Original Article

Effect of remifentanil on the recovery profile after head and neck surgeries: A prospective study

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Abstract

Background and Aims: Development of opioid tolerance in the perioperative period due to remifentanil remains controversial. We evaluated occurrence of opioid tolerance and other adverse effects due to remifentanil in patients undergoing head and neck surgery.

Material and Methods: We recruited adult participants with ASA status I to III who received general anesthesia for approximately 2 h for elective head and neck procedures. Remifentanil infusion was used in one group and intermittent boluses of morphine or fentanyl were administered in another group. Postoperative pain was treated with intermittent boluses of morphine and fentanyl in post-anaesthesia care unit (PACU) to achieve a numerical rating scale score of 3. Opioid requirement was assessed as an indicator of opioid tolerance. Patients were also evaluated for time to discharge from PACU.

Results: We studied 222 adults aged between 21 and 80 years. One hundred and eleven patients received a combination of remifentanil infusion and morphine boluses, and another 111 patients received only fentanyl and/or morphine boluses intraoperatively. Fifty-one patients in the remifentanil group and 25 in the fentanyl/morphine group required opioids in the PACU. Opioid requirement were significantly more (mean ± SD, 44.98 ± 59.7 Vs 20.23 ± 46.66 mcg. kg^{-1}; $P = 0.001$) and required longer time to discharge from PACU in the remifentanil group compared to the fentanyl/morphine group (Mean ± SD, 88.6 ± 39.5 min Vs 73.1 ± 38.4 min; $P < 0.001$). No difference in the incidence of adverse effects in two groups was noted.

Conclusion: At clinically relevant doses, intraoperative remifentanil infusion appears to increase opioid consumption in the immediate postoperative period. This can result in delayed discharge from PACU for patients undergoing elective head and neck procedures.

Keywords: Head and neck surgery, opioid tolerance, remifentanil

Introduction

Remifentanil is one of the most common short-acting opioids used for prolonged surgeries. Better pharmacokinetic profile allows easy titration to various surgical stimulations including pain and hemodynamic changes.[1] It has also been widely used as a hypotensive anesthetic agent to minimize bleeding and for improved visualization of the operative region.[2,3]

Recent studies have shown that ultra-short acting opioids have been associated with increase in pain scores and analgesic requirements in the immediate postoperative period.[4,5] The proposed molecular mechanisms for this observation

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involve the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response.[6] However, there are few contradictory reports on opioid-induced hyperalgesia, showing that intraoperative remifentanil infusion does not increase opioid consumption in the spine and colorectal surgeries.[7,8] Furthermore, the effects of intraoperative use of remifentanil on recovery profile such as nausea, vomiting, shivering, incidence of respiratory depression, and the time to discharge from the post anesthesia care unit (PACU) has been inconsistent.[9] Remifentanil has been widely used for head and neck surgeries to achieve hypotensive anesthesia to minimize the intraoperative blood loss. However, the effect of using intraoperative remifentanil infusion on the postoperative pain and analgesics requirements are not well described in head and neck surgeries. The goal of this prospective observational study was to identify the effect of intraoperative remifentanil infusion on PACU opioid usage and occurrence of significant adverse events compared to the intraoperative use of morphine/fentanyl in head and neck surgeries requiring at least 2 h.

Material and Methods

This prospective observational study was conducted among 222 adults aged between 21 and 80 years, over a period of six months in a single academic medical center. All patients were American Society of Anesthesiologists (ASA) physical status I to III and scheduled for elective head and neck surgery with a minimum expected duration of 2 h warranting general anesthesia. The methodology followed the international guidelines for observational studies,[10] and was approved by the Sing Health centralized Institutional Review Board (CIRB), Singapore (ref no. 2011/421/D). The requirement for written informed consent was waived by the CIRB in view of the nature of the study. We obtained verbal consent from the patients prior to the procedure.

