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ORIGINAL ARTICLE

Remifentanil versus fentanyl compared in a target-controlled infusion of propofol anesthesia: quality of anesthesia and recovery profile

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Abstract
Purpose The aim of the present study was to compare the clinical properties of fentanyl versus remifentanil in a target-controlled infusion (TCI) of propofol anesthesia regimen with bispectral index (BIS) monitoring.
Methods Forty consenting patients scheduled for elective septorhinoplasty were prospectively studied as one of two groups: fentanyl (group F) or remifentanil (group R). After loading boluses of fentanyl 3 μg kg^{-1} or remifentanil 1 μg kg^{-1} were administered, the continuous infusion of fentanyl or remifentanil was started at a rate of 0.03 or 0.15 μg kg^{-1} min^{-1}, respectively. Propofol infusion was then commenced with a 3 μg ml^{-1} effect site concentration (Ce) by means of a TCI device. The Ce propofol was adjusted to keep BIS at 50 ± 10.
Results The general mean value of propofol Ce for group F and group R was 4.0 and 3.5 μg ml^{-1}, respectively. As to the recovery profile, the eye opening time (mean, 6.7 vs. 4.6 min), extubation time (mean, 7.3 vs. 4.7 min), and orientation time (mean, 7.6 vs. 4.9 min) were found to be significantly longer in group F than in group R.
Conclusion We concluded that in propofol-based TCI anesthesia under BIS supervision for septorhinoplasty operations, remifentanil was better than fentanyl, especially with respect to emergence from total intravenous anesthesia (TIVA). Furthermore, the durations of anesthesia and operation were rather short, which indicates that fentanyl can be safely used.

Keywords Target-controlled infusion · Propofol · Remifentanil · Fentanyl · Bispectral index

Introduction

The target-controlled infusion (TCI) system is an anesthetic dosing technique that has been developed during the past decade [1]. Following the development of this computer-assisted infusion system and the availability of short-acting anesthetics, total intravenous anesthesia (TIVA) has become increasingly popular. The pharmacokinetic and pharmacodynamic properties of propofol and the short-acting properties of recent synthetic opioids such as remifentanil make them highly suitable for continuous infusion [2].

In terms of analgesic intensity, lack of response to surgical incision, and management of intraoperative stress, remifentanil exhibits similar effects to fentanyl in adult healthy volunteers and surgical patients [3]. Fentanyl, inexpensive and easy to administer, has been the most common opioid used in standard anesthesia practice for this purpose. Rapid and safe emergence from anesthesia as well as rapid respiratory recovery and safe extubation is very important, especially in patients undergoing ear–nose–throat surgery. Remifentanil has a pharmacokinetic profile characterized by a rapid equilibration with the central compartment, easy titratability, and a short-termination half-life independent of infusion duration. Consequently, remifentanil would be expected to exhibit a smooth onset of opioid-like effects with rapid recovery and minimal residual sequelae [4].

This study was presented at First World Congress of Total Intravenous Anesthesia TCI, 10th Anniversary EUROSIVA, Venice, Italy, September 27–29, 2007.

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The aim of the present study was to compare the clinical properties of fentanyl versus remifentanil in a TCI of propofol anesthesia regimen with bispectral index (BIS) monitoring with special regard to recovery profile from anesthesia in patients undergoing ear–nose–throat surgery.

Methods

Following the approval of the study by local ethics committee, and after informed consent was obtained, 40 patients classified as American Society of Anesthesiologists physical status (ASA) I–II who were scheduled for elective septorhinoplasty were enrolled in this prospective study. Patients were randomly assigned in a double-blind manner to either the fentanyl (group F, $n = 20$) or the remifentanil group (group R, $n = 20$). Exclusion criteria were ages younger than 18 years or older than 65 years and receipt of analgesics or sedatives within 24 h before the study. Patients were also excluded if they were significantly hypertensive (diastolic blood pressure > 100 mmHg) or hypotensive (systolic blood pressure < 100 mmHg), or if they presented any previous signs of bradyarrhythmic heart disorders.

