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Ketamine reduces the dose of remifentanil required during prolonged head and neck surgery: a propensity-matched analysis

Tasuku Fujii[1] and Kimitoshi Nishiwaki[2]

[1]*Department of Anesthesiology, Nagoya University Hospital, Nagoya, Japan*
[2]*Department of Anesthesiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

ABSTRACT

High-dose opioids induce hyperalgesia and tolerance, which negatively affects postoperative recovery. Prolonged surgery inevitably requires higher opioid doses. Ketamine reduces perioperative opioid consumption and prevents opioid-induced tolerance. However, its effects in cases of prolonged surgery remain unknown. This study aimed to evaluate the dose of intraoperative remifentanil, an ultrashort-acting μ-opioid agonist, administered after an intravenous ketamine bolus during prolonged head and neck surgery. This single-center, retrospective, observational study included 251 patients who underwent head and neck surgery (operation time ≥8 h) between January 2015 and December 2019. The participants were stratified into two groups: those who received an intravenous bolus of ketamine and those who did not (ketamine group and non-ketamine group, respectively). Propensity score-matching was used to match patients in a 1:1 ratio between the two groups, based on their covariates. The difference in intraoperative remifentanil dose administered between the two groups was assessed. After 1:1 propensity score-matching, 89 matched patients were selected from each group. The mean ± standard deviation dose of remifentanil administered was significantly lower in the ketamine group than in the non-ketamine group before (0.15±0.05 vs 0.17±0.05 μg/kg/min; P=0.01) and after matching (0.15±0.06 vs 0.17±0.05 μg/kg/min; P=0.03). In conclusion, intravenous ketamine administration may reduce the intraoperative dose of remifentanil required during prolonged head and neck surgery. However, further studies are required to evaluate the effect of this finding on enhanced recovery after surgery.

Keywords: head and neck surgery, ketamine, opioid, remifentanil

Abbreviations:
NMDA: N-methyl-D-Aspartate
SD: standard deviation

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Corresponding Author: Tasuku Fujii, MD, PhD

Department of Anesthesiology, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2340, Fax: +81-52-744-2342, E-mail: plus9@med.nagoya-u.ac.jp

INTRODUCTION

Opioids are commonly used perioperatively as multimodal analgesics. The potential adverse effects of opioids include their tendency to induce hyperalgesia and tolerance at higher doses.[1] Opioid-induced tolerance requires increased opioid doses to achieve the same analgesic effect. In contrast, opioid-induced hyperalgesia leads to a reduced pain threshold after repeated opioid use. All these factors can negatively affect the quality of postoperative analgesia and enhanced recovery after surgery.[2,3] Therefore, a minimum-necessary use of perioperative opioids seems to be ideal. However, prolonged surgery inevitably results in high total exposure to intraoperative opioids.

Remifentanil is widely used as an intraoperative opioid because of its extremely rapid pharmacokinetics. However, the use of high-dose remifentanil is associated with high risks of hyperalgesia and tolerance.[4,5] Interestingly, the mechanisms underlying one of these effects involve N-methyl-D-Aspartate (NMDA) receptors.[6,7] Ketamine is widely used as a non-competitive NMDA receptor antagonist that reduces perioperative opioid comsumption.[8,9] The effects of using ketamine during prolonged head and neck surgeries have not been clarified. We predicted that intraoperative intravenous ketamine administration could reduce the analgesic dose of remifentanil required during prolonged surgery. Therefore, our study retrospectively assessed the effects of intraoperative ketamine administration on the dose of remifentanil administered during prolonged head and neck surgeries.

MATERIALS AND METHODS

Study Design and Patients

This single-center, retrospective, observational study (reference number: 2020–0049) was approved by the Ethics Committee of Nagoya University Hospital, Nagoya, Japan, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Information and an opt-out document related to this observational study are available on our institution's website. Written informed consent was not obtained from the patients, as the opt-out method was used for recruiting all participants who underwent head and neck surgery between January 2015 and December 2019. Those patients whose operation duration was ≥8 h were included in the study. The patients with an American Society of Anesthesiologists physical status score of ≥3 and those admitted for emergency operations were excluded. Based on these criteria, 251 patients were identified and stratified into two groups: those who received an intraoperative intravenous bolus of ketamine (ketamine group) and those who did not (non-ketamine group).