We believe observational study design would be pragmatic, and recruiting 222 patients for a randomized control design would have been a challenge in our clinical setting. Patients with a previous history of either drug or alcohol abuse, those who have been using opioids for a long time, any mental disorder with difficultly in understanding the pain scoring system, and surgical procedures warranting elective postoperative ventilation were excluded from this study. This study was not randomized and the choice of intraoperative opioid was left to the discretion of the staff anesthesiologist.

Our patients were not premedicated and were instructed about the 11-point numerical rating scale (NRS) prior to anesthesia induction. Upon arrival in the operating room, patients were monitored with ECG, noninvasive arterial pressure, and pulse oximetry. Induction of anesthesia was achieved with intravenous propofol 2.0–3.0 mg.kg^{-1} and remifentanil infusion at 0.5 mcg kg^{-1} min^{-1} initially for tracheal intubation. Remifentanil infusion was titrated to heart rate and blood pressure in the remifentanil group. Patients were also given morphine as intermittent boluses approximately 30–45 min prior to the anticipated end of surgery. The fentanyl/morphine group received intermittent boluses of morphine or fentanyl that was titrated by the attending anesthesiologist to surgical stimulation throughout the procedure. The choice of intraoperative opioid, dose of intraoperative opioids (both remifentanil and morphine/fentanyl) volatile agent, and muscle relaxants were left to the discretion of the staff anesthesiologist. Parameters including the type of inhalational anesthetic agent, method of airway establishment, duration of surgery, amount of remifentanil used (mcg.kg^{-1}), and the amount of morphine or fentanyl (mcg.kg^{-1}) were monitored throughout the surgical procedure.

Upon arrival to PACU, all patients were assessed for pain using NRS every 15 min until discharge from PACU. Intravenous morphine or fentanyl were used to treat the immediate postoperative pain in PACU till the NRS was less than or equal to 3, as per our institutional PACU acute pain management protocol. Maximum NRS, amount of morphine or fentanyl used for rescue analgesia, occurrence of either nausea or vomiting, and the antiemetic used were recorded every 15 min. The total opioids administered in PACU, duration of the PACU stay (defined by time since admission to decision made for discharge by PACU anesthesiologist), and occurrence of other potential side effects that influence the quality of recovery such as drowsiness, nausea, vomiting, shivering, and evidence of respiratory suppression (desaturation or bradypnea) were documented when the patients were discharged from PACU. Fentanyl doses were converted to equivalent morphine doses (fentanyl 100 mcg is equal to morphine 10 mg) to calculate the total amount of opioids used intraoperatively and in the PACU.[11]

Statistical analysis

Our primary outcome was total requirement of opioids in the PACU, and the secondary outcomes were duration of PACU stay and the adverse effects of remifentanil that influence the recovery, as stated above. The preliminary data of 15 patients, who underwent head and neck surgery for more than 2 h and those who received only fentanyl/morphine intraoperatively, demonstrated a mean (SD) morphine requirement in PACU of 0.0334 (0.067) mg.kg^{-1}. To detect 35% difference in opioid consumption among remifentanil and fentanyl/morphine (control) group with a power of

Table 1: Patient characteristics

Demographic variable	Remifentanil group (*n*=111)	Morphine/fentanyl group (*n*=111)	*P*
Age	45.58+18.04	48+16.39	0.192
Gender			
Male	64 (57.7)	54 (48.6)	0.179
Female	47 (42.3)	57 (51.4)	
Weight (kg)	64.93+14.78	65.81+16.26	0.672
ASA			
I	34 (30.6)	28 (25.2)	0.484
II	65 (58.6)	66 (59.5)	
III	12 (10.8)	17 (15.3)	
Specialty			
ENT	61 (55)	52 (46.8)	**<0.001**
GS	13 (11.7)	35 (31.5)	
Dental	25 (22.5)	9 (8.1)	
Plastic	12 (10.8)	15 (13.5)	
Type of surgery			
Superficial	56 (50.5)	76 (68.5)	**0.006**
Deep	55 (49.5)	35 (31.5)	
Duration of surgery (Hours)			
2-4 h	59 (53.2)	70 (63.1)	0.292
4-6 h	23 (20.7)	30 (27)	**0.022**
>6 h	29 (26.1)	11 (9.9)	**0.040**
Intra-operative opioid dose in morphine equivalent_(mcg.kg^{-1})*	160.4+105.2	259.3+152.3	**<0.001**

