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Landiolol, an Ultra-short Acting β1-Adrenoreceptor Antagonist, for Treatment of an Abrupt Tachycardia in Patients Undergoing Total Knee Arthroplasty under General Anesthesia

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Abstract

Tachycardia and hypertension due to surgical and tourniquet pain often occur suddenly during general anesthesia for total knee arthroplasty. We evaluated the dose-related effects of landiolol on an abrupt tachycardic response in this clinical setting, since this agent is able to suppress the cardiovascular responses associated with sympathetic stimulation.

After approval by the local ethical committee and informed consent, 114 patients, aged 51–89 yr, undergoing total knee arthroplasty under general anesthesia were enrolled in this study. Following general anesthesia induction with fentanyl 1–2 μg/kg, propofol 1.5–2 mg/kg and 5% sevoflurane, a laryngeal mask airway was inserted, and anesthesia was maintained with 1% sevoflurane, droperidol 5 mg and 50% N_2O in oxygen. Thereafter, supplemental fentanyl 0.5–1 μg/kg was injected repeatedly to keep the end-tidal CO_2 tension of 30–45 mmHg, and spontaneous respiratory rate of 10–25 breaths/min. When a tachycardic response (defined as heart rate of more than 90 beats/min for more than 3 minutes) was observed, landiolol or normal saline (as a time control group) was randomly infused continuously at a rate of 40 or 80 μg/kg/min, or of 0.24 mL/kg/h, respectively, until the end of surgery or tourniquet deflation. Hemodynamic and respiratory variables were recorded at 1–5 minute intervals. Data were analyzed by analysis of variance or Student's t-test with Bonferroni's correction for comparisons among groups or within each group, with $p < 0.05$ being significant.

Tachycardic responses developed in 50 of 114 patients (44%) studied. There were no significant differences in demographic data among patients who received landiolol 40 μg/kg/min (n=24), landiolol 80 μg/kg/min (n=20), and saline (n=6). Heart rate decreased at 1 minute after the start of landiolol infusion and remained below pre-administration values ($p < 0.05$) in patients receiving landiolol 40 and 80 μg/kg/min, while heart rate unchanged in control patients. Mean blood pressure remained unchanged as compared with pre-infusion values in all groups. When compared with the control group, heart rate was lower 5 and 4 minutes after the start of landiolol infusion ($p < 0.05$) in patients given landiolol of 40 and 80 μg/kg/min, respectively.

These data show that landiolol infusion at a rate of 80 μg/kg/min provided more rapid suppression of an abrupt tachycardia in patients undergoing total knee arthroplasty under general anesthesia. The prompt treatment of tachycardia by landiolol seems appropriate, particularly for the older patients who are likely to have occult ischemic heart disease.

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Key words; landiolol, tachycardia, total knee arthroplasty, ultra-short-acting β_1-selective adrenoreceptor antagonist

Introduction

Landiolol (Onoact®, ONO PHARMACEUTICAL CO., LTD) is an ultra-short-acting β_1-selective adrenoreceptor antagonist[1], and is able to suppress the cardiovascular responses associated with sympathetic stimulation such as tracheal intubation[1~3] and removal of phechromocytoma[4,5]. Pharmacological characteristics of landiolol include no intrinsic sympathomimetic activity, a shorter plasma half-life of approximately 4 minutes due to a rapid hydrolysis of its alkyl ester link mediated primarily via an esterase in the red blood cell cytosol, and a higher cardioselectivity with a potency ratio (β_1/β_2) of 255; these properties of landiolol are superior to those of esmolol, an ultra-short-acting, cardioselective β_1-adrenergic receptor antagonist (9 minutes and 33 in plasma half-life and cardioselectivity, respectively)[6~9].

It is well known that tachycardia and hypertension due to surgical and tourniquet pain often occur abruptly during general anesthesia in patients undergoing total knee arthroplasty[10~12]. Meanwhile, patients who need total knee arthroplasty are usually older and obese[13~18], and most likely to have other significant comorbidities that may compound the difficulties in anesthetic management; the common coexisting diseases include hypertension, diabetes mellitus and coronary artery disease[15,19~23].