Outcome Measures

The primary outcome measure was the difference in the required intraoperative opioid dose, especially the dose of remifentanil, between the two groups, depending on the intraoperative intravenous bolus of ketamine. The remifentanil dose was calculated as the total dose of remifentanil divided by the patient's weight and the anesthesia delivery time (μg/kg/min). Furthermore, correlations between the intravenous ketamine (mg/kg) and intraoperative remifentanil doses (μg/kg/min) were evaluated. All patient data were acquired via anesthesia charts and medical records.

Statistical Analyses

The baseline and intraoperative characteristics of patients were compared using Student's t-test,

Mann–Whitney U test, or Fisher's exact test. Patients who received intraoperative ketamine were individually matched (1:1) with those who did not, based on the similarity of the propensity score that was calculated using a logistic regression model. The covariates for the logistic regression model were age, sex, body mass index, operation/anesthesia time, intraoperative fluid balance, blood transfusion, total intravenous anesthesia with propofol, nonsteroidal anti-inflammatory drug use (flurbiprofen), surgical procedure (free flap reconstruction), and intraoperative dose of fentanyl (μg/kg/min). The caliper distance for matching was defined at 0.1 of the pooled standard deviation (SD) of the logit score. Concerning the primary outcome, the differences in the mean intraoperative remifentanil dose between the groups were statistically analyzed using Student's t-test. Multiple linear regression analysis was used to assess the association of the remifentanil dose with intravenous ketamine. In addition, the correlation between the intraoperative ketamine and remifentanil doses was analyzed using Spearman's rank correlation coefficient. Categorical and continuous variables are expressed as numeric values (proportion) and as means ± SDs or medians [interquartile ranges], respectively. *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using R software, version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We analyzed the data of 251 patients who underwent head and neck surgeries (operation time ≥8 h). Propensity scoring was used to select matched patients (1:1) between the two groups based on their covariates. Finally, 89 matched patients were selected from each group, and no significant differences were found between the two groups with respect to their baseline and perioperative characteristics (Table 1).

Table 1 Baseline characteristics and intraoperative data from each group before and after propensity score-matching

	Before matching			After matching		
	Ketamine (+) *n*=129	Ketamine (–) *n*=121	*P*-value	Ketamine (+) *n*=89	Ketamine (–) *n*=89	*P*-value
Age; years	65 [55–72]	67 [55–72]	0.84	65 [55–72]	64 [54–73]	0.91
Sex; Male/female	78/51	77/44	0.70	57/32	50/39	0.36
BMI; kg/m^2	22.0 ± 4.3	21.2 ± 3.4	0.12	21.5 ± 3.9	21.5 ± 3.5	1.00
Operation time; min	674 ± 118	648 ± 115	0.09	662 ± 119	652 ± 120	0.56
Anesthesia time; min	775 ± 120	742 ± 120	0.03*	759 ± 118	748 ± 127	0.53
In-Out balance; mL	3002 [2250–3776]	2733 [2192–3800]	0.45	2955 [2067–3748]	2878 [2114–3800]	0.95
Blood transfusion	73 (57%)	81 (67%)	0.12	53 (60%)	55 (62%)	0.88
TIVA with propofol	6 (5%)	4 (3%)	0.75	4 (5%)	3 (3%)	1.00
NSAIDs (flurbiprofen)	28 (22%)	22 (18%)	0.53	15 (17%)	18 (20%)	0.70
Free flap reconstruction	98 (76%)	85 (70%)	0.32	67 (75%)	63 (71%)	0.61
Fentanyl dose; ng/kg/min	23.8 ± 5.6	22.4 ± 6.2	0.07	22.8 ± 5.5	23.3 ± 6.5	0.59

Values are presented as means ± standard deviations, medians [interquartile ranges], or numbers (proportion, %) of patients.
BMI: body mass index
TIVA: total intravenous anesthesia
NSAIDs: nonsteroidal anti-inflammatory drugs

As the primary outcome, the mean remifentanil dose was significantly lower in the ketamine

than that in the non-ketamine group before (0.15 ± 0.05 vs 0.17 ± 0.05 μg/kg/min; $P = 0.01$) and after matching (0.15 ± 0.06 vs 0.17 ± 0.05 μg/kg/min; $P = 0.03$), respectively (Table 2). The correlation between the ketamine and remifentanil doses was very weak, with the correlation coefficient being –0.13 (95% confidence interval, –0.24 – –0.01; $P = 0.04$). Additionally, the total opioid dose (ie, the sum of the remifentanil and fentanyl doses) was also significantly lower in the ketamine than in the non-ketamine group (0.17 ± 0.06 vs 0.19 ± 0.06 μg/kg/min; $P = 0.03$; Table 2).