No premedication was given. Standard monitoring included electrocardiogram, noninvasive blood pressure, pulse oximetry (SpO_2), and end-tidal carbon dioxide ($ETCO_2$). The Quatro Sensor electrodes were placed on the patient's forehead, and BIS values were displayed using an Aspect electroencephalogram monitor (A-2000 BIS XP Platform; Aspect Medical Systems, Newton, MA, USA). Muscle relaxation was monitored with a train-of-four nerve stimulator (TOF Watch SX; Organon, Ireland). An anesthetist who was not aware of the study drug (supplied as coded bolus and infusion syringes) recorded all perioperatively obtained measurements, 1 min after the induction (beginning of propofol infusion), when loss of consciousness (LOC) was ensured through loss of eyelid reflex and verbal contact, 1 and 5 min after tracheal intubation, 1, 5, and 10 min after incision, then with 10-min intervals and at tracheal extubation. The records of the patients were also followed up and kept at the postanesthesia care unit (PACU). On arrival in the operating room, baseline values for BIS, heart rate (HR), mean arterial pressure (MAP), and pulse oximetry were obtained, and an intravenous catheter was placed. Before induction of anesthesia, patients breathed 100% oxygen for 5 min and were given 5 ml kg^{-1} intravenous saline solution.

In group F, the intravenous fentanyl loading dose, 3.0 μg kg^{-1} over 120 s, was administered and maintenance was achieved with an infusion rate of 0.03 μg kg^{-1} min^{-1}. In group R, the intravenous remifentanil loading dose, 1.0 μg kg^{-1} over 120 s, was administered and maintenance was achieved with an infusion rate of 0.15 μg kg^{-1} min^{-1}. The dilution of fentanyl was 0.5 mg in 50 ml and that of remifentanil was 2.5 mg in 50 ml saline solution, which provided equal infusion rates for maintenance in both groups. Propofol was administered by TCI (Orchestra Base Primea; Fresenius Kabi, France) with an effect site concentration (Ce) of 3 μg ml^{-1}, using Schnider's pharmacokinetic model.

After LOC, the TOF monitor was switched on and tracheal intubation was facilitated with rocuronium bromide 0.6 mg kg^{-1}. All patients were ventilated with a fresh gas flow of 4 l min^{-1} of oxygen and air mixture to maintain $ETCO_2$ between 30 and 35 mmHg (Draeger, Julian Plus, Germany). Before the surgery was started, 4 ml lidocaine 2% with adrenaline (0.05 mg) was diluted with 4 ml saline solution and the yielded 8 ml was injected by the surgeon on the operation area.

Fentanyl and remifentanil were infused continuously at a fixed rate, while the Ce propofol infusion was adjusted in increments of 0.5 μg ml^{-1} (increased or decreased), to keep BIS value at 50 ± 10. Hypotension (a decrease in MAP of more than 20% from baseline values) was treated with IV fluids. When this treatment proved inadequate, ephedrine was administered intravenously. Bradycardia (HR < 50 bpm) was treated with IV atropine. At the end of surgery all anesthetics were discontinued without tapering, and the lungs were ventilated with 100% oxygen at a fresh gas flow of 6 l min^{-1}. Residual neuromuscular block was reversed at the end of the operation in patients who showed incomplete recovery of neuromuscular function. The patients were extubated when adequate spontaneous ventilation and response to verbal command were established. Emergence from anesthesia was assessed as the time from the end of operation until the time of orientation (recalling name and date of birth). During the emergence time, times of eye opening, extubation, and orientation were recorded.

Thereafter, the patients were directly transferred to the PACU, where further recording was done by an independent, blinded observer, who was unaware of the administered anesthesia regimen. Postanesthesia recovery was scored for PACU discharge eligibility using the Aldrete Recovery Scoring (ARS). The criterion for discharge from PACU was defined as ARS greater than 9. During the observation period in PACU, hemodynamic parameters were recorded as well as side effects such as shivering, nausea, and vomiting. Patients were asked every 5 min, until discharge from the PACU, to indicate pain experience on a numeric rating scale (NRS: 0 = no pain; 10 = unbearable pain).

Twenty patients per treatment group were necessary to detect a reduction of 15% in the mean levels of the characteristics of emergence from anesthesia with a level of significance of $P < 0.05$ and a statistical power of 0.90. Parametric analysis of variance and nonparametric analysis

(Mann–Whitney U test) were performed. The analyses were considered to be statistically significant when the P value of the Mann–Whitney U test was lower than 0.05. The differences for MAP and HR was tested each time at a significance level of 0.025 with the Bonferroni correction for multiple comparisons performed on the same response variable evaluated at different times.