** P<0.05 is considered significant. Data are presented in Mean+/-SD or Number (proportion)*

Table 2: Pain scores in PACU since admission

Time of post-operative pain assessment	Remifentanil group	Morphine/ fentanyl group	*P*
15 min	2.75 (3.06)	1.84 (2.61)	0.018
30 min	3.57 (3.17)	2.23 (2.77)	0.001
45 min	3.23 (3.60)	2.01 (2.45)	0.004
60 min	2.77 (3.45)	1.99 2.37)	0.067
75 min	1.71 (1.85)	1.65 (2.22)	0.835
90 min	1.16 (1.73)	1.11 (1.87)	0.836

Presented in Numerical Rating Score (NRS) Mean (SD)

90% at 0.05 level of significance, estimated sample size was 109 patients per group. The 35% difference in opioid use was chosen arbitrarily based on our clinical experience. SPSS statistical software version 21 was used to analyze the data (SPSS Inc., Chicago, IL), and $P < 0.05$ was considered significant. Univariate analysis was performed using Chi-square test or Fisher's exact test for categorical variables and the independent sample *t*-test or one-way analysis of variance for continuous variables. Multiple linear regression analysis was performed to assess the effect of intraoperative remifentanil on postoperative opioid requirement in PACU after taking into account the age, nature of the surgery, usage of volatile agents, and the duration of surgery. Preliminary analyses were conducted to ensure that there was no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity.

Results

Both groups were comparable for age, gender, weight, and ASA status. However, there was statistically significant difference in the distribution of surgical specialties between the two groups ($P < 0.001$). To assess the effect of invasiveness of the surgery, we stratified the surgeries into superficial and deep surgeries. Surgeries only involving the skin, soft tissues, thyroid, and salivary glands were categorized as superficial and those involving muscles and bone were grouped under deep surgeries. Remifentanil was deep surgeries, while morphine/fentanyl were used more often for superficial surgeries intraoperatively ($P = 0.006$). Post-hoc subgroup analysis of the duration of surgeries in three groups showed that remifentanil was preferentially used for surgeries lasting more than 6 h ($P = 0.007$). The intraoperative remifentanil infusion range was between 0.0086 and 0.2144 mcg.kg^{-1}.min^{-1} with the mean (SD) infusion rate of 0.081 (0.048) mcg.kg^{-1}.min^{-1}. A higher dosage of intraoperative opioid in morphine equivalent was observed in morphine/fentanyl group compared to remifentanil group [Table 1].

We found significantly higher pain scores (NRS) at 15, 30, and 45 min since PACU admission in remifentanil group [Table 2]. Furthermore, a significantly higher incidence and dosage of PACU opioid usage and a longer duration of PACU stay were noticed in the remifentanil group [Table 3].

Table 3: Opioid usage and duration of stay in PACU

	Remifentanil group	Morphine/fentanyl group	*P*
Incidence of opioid usage PACU	45.9%	22.5%	<0.001
PACU opioid dose in morphine equivalent mcg.kg-1	0.00 (0.00-227.3)	0.00 (0.00-260.0)	0.001
Time spent in the PACU (min)	77.5 (30-255)	65 (30-285)	<0.001

Data are presented as percentage or median (range)

Table 4: PACU opioid dose in morphine equivalent (mcg.kg^{-1}) in different specialties

Surgical speciality	Remifentanil group	Morphine/ fentanyl group	*P*
ENT	0.0 (0.0,51.7)	0.0 (0.0,32.6)	0.412
General surgery	39.7 (0.0,105.9)	0.0 (0.0,0.0)	0.001
Dental	61.6 (0.0,114.3)	0.0 (0.0,89.5)	0.352
Plastic surgery	70.5 (0.0,118)	0.0 (0.0,28.9)	0.026

Data are presented as median (IQR)

A post-hoc subgroup analysis in surgical specialties showed that significantly higher doses of opioid were used in the PACU in remifentanil group only in general and plastic surgical procedures, but the opioid usage in PACU was comparable for ENT and dental surgical procedures [Table 4].