The incidence of myocardial ischemia has been reported to increase by three-fold when control of heart rate (HR) was targeted to more than 100 beats/min[24]. Conversely, the frequency of perioperative myocardial infarction has been reduced to approximately one-fourth by managing HR of less than 100 beats/min[25]. According to American College of Cardiology/American Heart Association guidelines, it is recommended that HR should be kept between 60–65 beats/min in perioperative management[26]. Thus, it is evident that avoidance of tachycardia during anesthesia and postoperative period seems crucial particularly in these elderly, obese and hypertensive patients with apparent ischemic heart disease as well as in otherwise normal patients who may have occult coronary heart disease that has never been diagnosed preoperatively.

However, there is no clinical investigation evaluating the dose-related hemodynamic effects of landiolol in patients undergoing total knee arthroplasty. Based on these considerations, we evaluated the effects of different infusion rates of landiolol on an abrupt tachycardic response in this clinical setting.

Methods

We enrolled 114 patients undergoing total knee arthroplasty classified as ASA physical status 1, 2 or 3. They were aged from 51 to 89 years old (mean age was 74.9 years old), and received general anesthesia alone without epidural or subarachnoid anesthesia for surgery because of the following reasons; patient refusal, cutaneous disorders at the insertion site, active neurologic disease, and preoperative impaired coagulation status precluding safe puncture such as recent anticoagulant or antiplatelet therapy. The study was approved by our local ethics committee and written informed consent was obtained from each patient. Most of patients had a history of cardiovascular disorders such as hypertension, diabetes mellitus, disorders known to affect autonomic functions, and those taking medications known to affect cardiovascular functions. All patients received 150 mg ranitidine (H2-blocker) orally as preanesthetic medication 90 min before arrival in the operating room (OR).

Before arrival in the OR, a 20-gauge IV cannula was inserted and lactated Ringer's solution was administered at a rate of 3 mL/kg/h in the ward. Then, lactated Ringer's solution or 6% hetastarch was infused at a rate of approximately 20 mL/kg/h throughout the study in the OR. Standard lead II electrocardiography and an automated blood pressure (BP) cuff at the contralateral arm were applied. HR was determined as an average of 4-sec intervals recorded on the electrocardiography (ECG) monitor, and systolic, diastolic

and mean BPs were measured at an interval of 1–2.5 minutes.

General anesthesia was induced with fentanyl 1–2 μg/kg, propofol 1.5–2 mg/kg and inspired concentration of sevoflurane, 5%. A laryngeal mask airway (number 3 or 4) was inserted, and the cuff was inflated with 20–30 mL of air. Anesthesia was maintained with droperidol 5 mg IV, end-tidal concentration of sevoflurane, 1%, and 50% nitrous oxide in oxygen with 6 L/min of the background gas flow. Several minutes later, spontaneous respirations appeared in all patients. Thereafter, we injected fentanyl 0.5–1 μg/kg intermittently, to keep the end-tidal CO_2 tension between 30 and 45 mmHg, and patient's spontaneous respiratory rate between 10 and 25 breaths/min. Surgical procedure started immediately after the tourniquet was inflated to keep the cuff pressure between 280 and 320 mmHg. Then, the tourniquet cuff was deflated and removed just after the implantation of artificial joints using bone cement.

Hypotension was defined as a decrease of mean BP of more than 20% of pre-anesthesia value, and ephedrine 5–10 mg was given IV for treatment of hypotension. On the other hand, hypertension was defined as an increase of mean BP of more than 20% of pre-anesthesia value. As a rescue drug, nicardipine 0.5–1 mg was given IV.

A tachycardic response was defined as HR of more than 90 beats/min for more than 3 minutes, based upon the fact that the incidence of myocardial ischemia increased by three-fold if target HR >100 beats/min[24]. The patients who developed tachycardic responses were randomly assigned (sealed envelopes) to one of three groups according to the infusion rate of landiolol. Saline group as a time control group received normal saline at a rate of 0.24 mL/kg/h, while landiolol-40 and landiolol-80 groups received landiolol at a rate of 40 and 80 μg/kg/min, respectively. Landiolol or normal saline was infused continuously until the end of surgery or tourniquet deflation. HR, BPs, respiratory rate, and end-tidal CO_2 tension were recorded at 1–5 minute intervals. Only 6 patients without apparent ischemic heart disease were allowed to receive saline instead of landiolol because of medical and ethical reasons, according to recommendation offered by the ethics committee.