Results

There were no significant differences between the groups with regard to demographics data, duration of surgery and anesthesia, and the time required for LOC (Tables 1, 2).

During the follow-up period (Fig. 1), there were no statistically significant differences between the groups with regard to the general mean values of MAP ($P = 0.179$). The general mean value of MAP for group F was 81.4 ± 9.99 mmHg; this value was found to be 76 ± 9.99 mmHg for group R. The change levels that occurred in time in MAP values were similar between the groups ($P = 0.478$). In the first minute of induction, there was a slight decrease in MAP in both groups; however, there was no significant difference between the groups. In the LOC period of the patient, the decrease in MAP continued. In the first minute of intubation, there was an insignificant increase in MAP in both groups. In the later periods of anesthesia, MAP values were observed to be parallel to each other in both groups and were below the baseline. After extubation, MAP values reached the baseline value in both groups. In general, MAP values were observed to be within normal limits.

During the follow-up period (Fig. 2), there were no statistically significant differences between the groups with regard to general mean values of HR ($P = 0.879$). The general mean value of HR for group F was 81.5 ± 13.44 bpm; this value was found to be 80.7 ± 13.44 bpm for group R. As to the HR values, in terms of the control values in both groups, insignificantly higher values were observed in group R. However, 1 min after the induction and in the periods of LOC, the values for both groups decreased insignificantly. In the first minute of intubation, there was an insignificant increase in HR in both groups. Following this period, the values for both groups were parallel to each other until the 35th minute. After extubation, HR values reached the baseline value in both groups. However, the falls and increases in the heart rate were within normal limits.

During the follow-up period (Fig. 3), statistically significant differences were observed between the groups with regard to propofol Ce values ($P = 0.040$). The general mean value of propofol Ce for group F was 4.0 ± 0.56 μg ml^{-1}; this value was found to be 3.5 ± 0.57 μg ml^{-1} for group R. The levels of change that occurred in time in propofol Ce levels were similar between the groups ($P = 0.240$).

In our study, it was observed that propofol consumption (see Table 2) was significantly higher in group F when compared to group R (mean, 1399.8 ± 508.1 vs. 905.6 ± 287.1 mg) ($P < 0.001$). The amount of total opioid used was approximately 230 ± 86.3 μg for group F; it was found to be approximately 1067 ± 340.9 μg for group R.

In the recovery profile (Table 3), eye opening time was significantly longer in group F than in group R ($P = 0.002$). The duration of this time was approximately 6.7 ± 2.6 min in group F and approximately 4.6 ± 2.9 min in group R. Extubation and orientation times were also found to be significantly longer in group F (mean, 7.3 ± 2.6 and 7.6 ± 2.6 min) than in group R (mean, 4.7 ± 3.7 and 4.9 ± 3.8 min) ($P < 0.01$).

In the PACU, the rate of patients' ARS (Fig. 4) to reach 10 in group F was 30% at the 5th minute, 90% at the 15th minute, and 100% at the 30th minute. In group R, this rate was 75% at the 5th minute and 100% at the 15th and 30th minutes. A significant difference with regard to this rate among the patients was found only at the 5th minute ($P = 0.004$). Again in the PACU, during the first 30-min follow-up, two patients in the fentanyl group (10%) and four patients in the remifentanil group (20%) stated that they had pain. However, because the NRS values were not greater than 3 in both groups, additional analgesia was not administered. In terms of side effects, one patient in each group suffered from shivering in the PACU.

Discussion

In the present study, remifentanil was compared with fentanyl in two groups of patients receiving a TCI-propofol

Table 1 Patient demographic characteristics (mean ± SD)

	Group F ($n = 20$)	Group R ($n = 20$)	P value
Gender (M/F)	9/11	7/13	NS
ASA physical status (I/II)	18/2	19/1	NS
Age (years)	29 ± 8	26 ± 8	NS
Weight (kg)	68 ± 15	62 ± 9	NS
Height (cm)	170 ± 8	169 ± 9	NS

ASA American Society of Anesthesiologists

Table 2 Characteristics of anesthesia management (mean ± SD)