Multiple regression analysis showed that only intraoperative use of remifentanil infusion was significantly associated with higher doses of opioid usage in the PACU. Invasiveness and subspecialty of surgery, doses of long-acting opioids used intraoperatively, duration of surgery, or the type of volatile anesthetic agent used were not associated with more opioid consumption in the postoperative period [Table 5]. There was no significant difference in other adverse events occur in the PACU due to intraoperative opioid use [Table 6].

Discussion

Based on our limited observation the intraoperative use of remifentanil infusion in head and neck surgery lasting at least 2 h is associated with significantly higher pain scores and opioid requirement in the PACU. Furthermore, we found that intraoperative remifentanil use also increases the duration of stay in PACU, and is an independent predictor for high doses of opioid use.

The main strength of our study was using PACU opioid dose which is a well-defined objective primary outcome. Most studies investigating the effect of remifentanil infusion on the development of opioid-induced hyperalgesia have used postoperative pain score as the primary outcome. However, pain score is a subjective outcome and identifying a clinically significant difference is often challenging. As per our knowledge, the percentage of the additional opioid requirement to demonstrate the development of remifentanil induced hyperalgesia (RIH) has never been reported. We believe 35% difference in PACU opioid dose would be able to demonstrate the RIH.

A systematic review on remifentanil for general anesthesia by Komatsu *et al*. demonstrated that patients receiving remifentanil required additional postoperative analgesics at a 40% more frequency than those administered morphine or fentanyl.[9] However, we found that the requirement of postoperative analgesics in remifentanil group was almost 100% more than conventional opioids such as morphine or fentanyl (frequency of 51 vs 25 patients). Komatsu *et al*. also demonstrated that the difference in the additional analgesic requirement is smaller in patients with a high postoperative analgesic requirement such as major abdominal and pelvic surgeries and larger in patients with low post analgesic requirement such as head and neck surgeries, mastectomies, or arthroscopies. All our participants had a low expectation of postoperative analgesic requirement, which was confirmed by the lesser intraoperative requirement of analgesics in the fentanyl/morphine group. Overall, our observation of more analgesic requirement to remifentanil use is consistent with previous systemic review.

On the other hand, it is obvious that expected postoperative pain and analgesic requirement may vary depending on the invasiveness of surgery. For example, patients who had a radical neck dissection or mandibular osteotomy are expected to have higher pain scores than those who underwent thyroidectomy. To address this question, we classified the invasiveness of the surgeries into superficial and deep surgeries. However, our multiple regression analysis did not identify invasiveness of surgery as a risk factor for the higher opioid requirement in PACU.

We found that the time to discharge from PACU was significantly longer in the remifentanil group (88.6 Vs 73.1, mean time in min). Even though our study was not powered to PACU discharge time, this finding appears self-explanatory. A similar finding was demonstrated in children undergoing adeno-tonsillectomies in the ambulatory surgical unit in which remifentanil use was associated with earlier extubation time, however greater pain in remifentanil group caused delay in PACU and hospital discharge in remifentanil group.[12]