Data were expressed as mean±SD. Patient characteristics and intraoperative data were compared using analysis of variance (ANOVA) and unpaired Student's t-test. Student t-test with Bonferroni's correction was used for comparisons among groups or within each group. Testing for significance in the incidence among groups was accomplished by chi-squared analysis. *P* value of less than 0.05 was considered statistically significant.

Results

Tachycardic responses were observed in 50 patients of 114 patients (44%) studied. Six, 24, and 20 patients received saline, and landiolol at a rate of 40 or 80 μg/kg/min, respectively. There were no significant differences among the three groups with respect to age, height, weight, gender ratio, and medication for coexisting diseases (**Table 1**). Most of patients were female and were given antihypertensive drugs. **Table 2** shows intraoperative data. As shown in this table, the total dose of fentanyl was significantly smaller in patients receiving landiolol 80 μg/kg/min as compared with the other two groups ($p<0.05$). But, there were no differences among groups in number of patients given ephedrine or nicardipine and total doses of these drugs before landiolol or saline infusion and other intraoperative data.

Because the tourniquet cuff was deflated or surgery ended 30 minutes or later following the start of landiolol or saline infusion in all patients of each group, the hemodynamic data until 30 minutes during landiolol or saline infusion were subjected to data analyses. **Fig. 1** shows changes in HR during 30-minute infusion of landiolol or saline. HR decreased below pre-administration values 1 minute after the start of landiolol infusion in both landiolol groups ($p<0.05$), but HR unchanged in control patients. When compared with the control group, HR was significantly lower at 5–30 minutes in the landiolol-40 group, and

Table 1 Patients' demographic data

Group	Saline (n=6)	Landiolol 40μg/kg/min (n=24)	Landiolol 80μg/kg/min (n=20)
Age (years)	76.3±5.7	75.1±6.6	75.4±5.5
Body height (cm)	152.0±5.8	150.3±5.4	149.4±6.8
Body weight (kg)	56.3±8.4	58.1±9.3	58.2±8.8
Gender (female/male)	6/0	21/3	18/2
ASA physical status classification (1/2/3)	1/5/0	0/23/1	0/18/2
Coexisting diseases			
Number of patients with hypertension (%)	4 (67%)	18 (75%)	14 (70%)
Number of patients with diabetes mellitus (%)	0 (0%)	4 (17%)	4 (20%)
Number of patients with ischemic heart disease (%)	0 (0%)	1 (4%)	0 (0%)
Number of patients with atrial fibrillation (%)	0 (0%)	0 (0%)	2 (10%)
Concurrent medication			
Number of patients receiving angiotensin II receptor blockers (%)	2 (33%)	12 (50%)	8 (40%)
Number of patients receiving angiotensin converting enzyme inhibitors (%)	0 (0%)	0 (0%)	1 (5%)
Number of patients receiving calcium channel blockers (%)	3 (50%)	11 (46%)	10 (50%)
Number of patients receiving β-blockers (%)	1 (17%)	1 (4%)	0 (0%)
Number of patients receiving diuretics (%)	0 (0%)	3 (13%)	2 (10%)
Number of patients receiving digitalis (%)	0 (0%)	0 (0%)	1 (5%)
Number of patients receiving oral hypoglycemic agents (%)	0 (0%)	4 (17%)	2 (10%)
Number of patients receiving insulin (%)	0 (0%)	0 (0%)	2 (10%)

Values are mean±SD, or number of patients (percentage)

Table 2 Patients' intraoperative data

Group	Saline (n=6)	Landiolol 40μg/kg/min (n=24)	Landiolol 80μg/kg/min (n=20)
Duration of tourniquet inflation (min)	71.7±8.2	73.3±13.8	68.1±9.3
Start time of saline or landiolol infusion after tourniquet inflation (min)	24.2±18.4	19.9±8.9	16.8±11.6
Duration of saline or landiolol infusion (min)	43.0±15.7	46.7±5.5	45.5±13.7
Operating time (min)	69.8±8.0	75.5±22.4	67.4±13.6
Anesthesia time (min)	89.0±10.7	94.4±22.8	85.8±18.0
Total volume of infused fluid (ml)	983±160	960±281	973±181
Volume of Ringer's solution (ml)	500±141	463±268	468±179
Volume of hetastarch (ml)	483±41	498±70	495±22
Urine output (ml)	567±236	440±253	443±394
Total dose of fentanyl (μg)	325±76	299±83	240±45*
Total dose of propofol (mg)	100±13	104±21	109±17
Number of patients given ephedrine (%)	6 (100%)	22 (92%)	18 (90%)
Total dose of ephedrine before saline or landiolol infusion (mg)	5.8±2.0	10.0±7.8	8.3±7.3
Number of patients given nicardipine (%)	5 (83%)	15 (63%)	11 (55%)
Total dose of nicardipine before saline or landiolol infusion (mg)	0.8±0.4	0.7±0.6	0.7±0.8

Values are mean±SD, or numbers (percentage). *P=0.007 compared with the other two groups.