	Group F ($n = 20$)	Group R ($n = 20$)	P value
LOC (min)	3.2 ± 2.3	4.0 ± 3.2	NS
Duration of surgery (min)	97.7 ± 47.6	83.8 ± 27.2	NS
Duration of anaesthesia (min)	119.1 ± 47.4	109.4 ± 28.8	NS
Propofol total dose (mg)	1399.8 ± 508.1	905.6 ± 287.1	<0.001
Propofol (mg kg^{-1} h^{-1})	11.20 ± 3.02	8.12 ± 1.12	<0.001
Fentanyl total dose (μg)	230.1 ± 86.3	–	–
Fentanyl (μg kg^{-1} h^{-1})	1.74.1 ± 0.22	–	–
Remifentanil total dose (μg)	–	1067.2 ± 340.9	
Remifentanil (μg kg^{-1} h^{-1})	–	9.08 ± 10.27	–

LOC loss of consciousness

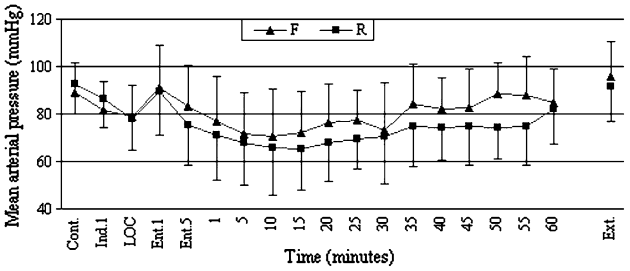

Fig. 1 Mean arterial pressure values of fentanyl and remifentanil groups (mean ± SD). *C* control, *Ind* induction, *LOC* loss of consciousness, *Int* intubation, *Inc* incision, *Ext* extubation, *F* fentanyl, *R* remifentanil

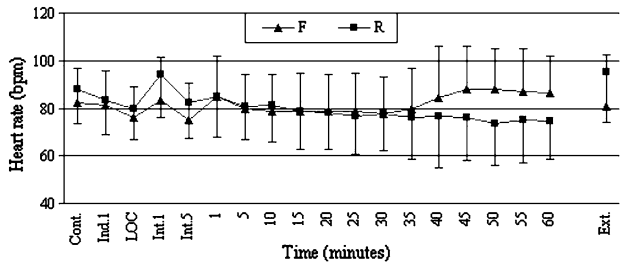

Fig. 2 Heart rate values of fentanyl and remifentanil groups (mean ± SD). *C* control, *Ind* induction, *LOC* loss of consciousness, *Int* intubation, *Inc* incision, *Ext* extubation, *F* fentanyl, *R* remifentanil

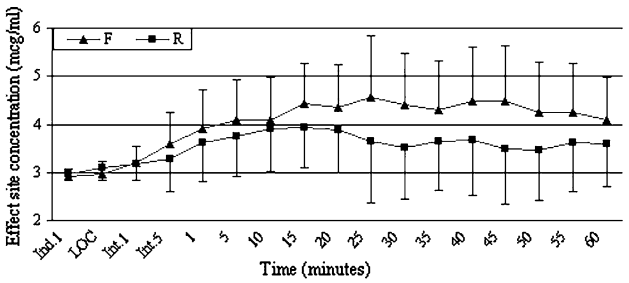

Fig. 3 Effect-site concentration (Ce) of propofol in fentanyl and remifentanil groups (mean ± SD). *C* control, *Ind* induction, *LOC* loss of consciousness, *Int* intubation, *Inc* incision, *Ext* extubation, *F* fentanyl, *R* remifentanil

anesthesia regimen. Although the Ce for propofol TCI with Schnider's pharmacokinetic model [5] was used, opioid drugs were manually infused in a controlled manner. Fentanyl and remifentanil infusions were given at constant doses simultaneously with propofol, the infusion of which was started with a Ce of 3 μg ml^{-1} and titrated in increments or decrements of 0.5 μg ml^{-1} to maintain the BIS index within 40–60.