Table 5: Multiple linear regression analysis results for PACU

Factor	B	SE(B)	β	*t*	Sig.(*P*)
Age	-0.348	0.249	-0.110	-1.399	0.163
Nature of Surgery					
Superficial	Reference				
Deep	0.743	9.564	0.007	0.078	0.038
Usage of volatile agent					
Desfluorane	Reference				
Sevo + Iso	-15.053	11.931	-0.084	-1.262	0.208
Intraoperative opioid usage (mcg.kg^{-1})	0.025	0.03	0.064	0.838	0.403
Type of surgery					
ENT	Reference				
General surgery	3.988	9.793	0.03	0.407	0.684
Dental	12.869	14.899	0.085	0.864	0.389
Plastic surgery	6.298	11.904	0.038	0.529	0.597
Operation time					
>6 h	Reference				
4-6 h	-20.161	11.568	-0.156	-1.743	0.083
2-4 h	-20.239	11.434	-0.182	-1.77	0.078
Usage of remifentanil					
No	Reference				
Yes	20.468	8.441	0.187	2.425	0.016

B=Regression coefficient, SE=Standard error, β=Weights

Table 6: Other significant adverse effects

Side effect	Remi (111)	Morphine/fentanyl (111)	*P*
None	76 (68.5)	89 (80.2)	0.065
Confusion	0	0l	-
Drowsiness	9 (8.1)	4 (3.6)	0.153
Head ache	2 (1.8)	2 (1.8)	1.000
Nausea	21 (18.9)	15 (13.5)	0.275
Vomiting	10 (9)	5 (4.5)	0.181
Dizziness	5 (4.5)	2 (1.8)	0.249
Chest tightness	2 (1.8)	0 (0)	0.155
Restlessness	2 (1.8)	0 (0)	0.155

Data are presented as Number (proportion)

Our finding of a statistically significant difference in pain scores only during the first 45 min since PACU admission is self-explanatory. This is due to aggressive pain control in PACU using intravenous opioids with the target of NRS below 3, as per our departmental PACU discharge criteria.

The mechanism for intraoperative remifentanil usage causing higher requirements of postoperative analgesics is not clearly identified. Possible postulations made to explain this effect includes development of acute opioid tolerance (AOT) or the opioid-induced hyperalgesia (OIH) caused by remifentanil.[13] OIH is defined as a state of nociceptive sensitisation characterized by a paradoxical response, whereby a patient receiving opioids for treating pain might have an increased sensitivity to painful stimuli.[14,15] Meanwhile, the AOT is defined as an increase in the dose required maintaining adequate analgesia in patients receiving opioid medication for the treatment of pain in clinical settings.[14,15] However, OIH is often confused with AOT because of the manifestations of similar symptoms.

The interest in OIH was triggered by a few animal studies even before the invention of remifentanil. Studies on rodents since the early 1970s suggested that administration of opioids paradoxically may increase the sensitivity to pain and potentially may aggravate pre-existing pain.[16,17] OIH and AOT secondary to remifentanil infusion are mainly influenced by the dose and duration of infusion. A study among volunteers demonstrated that hyperalgesia and allodynia to frey hair stimulations adjacent to the surgical wound were significantly greater with a higher dose of remifentanil infusion at 0.4 mcg.kg^{-1}.min^{-1} compared to a low dose infusion at 0.05 mcg.kg^{-1}.min^{-1}.[18] Another study measured the analgesic effect of remifentanil infusion by cold and mechanical noxious stimulation in healthy volunteers, and showed the analgesic effects reached its maximum at 60–90 min. Subsequently, the analgesic effect began to decline despite the continuous remifentanil infusion, and after 3 hours it was only 25% of its peak value.[19] Our finding of higher PACU opioid requirement with intermediate dose of intraoperative remifentanil use (0.08 mcg.kg^{-1}.min^{-1}) strengthens the conclusions of above volunteer studies.

However, studies done in various surgical procedures disprove the above observation of AOT and OIH.[20,21] Patients in these studies received remifentanil with either nitrous oxide or

propofol infusion, and the negative result of this studies can be explained by the inhibitory effect of nitrous oxide and propofol on the development of AOT/OIH.[22,23] Nitrous oxide is an NMDA antagonist,[24] and reduces the development of OIH in rats in a dose-dependent manner.[25] Recently Echevarria *et al*. demonstrated that the intraoperative administration of 70% nitrous oxide significantly reduced the postoperative OIH in patients receiving remifentanil (0.3 $mcg.kg^{-1}.min^{-1}$) anesthesia for septorhinoplasty.[26] However, nitrous oxide is not widely used in clinical practice due to adverse effects.

