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Effects of Landiolol Administration under Remifentanil Anesthesia on Heart Rate and Sympathetic Nervous Activity: A Single Blind, Randomized Control Study

Shiori Sakuma[1], Keiko Kume[1], Nobutada Morioka[2]* and Makoto Ozaki[1]

[1]Department of Anesthesiology, Tokyo Women's Medical University, Japan
[2]Department of Anesthesiology, Yachiyo Medical Center, Director of Central Operating Theater, Tokyo Women's Medical University, Japan

***Corresponding author:** Nobutada Morioka, Department of Anesthesiology, Yachiyo Medical Center, Tokyo Women's Medical University, Yachiyo City, Chiba, Japan, Tel: +81-47-450-6000; Fax: +81-47-458-7047; E-mail: nmorioka@twmu.ac.jp

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Abstract

Many studies demonstrated that administration of β blockers in the perioperative period of cardiac surgery reduced the rate of complications such as a trial fibrillation after surgery and had a beneficial effect on survival rate. In many of the reports, β blockers were administered continuously after surgery. In this study, we assessed the effectiveness of intraoperative use of a short-acting β blocker (administered in dose escalation) for reducing sympathetic nervous activity in patients under anesthesia with remifentanil and without arrhythmia, by calculating the LF/HF ratio on the basis of the R-R interval obtained on electrocardiography before and after surgery. The subjects were 20 patients who received a short-acting β blocker, landiolol, in dose escalation during elective laparoscopic nephrectomy under total intravenous anesthesia with remifentanil and propofol. The LF/HF ratio, calculated using a Holter monitor in the postoperative period, was compared with that calculated in the preoperative period. In the postoperative period, LF/HF ratio in the landiolol group (1.84 ± 0.79) was significantly lower than that in the control group (2.68 ± 1.66). In the preoperative period, LF/HF ratio in the landiolol group (3.07 ± 1.61) and in the control group (3.04 ± 1.56). No significant differences in mean, maximum, and minimum heart rates during surgery were found between the two groups. Furthermore, no significant difference was found in the development of tachyarrhythmia after surgery between the two groups. Intraoperative administration of landiolol influences the variation in the R-R interval in the postoperative period, despite the fact that the effect of the short-acting drug was supposed to have disappeared.

Keywords: Landiolol; Remifentanil; Bradycardia; Sympathetic nervous activity; β blockers

Introduction

The ultrashort-acting opioid remifentanil (Ultiva Intravenous, Jansen Pharma Co. Ltd., Tokyo) is easily titratable owing to rapid onset and offset and allows the safe induction and maintenance of deep anesthesia. Similar to other opioids, its characteristic actions include the induction of hypotension and bradycardia as a result of circulatory suppression [1,2]. Owing to these characteristics, intraoperative bradycardia is more likely to occur with remifentanil than with other opioids. However, the frequency of intraoperative tachyarrhythmia occurrence also tends to be reduced [3]. Decreased heart rate is thought to be caused by a decrease in sympathetic nervous activity (SNA) and increase in vagal tone mediated by central μ receptors [4]. Electrophysiological studies in humans and animals have shown that remifentanil induces a dose-dependent suppressive effect on sinus and AV node function [5,6]. The perioperative administration of β-blockers is reportedly effective for the prevention of myocardial ischemia and tachyarrhythmia, the inhibition of inflammatory cytokines, and the stabilization of intravascular plaques [7,8]. The control of heart rate is very important, especially for perioperative patients with concomitant cardiovascular disease. Therefore, the perioperative use of β-blockers has been shown to be effective for the prevention of tachycardia arising from the excitation of sympathetic neurons; their intraoperative use has also been reported [9,10]. The change in heart rate is interpreted as the result of decreased automaticity and conduction [11].