The important characteristics of an opioid drug used during septorhinoplasty operations include hemodynamic stability and rapid emergence and recovery profiles. Remifentanil may be useful in ear–nose–throat surgery because of its ultrashort duration of action, allowing a more predictable emergence and recovery. The clinical advantages of remifentanil such as the rapid onset and offset with a context-sensitive half-time of only 3–5 min irrespective of the duration of infusion would make it difficult to compare with those of longer-acting opioids such as fentanyl [2, 6–8]. Furthermore, remifentanil is the most preferred opioid for use in conjunction with propofol-based TCI anesthesia, but in the present study, the standard regimen of fentanyl infusion at the given doses demonstrated comparable clinical features with the standard regimen of remifentanil. In this study, we selected the administration regimens of fentanyl and remifentanil according to the standard dose schemes used at our clinic. At the doses used in this study, even durations of adequate spontaneous respiration and safe extubation were significantly shorter in the remifentanil group when compared with the fentanyl group, yet we considered that clinically ignorable.

The BIS index monitor was used to titrate the propofol dose to a specific endpoint and to show that each group received a "pharmacodynamically similar" dose of the hypnotic drugs. Also, BIS was successful in reducing the anesthetic agent average consumption and accelerating recovery and was proven to be useful for measuring the depth of anesthesia when using propofol TCI [9–12]. An

Table 3 Characteristics of emergence from anesthesia (mean ± SD)

	Group F ($n = 20$)	Group R ($n = 20$)	P value
Spontaneous eye opening time (min)	6.7 ± 2.6	4.6 ± 2.9	0.002
Extubation time (min)	7.3 ± 2.6	4.7 ± 3.7	<0.001
Orientation time (min)	7.6 ± 2.6	4.9 ± 3.8	<0.001

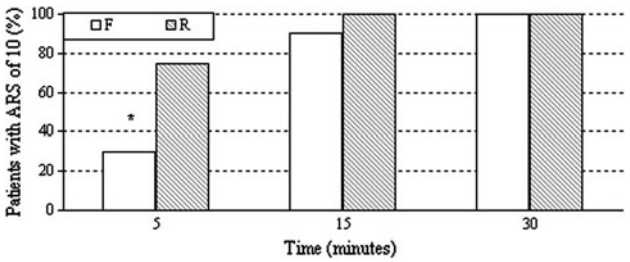

Fig. 4 Aldrette Recovery Scoring (ARS) of fentanyl (*F*) and remifentanil (*R*) groups (*$P < 0.5$ vs. the fentanyl group)

index value less than 60 has been correlated with LOC and loss of recall in 95% of patients [13]. With the TCI system, foreseeing the depth of anesthesia by targeting the required Ce or plasma concentration (Cp) has made TIVA favorable by ensuring more stable anesthesia control. On the other hand, stimulus intensity to the type of surgery might affect the depth of hypnosis and, thus, might require the anesthesiologist to alter the Ce. In this study, although the hypnotic level was controlled by the use of a BIS monitor, the problems that might have occurred as a result of insufficient muscle relaxation were also eliminated by the use of neuromuscular monitoring (TOF).

The addition of either fentanyl or remifentanil as a component of TIVA can decrease somatic and autonomic responses to airway manipulations and improve hemodynamic stability during induction [14, 15]. Fentanyl is more likely to be chemically stable. Even in large bolus doses, fentanyl has often been used for induction of anesthesia in patients with heart disease, owing to its cardiac stability and its ability to blunt hemodynamic responses to tracheal intubation [14]. Although remifentanil allows easy titration of analgesia and anesthesia, it may cause hypotension and bradycardia when combined with propofol [8, 16, 17]. Joshi et al. [8] observed similar frequency of adverse effects with both remifentanil and fentanyl except for the higher frequency of hypotension associated with the use of remifentanil. In the present study (see Figs. 1, 2), throughout the follow-up period, there were no statistically significant differences with regard to the general mean values of MAP and HR between the groups.

In diverse inpatients and outpatients, and according to numerous anesthesiologists, remifentanil was associated with a consistently stable intraoperative course and somewhat faster emergence than fentanyl. Faster emergence was accompanied by earlier response to verbal command, earlier discharge from the operating room for outpatients, and earlier eligibility for discharge home for outpatients. Frequencies of postoperative nausea and vomiting were similar [6, 8, 18, 19].