In terms of adverse effects of remifentanil in the PACU, postoperative nausea and vomiting (PONV) was not significantly different in the two groups and was similar to the findings of the previous studies.[27] Furthermore, the difference in the incidence of PONV is almost 50%. We attribute this higher difference to greater doses of opioid requirement in the PACU for remifentanil group. We also noticed that the remifentanil group had a similar incidence of drowsiness , chest tightness and shivering in the PACU as the conventional opioid group.

Our study has following limitations. First, this was a prospective observational study and the patients were not randomized or matched. This would have potentially introduced an unequal distribution of known and unknown confounders between the groups compared. We chose an observational study design since the use of intraoperative remifentanil infusion widely varies among the anesthesiologists according to their personal preference, type, and invasiveness of the surgery. We believed observational study design would be pragmatic and recruiting 222 patients for a randomized control design would be challenging in our setting. The staff anaesthesiologist was not blinded and allowed to decide the group according to his/her preference. However, PACU nursing staff who collected the recovery profile data were blinded to the intraoperative opioids used. Second, we could not control the amount of intraoperative morphine or fentanyl administered, as well as the distribution of the specialties and invasiveness of surgeries. These factors significantly differ between cases and control and could influence the study results. However, this could depict the real-life practice, and furthermore, a multiple regression analysis showed that only the use of remifentanil influences the opioid consumption in the PACU. Third, we collected data only during the PACU stay and did not assess the pain scores and analgesic requirements after discharge from a PACU. In our experience, head and neck surgeries are expected to be less painful postoperatively, and we do not routinely prescribe opioid analgesia for these patients after discharge from PACU. Furthermore, we did not collect data on the time of stoppage of remifentanil infusion. Remifentanil-related side-effects such as drowsiness and tightness of the chest could have been missed in the PACU due to its ultra-short action if the infusion was stopped earlier than the end of the surgery. Finally, our data were skewed due to lower incidence of PACU opioid requirement. However, we found that the skew was present in both groups and when the data was presented in median and interquartile ranges (IQR) observed similar findings when we analyzed with nonparametric test.

Conclusion

In conclusion, at clinically relevant doses, intraoperative remifentanil infusion appears to increase the opioid consumption in the immediate postoperative period, and thereby delays the discharge from PACU in patients undergoing elective head and neck procedures of more than 2 h duration. However, observational study design and our findings of differences in the amount of intraoperative long-acting opioid usage and invasiveness of surgeries hinder us from making such conclusion. A randomized control trial with adequate sample size and appropriate methodology considering the effect of intraoperative opioid dose should be conducted to confirm our observations.

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Conflicts of interest

There are no conflicts of interest.

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CONFERENCE CALENDAR July-Sepetember 2018

Name of conference	Dates	Venue	Name of organising Secretary with contact details
PRAC 2019	5th -7th April 2019	Hyatt Pune	Dr Sandeep Diwan PRAC in-Charge, Academic Director, Dept of Anesthesia Sancheti Hospital, Pune Email: Sandeep.prac@gamil.com www.pracsancheti.com
9th National Conference of the Academy of Regional Anesthesia, India	4th -7th July 2019	Coimbatore	Dr. Balavenkatasubramanian Dr. Maheshwari S Kumar Conference Secretariat Address: Ganga Medical Centre & Hospitals Pvt. Ltd. 313, Mettupalayam Road, Saibaba Koil, Coimbatore,Tamil Nadu 641043, India. Mobile : + 91 98422 45757 Phone : + 91 422 2485000 Fax : + 91 422 2451444 Email: registration@aoraindia2019.com www.aoraindia2019.com