One of the β blockers, landiolol (Onoact. Ono Pharmaceutical CO., LTD. Osaka), is a short-acting agent characterized by high β1 selectivity. It is less likely to induce hypotension than esmolol and has a very short half-life of just 4 minutes with high titrability as a β blocker. Many effects induced by perioperative administration are reportedly attributable to its characteristics as a short-acting agent [12-17]. Patients under anesthesia with remifentanil and propofol tend to have bradycardia due to increased vagal tone [5,6,18]. We hypothesized that the intraoperative use of ultra-short-acting β blockers (that suppress abnormal conduction pathways) can reduce SNA even after surgery when the effect is expected to have disappeared. This study tested this hypothesis by investigating the postoperative tachyarrhythmia arrythmia and change in R-R interval on electrocardiography by using a Holter monitor, as the index of SNA [19,20].

Methods

After approval of the study from the Ethics Committee of Tokyo Women's Medical University, 20 patients undergoing elective laparoscopic nephrectomy between 2012 and 2013 at Tokyo Women's Medical University Hospital were selected as study subjects in accordance with the Declaration of Helsinki. All study participants received oral and written explanations and submitted a signed consent form. The subjects included patients with an American Society of Anesthesiologists' Physical Status classification of 1-3. The exclusion criteria were as follows: patients who were taking β blockers or anti-arrhythmic drugs, patients with an atrioventricular block grade of ≥ 2, patients with asthma, and patients who were judged as unsuitable for study enrollment by the investigators. The primary objective of this study was to investigate the influence of intraoperative use of a short-acting β blocker on the decrease in SNA in the postoperative period.

Primary outcome

Change in SNA in the postoperative period by R-R interval calculation.

Secondary outcome

Tachyarrhythmia in the postoperative period and change in heart rate in the intraoperative period in the patients who received a short-acting β blocker.

Protocol

The subjects were randomly divided into two groups (control and landiolol administration) in accordance with a table of random numbers generated by Microsoft Excel.

Anesthesia

Total intravenous anesthesia was performed using propofol and remifentanil. Invasive arterial blood pressure, noninvasive arterial blood pressure, ECGs, oxygen saturation, encephaloelectrogram (BIS: Bispectral Index MEDTRONIC, Tokyo, Japan), and neuro-muscular blockade (TOF watch, NIHON KOHDEN Co. Ltd., Tokyo, Japan) were monitored. Anesthesia was induced with 4 μg/mL propofol (TCI: Target controlled infusion pump TERUMO) and 0.5 μg/kg/min remifentanil; when the patient fell asleep, rocuronium was administered at 0.7 mg/kg and intubation was performed. After intubation, propofol and remifentanil were titrated to 2.5 ± 0.5 μg/mL and 0.25-1.0 μg/kg/min, respectively, to maintain heart rate (40-60 bpm), blood pressure (80-120 mmHg), and BIS (40-60) prior to the start of surgery. The doses were titrated and fixed to maintain the same levels even after pneumoperitoneum. The patients were ventilated in a pressure-limited mode with a tidal volume of approximately 8 mL/kg at a respiratory rate of 10/minute. This condition was maintained until completion of the operation in the control group. Rocuronium (10 mg) was administered each time T1 appeared and antagonized by sugammadex upon completion of the operation. Anesthesia was performed by the same anesthesiologist in all cases. In the landiolol group, the administration of landiolol was initiated at 5 μg/kg/min after the confirmation of stable circulatory dynamics after pneumoperitoneum. Postoperative analgesia was patient-controlled and provided by fentanyl.

Method for administering landiolol

After the confirmation of stable circulatory dynamics and BIS after pneumoperitoneum, the administration of landiolol was initiated at 5 μg/kg/min and heart rates were subsequently observed for 5 min. If no change (more than 10% difference in heart rate at the time of induction) was observed, increments of 5 μg/kg/min were gradually added. This was repeated to increase the dose to a maximum of 50 μg/kg/min. Administration was discontinued when the operation was completed. The use of additional opioids, including antiarrhythmic drugs and fentanyl was prohibited; if their administration was required, the patient was eliminated as a study subject and the study protocol was discontinued. Otherwise, the criteria for study discontinuation were: bradycardia (≤ 40 bpm); systolic blood pressure either ≤ 70 mmHg or >120 mmHg; appearance of second degree or higher atrioventricular block; signs of heart failure; any indication of an asthma attack (appearance of wheezing), BIS either ≤ 40 or >60; or when a study doctor decided for any reason to discontinue the study protocol.