Suttner et al. [20] concluded that the TCI regimen where propofol and remifentanil allowed rapid recovery from anesthesia was associated with few postoperative side effects and permitted early discharge from the PACU. Wuesten et al. [19] reported that in patients undergoing ear–nose–throat surgery, TIVA with remifentanil and propofol provides more rapid respiratory recovery compared with TIVA with alfentanil and propofol. Davis et al. [21] compared intraoperative characteristics and recovery profile of fentanyl versus remifentanil-based general anesthesia for pediatric outpatient tonsillectomy and adenoidectomy. Remifentanil patients were extubated sooner; however, PACU and home discharge times were similar, and in addition, remifentanil patients had an increased incidence of postoperative pain [4].

It was shown that the quality of emergence from anesthesia in patients with cervical spine surgery was improved with fentanyl-based anesthesia, with no difference between the use of propofol TCI and sevoflurane as a concomitant sedative agent with fentanyl [22]. Magni et al. [23] stated that there were no differences in terms of emergence time and recovery of early cognitive function between sevoflurane–fentanyl and propofol–remifentanil-based anesthesia in patients undergoing craniotomy. In another study, Beers et al. [4] compared remifentanil and fentanyl as concomitant with sevoflurane in outpatient gynecological surgery, and they found out that incidence of intraoperative and postoperative adverse events, recovery times, opioid analgesic dosage, requirements in the postanesthetic care unit, and satisfaction survey responses were similar between the groups.

The dose of remifentanil used in group R was likely to yield an opioid effect greater than that obtained with fentanyl in group F; this is probably a limit of our study, but it points to an adequate level of analgesia with a faster recovery in the dose of fentanyl used. At the same time, in our BIS-controlled constant opioid adjuncted propofol-based TCI study, substantially more propofol was used in group F (54% more than in group R) (see Table 2), probably because of the combination of propofol and fentanyl pharmacokinetic profile. Vuyk et al. [24] hypothesize that

because pharmacokinetics of propofol and various opioids vary, it is conceivable that the optimal intraoperative propofol concentration varies with the selected opioid agent and the duration of infusion.

This study can be criticized for the fact that consumption of propofol could have been decreased by using a higher dose of fentanyl, but in that case, the recovery profile in the fentanyl group could have become worse. An infusion dose of fentanyl and remifentanil, standard in our routine anesthesia practice, that would provide an adequate level of analgesia with a faster recovery was our aim. Such studies controlling the doses of remifentanil, alfentanil, and fentanyl have been reported before, and equipotent doses result in prolonged recovery times for the comparator opioid and the need for opioid antagonists [25, 26].

In this study, upward propofol Ce titrations were significantly more frequent in group F and downward titrations were significantly more frequent in group R, although the BIS monitor was used to titrate the propofol dose to a specific endpoint. This finding indicates that the initial settings were too low in group F and vice versa. The propofol Ce value required to maintain the patient at a sufficient hypnotic level was lower in group R than in group F (mean, 3.5 vs. 4 μg ml^{-1}) (see Fig. 3). The duration of anesthesia was approximately 2 h in both groups. When the recovery profile is considered (see Table 3), the duration of adequate spontaneous respiration and safe extubation were significantly shorter in group R (mean, 4.7 min) compared with group F (mean, 7.3 min); however, it was clinically ignorable. In both groups, patients were extubated in a short period of time. Our assumption is that this difference is the result of the study design for standardization in both groups where fentanyl infusion was also discontinued at the end of the operation. At the 15th minute, the ARS was 10 in 100% of the patients in group R and in 90% of the patients in group F. Again in the same way, if fentanyl had been discontinued 10 min before the operation was over, a higher percentage of patients in group F would have reached an ARS of 10. For these reasons, emergence and recovery after approximately 2 h of anesthesia were generally accepted as rapid in both groups; nevertheless, all data showed a faster recovery in group R. There was no difference in the incidence of postoperative side effects among the groups. Because local anesthetic infiltration was performed on the operation area before the operation was started, the rate of painless cases was high in both groups.

Conclusion

The emergence from anesthesia, extubation time, ARS, and the quality of recovery showed statistically significant differences in the remifentanil group; however, the recovery profile in the fentanyl group was also clinically acceptable. Also, remifentanil does not provide any significant superiority over fentanyl in terms of hemodynamic parameters. We concluded that in propofol-based TCI anesthesia under BIS supervision for septorhinoplasty operations, remifentanil was better than fentanyl, especially with respect to emergence from TIVA anesthesia. Furthermore, the durations of anesthesia and operation were rather short, which indicates that fentanyl can be safely used.

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