4–30 minutes in the landiolol-80 group, respectively, after the start of landiolol infusion ($p<0.05$).

Fig. 2 shows changes in mean BP until 30 minutes after the start of landiolol or saline infusion. Although mean BPs remained unchanged as compared with pre-infusion values in all groups, they were lower at 20–30 minutes after landiolol infusion in the landiolol groups than the control group.

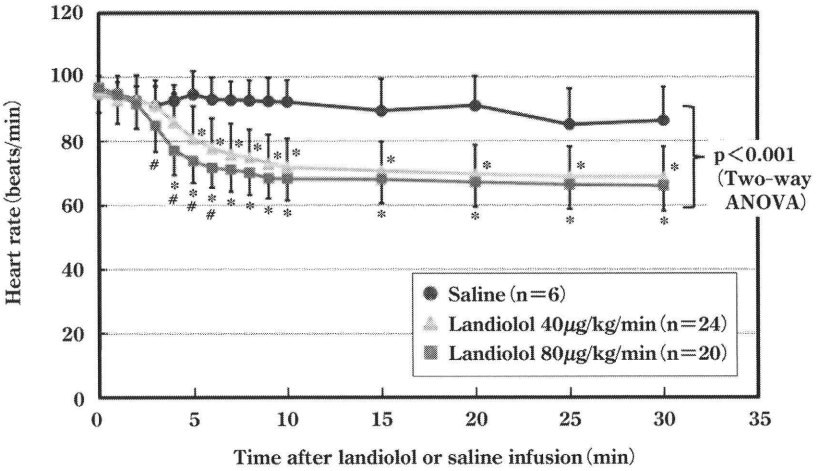

Figure 1 Changes in heart rate after landiolol or saline infusion

Values are mean±SD. Heart rate decreased below pre-administration values ($p<0.05$) 1 minute after the start of landiolol infusion in patients receiving landiolol, while heart rate unchanged in control patients. When compared with the control group, heart rate was lower in patients given landiolol.

*$p<0.05$ compared with saline control group. #$p<0.05$ compared with landiolol-40 group.

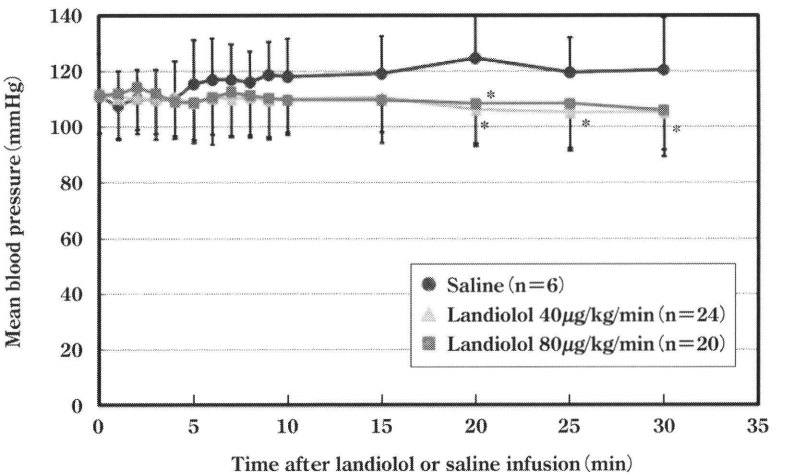

Figure 2 Changes in mean blood pressure after landiolol or saline infusion

Values are mean±SD. Mean blood pressure remained unchanged as compared with pre-infusion values in all groups, but was lower after landiolol infusion in both landiolol groups than the control group.

*$p<0.05$ compared with saline control group.