Method for analyzing SNA

The patients who received landiolol and those who did not receive landiolol in the perioperative and intraoperative periods were compared. The LF/HF ratio was calculated through the R-R interval obtained from Holter ECGs (Sampling frequency 125 Hz) and analyzed by using Computing Software (SCM-850S Fukuda Denshi Co., Ltd. Tokyo Japan).

Statistical analysis

Data were analyzed for all patients who were not withdrawn from the study. A paired t test was used for paired continuous data, and Student's t test was used for unpaired continuous data. A chi-squared test was used for categorical data. All analyses were two-tailed, with statistical significance considered at $P<0.05$. The mean ± standard deviation was used to express the variability of data. JMP® (SAS Institute Japan, Ltd., Tokyo, Japan) was used for the computation of statistical analyses.

Results

None of the patients dropped out of the study. The subjects were 20 patients (10 patients in each group). Patient backgrounds: There were no significant differences between the two groups for any surgical background factors. None of the patients in both groups had tachyarrhythmia in the postoperative period (Table 1). The administration of landiolol reached the maximum rate of 50 μg/kg/min in all cases. With regard to remifentanil, propofol, and rocuronium, there were no differences between the two groups (Table 2). No significant differences were found between the two groups in the preoperative heart rates recorded with a Holter monitor. The mean, maximum, and minimum heart rates during operations were also not different between the two groups (Table 3). Postoperative SNA was lower than preoperative SNA in the Landiolol group. In addition, a

Table 1: Patient profiles.

	Control Group	Landiolol Group
Number	10	10
Age	57.4 ± 13.6	57.1 ± 9.1
Sex (F/M)	9-Jan	7-Mar
Height (cm)	164.4 ± 8.9	164.4 ± 8.0
Weight (kg)	66.15 ± 16.6	63.6 ± 13.1
ASA PS (1/2/3)	3/5/2002	3/5/2/
Anesthesia time (min)	266 ± 30.2	257 ± 35.4
Surgical Time (min)	192.3 ± 26.5	184.8 ± 33.9
Tachyarrythmia event	none	none

Table 2: The maximal rates of administration and the total doses of remifentanil, propofol, and landiolol and the doses of rocuronium during surgery.

	Control Group	Landiolol group	P-value
maximum rate of Landiolol (microgram/kg/min)	N/A	50	
amount of Landiolol (mg)	N/A	365 ± 127	
maximum rate of Remifentanil (microgram/kg/min)	0.46 ± 0.08	0.425 ± 0.09	0.369
amount of Remifentanil (mg)	7.2 ± 2.4	6.3 ± 2.3	0.427
maximum rate to Propofol (microgram/ml)	2.60 ± 0.30	2.52 ± 0.26	0.54
amount of Propofol (mg)	1525 ± 549	1327 ± 376	0.36
amount of Rocuronium (mg)	85 ± 20	82 ± 13	0.653

Table 3: Preoperative, intraoperative maximal, minimal, and mean heart rates by group.

	Control	Landiolol	P-value
Pre-induction heart rate (bpm)	74.4 ± 13.8	77.2 ± 11.9	0.64
minimum heart rate (bpm)	51.3 ± 6.2	52.8 ± 7.6	0.63
maximum heart rate (bpm)	70.1 ± 7.8	65.3 ± 9.8	0.24
average of heart rate (bpm)	59.2 ± 7.8	58.7 ± 9.2	0.91

decrease between the control group and the Landiolol group was also seen for the postoperative phase. The LF/HF ratio in the Landiolol group was 3.04 before surgery and 1.87 after surgery and 3.07 and 2.66 in the control group, respectively. In the Landiolol group, the postoperative ratio was significantly lower than the preoperative ratio. The postoperative ratio in the Landiolol group was significantly lower than that of the control group (Table 4).