Table 2 Intraoperative remifentanil and total opioid doses in each group before and after propensity score-matching

	Before matching			After matching		
	Ketamine (+) *n*=129	Ketamine (–) *n*=121	*P*-value	Ketamine (+) *n*=89	Ketamine (–) *n*=89	*P*-value
Remifentanil dose; μg/kg/min	0.15 ± 0.05	0.17 ± 0.05	0.01*	0.15 ± 0.06	0.17 ± 0.05	0.03*
Total opioid dose; μg/kg/min	0.17 ± 0.06	0.19 ± 0.06	0.03*	0.17 ± 0.06	0.19 ± 0.06	0.03*

The total opioid dose corresponds to the sum of the remifentanil and fentanyl doses. Values are presented as means ± standard deviations.
*P <0.05

DISCUSSION

This study assessed the effects of intraoperative ketamine administration on the intraoperative dose of opioid used, especially the dose of remifentanil, during prolonged head and neck surgeries. Our findings suggested that intraoperative administration of an intravenous ketamine bolus reduced the need for intraoperative remifentanil use during such surgeries.

Head and neck surgeries that require reconstruction are prolonged operations in which increased total intraoperative opioid doses should be administered. Although opioids are necessary as multimodal analgesics, a minimal amount of opioid use is optimally effective in order to promote enhanced recovery after abdominal[10,11] and head and neck surgeries.[12-14] Our findings indicated that an intravenous bolus of ketamine may be effective in reducing the intraoperative total opioid dose, including the dose of remifentanil, during prolonged head and neck surgeries. Among the possible drug options, the use of ketamine,[15] nonsteroidal anti-inflammatory drugs,[16] propofol,[17] and others (ie, buprenorphine, α_2 agonists, methadone)[18] in abdominal or thoracic surgery has been suggested to reduce the risk of opioid-induced hyperalgesia and tolerance. In this study, the propensity score-matching procedure was performed to adjust for the use of nonsteroidal anti-inflammatory drug and the total intravenous anesthesia with propofol. After the propensity score-matching, the intraoperative remifentanil and total opioid doses were significantly lower in the ketamine than in the non-ketamine group.

The suggested mechanisms of opioid-induced hyperalgesia and tolerance include central sensitization at the dorsal horn of the spinal cord through the activation of NMDA receptors associated with the use of high-dose opioids and neurotransmitter release (eg, glutamate, substance P).[5-7] Ketamine, a non-competitive NMDA receptor antagonist, blocks this central sensitization.[5-7] This study suggested that the correlation between the total intravenous ketamine and intraoperative remifentanil doses was negative, and was extremely weak. Therefore, the total ketamine dose may not be related to the strength of the blocking effect of central sensitization.

In a previous review, Yu et al demonstrated that remifentanil infusion rates of >0.2 μg/kg/min

were associated with opioid-induced hyperalgesia.[5] In this study, the infusion rates of remifentanil were <0.2 μg/kg/min, and the difference in the intraoperative remifentanil dose between the two groups was only 0.02 μg/kg/min. However, owing to the prolonged nature of the surgery, this difference becomes larger. The total opioid consumption may also affect opioid-induced hyperalgesia and tolerance. However, some reports have shown that high-dose remifentanil administration does not affect postoperative pain responses.[19] Therefore, further studies are needed to verify the association between intraoperative opioid dose and postoperative pain.

Our study had several limitations. First, this was a single-center retrospective study, and the patients were not randomized based on the administration of intraoperative ketamine. Therefore, to obtain comparable groups with minimal bias, a propensity score-matching approach was used. Second, the administration schedule of ketamine varied in our study. Moreover, the types and doses of intraoperative opioids to be used were left to the discretion of individual anesthesiologists. However, our study results may be applicable in actual clinical settings. Further studies are needed to compare the differences in administration regimens (ie, single or multiple bolus administration, or continuous infusion/alterative administration schedule) using the criteria for intraoperative opioid administration. Finally, this study did not show the effects of ketamine on opioid-induced hyperalgesia or clinical outcomes, such as postoperative recovery. Further studies are needed to assess these clinical outcomes.

In conclusion, our findings suggest that an intravenous bolus of ketamine may lead to reduced use of intraoperative remifentanil during prolonged head and neck surgeries. Future studies should assess the effect of these findings on potential enhanced recovery after surgery in detail, while overcoming the limitations of our study.

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DISCLOSURE STATEMENT

All authors declare that they have no conflicts of interest.

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