No patient developed myocardial infarction or unstable angina pectoris during the study and postoperative periods. Premature atrial contractions occurred transiently during saline or landiolol infusion in 1, 3 and 2 patients of control, landiolol-40 and landiolol-80 groups, respectively. Likewise, premature ventricular contractions occurred transiently during landiolol infusion in 3 and 1 patients of landiolol-40 and -80 groups, respectively. Because these extrasystoles were of short duration, or monofocal, they required no treatment. Atrial fibrillations that noted preoperatively in 2 patients of the landiolol-80 group persisted during the entire study period.

Discussion

These data show that landiolol infusion at a rate of

80 μg/kg/min provided more rapid suppression of tachycardia and reduced intraoperative fentanyl requirement in patients undergoing total knee arthroplasty under general anesthesia, when compared with the landiolol-40 group or the control group. The results of clinical trials have advocated the perioperative use of β-adrenoreceptor antagonists in patients undergoing noncardiac surgery to alleviate adverse cardiac events[27~31]. Based on these reports, the prompt treatment of tachycardia seems essential particularly for the older diabetic patients who are most likely to have occult coronary artery disease because of silent ischemia[32]. In clinical practice, the use of landiolol may be suitable for the treatment of tachycardia in the elderly.

According to the manufacture's information on landiolol dosage[33], the initial infusion rate of 125 μg/kg/min during the first 1-minute period is followed by a continuous infusion rate of 10–40 μg/kg/min. It is conceivable that more rapid decline in HR might have occurred, if we used this regimen in the present study. But, because we intended to avoid an abrupt, profound bradycardia especially in older patients medicated with a negative chronotropic drug, we adopted infusion rates of 40–80 μg/kg/min the current study as referred to a previous report[8]. Actually, marked HR reductions did not develop in any patients, and restoration of normal sinus rhythm was not noted in any patients with premature atrial or ventricular contractions, or atrial fibrillation during landiolol infusion in the present study. There was no appearance of new arrhythmia due to landiolol and general anesthetics (fentanyl, sevoflurane and nitrous oxide) interaction in the present study. No increased occurrence of cardiac conduction disturbance even after a large dose of landiolol (80 μg/kg/min) in patients given fentanyl would exclude the possibility of serious interaction between landiolol and fentanyl. Furthermore, mean BPs remained unchanged as compared with pre-infusion values in all groups, regardless of statistically significant differences between the landiolol and control groups. These current findings may indicate trivial antiarrhythmic and hypotensive effects of landiolol as shown in the previous report[8].

There are several investigations showing the anesthetic-sparing effect of β-adrenoreceptor antagonists[34~39], or by antagonism of catecholamines in the brain[40]. Thus, these reports are likely to support our result that the total dose of fentanyl was significantly reduced in patients given landiolol 80 μg/kg/min.

Our study has several limitations. Since the HR border based on the incidence of myocardial ischemia/infarction is around 100 beats/min[24,25], we defined tachycardia as HR >90 beats/min for 3 minutes so that myocardial ischemia could be prevented and the patients would be secured from other adverse cardiac events. Thus, tachycardia occurred 44% of patients studied in the current study; this incidence seems high. Reflex tachycardia is a common occurrence after normalization of BP in hypertensive patients treated with vasodilators[41], although the magnitude of reflex tachycardia seems to be lesser after nicardipine injection when compared with other vasodilators[42]. Hence, this seemingly high incidence of tachycardia is more likely due to reflex HR acceleration secondary to arterial vasodilatory effect induced by nicardipine injection for the treatment of hypertension in most patients (**Table 2**). Also, droperidol used during anesthesia induction may have caused reflex tachycardia in some patients, because of arteriolar dilatation due to its α-blocking action. The analgesic and hypnotic effects were provided by total fentanyl doses of approximately 300 μg, end-tidal sevoflurane concentration of 1% and 50% nitrous oxide, and were titrated primarily by the continuous vigilance of end-tidal CO_2, respiratory rate and hemodynamic variables. Thus, general anesthesia might have been inadequate in some patients, because the anesthetic depth was not assessed by BIS monitoring in any patients of the present study. However, no patients recalled any anesthetic and intraoperative events in the current study. Lastly, the number of patients in the control group was only 6, because these patients without apparent ischemic heart disease were allowed to receive saline instead of landiolol because of medical

and ethical reasons.

In conclusion, the prompt treatment of tachycardia seems appropriate for the older patients who are likely to have occult coronary artery disease. The use of landiolol may be suitable for the treatment of an abrupt tachycardia, particularly in the elderly patients undergoing total knee arthroplasty using tourniquet, although further study is needed to be performed.

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