Discussion

Many studies have demonstrated the beneficial effect of perioperative β blockers in preventing complications such as paroxysmal atrial fibrillation in the perioperative period [21]. Given that β blockers reduce SNA and are also effective in preventing complications in patients without cardiac diseases such as atrial fibrillation, we considered that the intraoperative use of a short-acting β blocker alone is effective for the prevention of complications in patients undergoing elective laparoscopic nephrectomy under anesthesia with remifentanil and propofol who have no arrhythmic complications, including tachyarrhythmias such as atrial fibrillation. In this study, we intraoperatively administered landiolol in dose escalation and evaluated its effects by calculating the low frequency (LF)-to-high frequency (LF/HF) ratio based on the R-R interval obtained from a Holter monitor before and after surgery. The results showed no statistically significant differences between the two groups in patient background and surgery-related factors, including operation time. The mean intraoperative heart rate (the sum of heart beats/min divided by the measurement time) and the maximum and minimum heart rates during surgery were almost the same between the two groups. Furthermore, no significant difference in preoperative or postoperative heart rate was found between the two groups. Patients under total intravenous anesthesia tend to have bradycardia. Although small doses

Table 4: Comparison of low-frequency/high-frequency ratios between before and after surgery and between patients receiving and not receiving landiolol.

	Control	Landiolol	P-value
Pre Operative LF/HF	3.07 ± 1.61	3.04 ± 1.56	0.3
Post Operative LF/HF	2.68 ± 1.66	1.84 ± 0.79	0.03
P-value	0.48	0.08	

of remifentanil do not cause respiratory suppression and rarely cause bradycardia, intraoperative administration of remifentanil at 0.25-0.5 μg/kg/min causes bradycardia [22]. In this study, we assumed that the intraoperative use of β blocker reduced automaticity and suppressed abnormal conduction pathways without worsening bradycardia and did not produce a negative effect on the heart rate during surgery. The postoperative LF/HF ratio was significantly decreased in the landiolol group compared with that in the control group. This is considered to be due to the decreased SNA in the autonomic nervous system [19,20]. The mechanism of action of beta-1 blockers in this study was considered to be that the intraoperative administration of the short-acting agent reduced automaticity and suppressed abnormal conduction pathways, including the sinoatrial and atrioventricular nodes, which influenced the R-R interval in the postoperative period. In addition, the LF/HF ratio in the postoperative period was lower than that in the preoperative period in both groups. This might be due to the influence of remifentanil; however, further studies are needed because no studies have investigated the effects of agents other than remifentanil on this issue. Many studies have reported that perioperative administration of landiolol had a preventive effect on the development of complications such as atrial fibrillation and had a positive influence on postoperative mortality and morbidity [12-16]. The findings in this study may contribute to the understanding of the underlying mechanism. Despite the small sample size, the results of this study are considered important because of the high statistical power (0.75). However, the pathogenesis of complications such as paroxysmal atrial fibrillation was difficult to analyze in the perioperative period because of the small sample size. Further studies are needed to investigate the effects of dose, as a previous study reported that the development of arrhythmia was prevented by a small dose, finally, no consensus has been reached about the association between LF/HF ratio and autonomic function. This study demonstrated that the intraoperative administration of β blocker was associated with the variation in the LF/HF ratio, which provides an important implication for future studies in this area.

Limitations

In this study, the additive and synergistic effects of remifentanil and landiolol, at a maximum administration rate of 50 μg/kg/min, were studied. However, as the number of cases was not sufficient, further studies are required to achieve the statistical power required to prove that the synergistic effect was not induced solely by the opioid. Furthermore, as subjects with tachyarrhythmia were excluded, our data cannot be used as a reference for patients with a clinical requirement for opioid administration. Possible sources of bias are that the attending anesthesiologist was not blinded and an anesthesiologist participated in the whole study.

Conclusion

Intraoperative administration of a short-acting β blocker, landiolol, did not worsen remifentanil-induced bradycardia in the patients under intravenous anesthesia with remifentanil and propofol. The LF/HF ratio calculated from the R-R interval in the postoperative period

was lower than that calculated in the preoperative period and was also lower than that in the control group.

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Conflicts of Interest

All authors have no conflicts of interest to declare.

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