotensin II Receptor Blocker

WPW syndrome: Wolff-Parkinson-White syndrome

Fig. 1. Ratio of the appearance of each circulatory event by age group. Circulatory fluctuations were more frequently observed with increasing age. Bradycardia was more common in the 20s, 30s, or 60s, whereas hypotension was more common in the 50s to 70s age groups.

The type of oral procedures and associated circulatory fluctuations are shown in Fig. 3. Bradycardia often occurred during corrective surgery, bone-implant removal,

osteoplasty, tooth removal and cystectomy, sequestrectomy, and fracture reduction or open reduction, and internal fixation. Blood pressure changes and arrhythmia

Fig. 2. Time until the appearance of circulatory fluctuations after the administration of remifentanyl. In 11 cases, bradycardia occurred within 15 minutes after administration of remifentanyl. Hypotension often occurs within 60 minutes after remifentanyl administration.

Fig. 3. Number of appearances of circulatory fluctuations by procedure contents. Bradycardia often occurred during corrective surgery, bone-implant removal, osteoplasty, tooth removal and cystectomy, sequestrectomy, and fracture reduction or open reduction, and internal fixation.

events were most frequent during lumpectomy. Adrenaline-containing local anesthetics were used in all cases.

Discussion

While remifentanyl is often used during prolonged surgery and anesthesia, its half-life in the blood is extremely

short (3–4 minutes) compared to fentanyl and morphine (17,18). This study considered the effects of delayed revival due to prolonged surgery time. Furthermore, remifentanyl use inhibits cortisol and catecholamine secretion due to its potent analgesic effects, thereby controlling intraoperative urine volumes (3). This study showed a significant increase in urine volumes per unit of anesthesia time in the R Group. Moreover, the renal blood flow was also maintained, thus making remifentanyl an appropriate choice during prolonged anesthesia. In the other hand, high urine volumes may be one of trigger to promote bradycardia and hypotension, because urine volumes in the Event group were significantly higher than those in the Non-event group.

This study reported bradycardia and hypotension in the R Group in 2.8% and 1.5% cases, respectively. In clinical trials of medical surgery in Japan, hypotension and bradycardia were observed in 41.2% and 22.1% cases, respectively (12). Koitabashi et al. (19) reported systolic blood pressure falling to 45 mmHg due to the administration of remifentanyl 0.5 $\mu\text{g/kg/min}$ and bradycardia as low as 45 bpm in 20% of the patients. In contrast, Twersky et al. (20) showed similar results as the current study, with 1.9%–2.7% of otherwise healthy adults showing bradycardia with remifentanyl use (0.25 $\mu\text{g/kg/min}$) during head and neck surgeries. The gentler rate of remifentanyl administration (0.1–0.3 $\mu\text{g/kg/min}$) was used in our facility. Because it is possible to reduce the dose of analgesic, since the local anesthetic was used at all times during the oral surgery operation. Furthermore, adrenaline which is contained in the local anesthetics may reduce bradycardia and hypotension.

Hypotension due to remifentanyl use is thought to be caused by a direct muscle relaxant effect on the smooth muscles of the blood vessels through the intermediary of the μ opioid receptors of the peripheral nerves. Furthermore, the mechanism underlying bradycardia occurrence involves the intermediary of the opioid receptors, a potent parasympathetic nerve stimulation effect, a sympathetic nerve blocking effect (21), a parasympathetic nerve blocking effect due to the direct stimulation of μ opioid receptors of the central nervous system, and a negative chronotropic effect due to the direct stimulation of the μ opioid receptors of the sinoatrial node (22,23). Therefore, administration of ephedrine (has α and β effects in response to hypotension) and atropine sulfate (has a block-

ing effect on the parasympathetic nerve) in response to bradycardia are considered appropriate choices (19,24). In response to hypotension, ephedrine hydrochloride was administered, and remifentanyl was discontinued in response to hypotension in the current study. Furthermore, atropine sulfate was administered in 19 out of 22 cases of bradycardia. However, cases of atropine sulfate being ineffective in managing bradycardia during remifentanyl administration have been reported (25,26). Therefore, pre-administration of anticholinergics to prevent bradycardia may be considered.

No significant difference in circulatory fluctuations due to remifentanyl use for inducing anesthesia was observed, possibly due to its very short (few minutes) effective period, thus having no effect on the maintenance of anesthesia.

Regarding the relationship between the appearance of circulatory fluctuations during surgery and preoperative circulatory complications and medicines administered internally, in this study, no particular relationship was seen between preoperative circulatory complications or cardiovascular drugs and the appearance of intraoperative circulatory fluctuations. However, cases were admitted in which hypotension while maintaining anesthesia occurred due to the use of remifentanyl in patients treated with preoperative hypotensive drugs. The use of β blockers and calcium antagonists are considered to be risk factors for hypotension due to trigeminal-vagal nerve reflexes (27), and cases of sinus arrest produced have also been reported (28) for patients treated with internally administered $\alpha\beta$ blockers and calcium antagonists prior to surgery. As such, caution must be taken with respect to hypotension during remifentanyl anesthesia in cases in which patients are treated with cardiovascular drugs prior to surgery.

Regarding age and the intraoperative appearance of circulatory fluctuations, Nakajima (29) reported that patients in their 60s had a 10% higher rate of hypotension occurrence than those in their 40s to 50s, and intraoperative hypertension was significantly more frequent in patients in their 70s compared to those in their 40s. Furthermore, Reich et al. (30) cited age over 50 as a factor contributing to hypotension after the introduction of general anesthesia. The current study showed a similar trend with increased occurrence of circulatory fluctuations with age, and a particularly higher proportion of pa-

tients in their 50s and above showing hypotension compared to those in their 40s or younger. Positive chronotropic action with respect to β stimulation and blood vessel restriction with respect to catecholamine weakens with increasing age(31). Therefore, caution is advised while administering remifentanyl in the elderly due to its sympathetic nerve blocking effect. Furthermore, bradycardia occurs very quickly (within 15 minutes) of remifentanyl administration in many cases(32,33), highlighting the importance of circulatory monitoring, especially immediately after remifentanyl administration.

Among circulatory fluctuation indicators, bradycardia is often seen in cases of corrective surgery, bone-implant removal operations, open reduction, and internal fixation. Sudden bradycardia during orthognathic surgery has been reported(34,35). During maxillofacial surgery and cervical procedures where vagal reflexes such as trigeminal nerve stimulation and carotid sinus compression are likely to occur, it may be easy for parasympathetic nerve stimulation symptoms to occur during remifentanyl use with general anesthesia.

Conclusion

No difference was observed between the R and NR groups in the total number of appearances of circulatory fluctuations that required a response. However, the rate of bradycardia and hypotension occurrence was high when remifentanyl was used in general anesthesia. No effect was observed due to the method of treating the appearance of circulatory fluctuations. In all cases of bradycardia and hypotension under general anesthesia, remifentanyl was discontinued and atropine sulfate or ephedrine was administered with no further difficulties. The use of remifentanyl is effective in lengthening anesthesia times; however, instances such as hypotension in patients treated with preoperative hypotensive drugs and the elderly, need special attention. Though the dose of remifentanyl for general anesthesia is lower in oral surgery, such as corrective surgical procedures, than medical surgery, it may be easy to induce circulatory inhibition cause by remifentanyl which has parasympathetic nerve stimulation.

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Conflict of Interest

None of the authors have any conflicts of interest associated with this study.

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