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Efficacy of landiolol in attenuating hemodynamic responses to local epinephrine infiltration in patients undergoing vaginal total hysterectomy

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Abstract
Purpose. Local epinephrine infiltration often causes β_1-adrenoceptor-mediated tachycardia, hypertension, and arrhythmia. Landiolol, a short acting β_1-adrenoceptor blocker, may represent the most ideal agent to attenuate these adverse effects. In this study, we examined the effects of landiolol on the hemodynamic changes resulting from local infiltration of epinephrine.
Methods Thirty-six patients undergoing vaginal total hysterectomy under general anesthesia were randomly assigned to one of three groups: control group (n = 12), L5 group (n = 12), and L10 group (n = 12). In the control, L5, and L10 groups, the patients were given saline, landiolol 5 mg, and 10 mg, respectively, just before infiltration of epinephrine(1 : 300 000; total dose, about 100 μg) into the surgical field. Blood pressure and heart rate was assessed before and 5, 10, 15, 20, 25, 30 min after the initiation of epinephrine infiltration. If systolic blood pressure and heart rate exceeded 160 mmHg and 120 beats·min^{-1}, respectively, Ca blockers of either diltiazem 5 mg or nicardipine 1 mg and/or 2% sevoflurane were given.
Results Epinephrine infiltration significantly increased systolic blood pressure from 122 ± 15 to 170 ± 29 mmHg and heart rate from 63 ± 8 to 106 ± 10 beats·min^{-1}. In both the L5 and L10 groups, the increase in heart rate (from 69 ± 16 to 87 ± 16 beats·min^{-1}, $P < 0.01$, and from 70 ± 18 to 76 ± 9 beats·min^{-1}, $P < 0.01$, respectively) was significantly smaller compared to the control group, but the increase in systolic blood pressure was significantly attenuated in the L10 group (from 116 ± 18 to 140 ± 27 mmHg, $P < 0.01$). The number of patients given either Ca blockers or sevoflurane in the control group was significantly higher than that in the landiolol groups ($P < 0.01$).
Conclusion The present study suggests that landiolol 10 mg may be a more suitable dose than landiolol 5 mg to antagonize hyperdynamic states induced by local administration of epinephrine.

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Key words Epinephrine · Tachycardia · Hypertension · β-blocker

Although epinephrine infiltration is commonly used in vaginal total hysterectomy as a hemostatic agent, its application often causes hypertension, tachycardia, and arrhythmia [1]. It is also known that local epinephrine application sometimes induces potentially life-threatening arrhythmias [2–4]. As it has been reported that epinephrine-induced arrhythmia can be attenuated by β_1-blockers [5,6], the arrhythmic effects of epinephrine may be mediated, at least partly, via activation of β_1-adrenoceptors, although α_1-aderenoceptors have also been reported to be involved [7].

Landiolol, a novel short-acting β_1-adrenoceptor blocker, has recently become available for use in clinical practice. This agent is eightfold more selective for cardiac β_1-adrenoceptors (β_1/β_2 = 255) compared with esmolol [8], and its half-life of biological activity is about 3–4 min [8]. Low and colleagues showed that epinephrine locally administered into uterine cervical tissue was absorbed very rapidly (in less than 3 min) [9]. Thus, landiolol represents an ideal agent to attenuate or treat tachycardia and arrhythmia induced by local infiltration of epinephrine in patients undergoing vaginal total hysterectomy.

In the present study, we examined the effects of landiolol on the hemodynamic changes resulting from local infiltration of epinephrine in patients undergoing vaginal hysterectomy.

Methods

After approval of our open-label research protocol by the Kuroishi City Hospital ethical committee and with informed consent of the patients, 36 adult gynecologic

patients with uterine myoma undergoing elective vaginal total hysterectomy were randomly assigned to one of three groups: control group ($n = 12$), landiolol 5 mg group ($n = 12$), and landiolol 10 mg group ($n = 12$). Patients who were receiving antihypertensive or vasoactive agents were excluded from the study.

Diazepam 8–10 mg and roxatidine 75 mg were given orally as anesthetic premedication 90 min before the patient's arrival in the operating theater. After the patient's arrival in the operating theater, noninvasive monitoring of blood pressure, electrocardiogram, pulse oximetry, and end-tidal carbon dioxide was applied. Anesthesia was induced with propofol 1.0–1.2 mg·kg^{-1}, fentanyl 2 μg·kg^{-1}, and ketamine 0.4 mg·kg^{-1}. The trachea was intubated following muscle relaxation facilitated with vecuronium 0.1 mg·kg^{-1}. Anesthesia was maintained with propofol 6–8 mg·kg^{-1}·h^{-1}, and the infusion rate did not change during data collection. Fentanyl 5 μg·kg^{-1} was given preoperatively. Vecuronium was administered intermittently when required.

In the control and landiolol 5 and 10 mg groups, patients were given saline 2 ml or landiolol 5 or 10 mg in 2 ml saline, respectively, just before infiltration of epinephrine (1:300 000) into the surgical field. Blood pressure and heart rate was assessed before and 5, 10, 15, 20, 25, and 30 min after the start of epinephrine infiltration. If systolic blood pressure exceeded 160 mmHg with a heart rate less than 120 beats·min^{-1}, the patient was given nicardipine 1 mg and/or sevoflurane inhalation (2%). If the heart rate exceeded 120 beats·min^{-1} with or without a systolic pressure above 160 mmHg, the patient was given diltiazem 5 mg with or without sevoflurane inhalation (2%), respectively.

All data are expressed as means ± SD. Statistical analysis was by two-way repeated measures analysis of variance (ANOVA) followed by the Student-Newman-Keuls test using Sigma Sat for Windows (Jandel Scientific Software, Chicago, IL, USA) for intergroup comparison and one-way ANOVA or χ^2 test for between-group comparison as appropriate, with $P < 0.05$ considered significant.

Table 1. Demographic data[a]

Group	Age (yr)	Height (cm)	Weight (kg)	Total epinephrine (μg·kg^{-1})
Control	47 ± 4	153 ± 5	61 ± 10	1.78 ± 0.44
Landiolol 5 mg	53 ± 12	154 ± 4	61 ± 9	2.04 ± 0.73
Landiolol 10 mg	47 ± 7	156 ± 6	54 ± 8	2.34 ± 0.47

[a] Data are given as means ± SD. There are no significant differences between groups

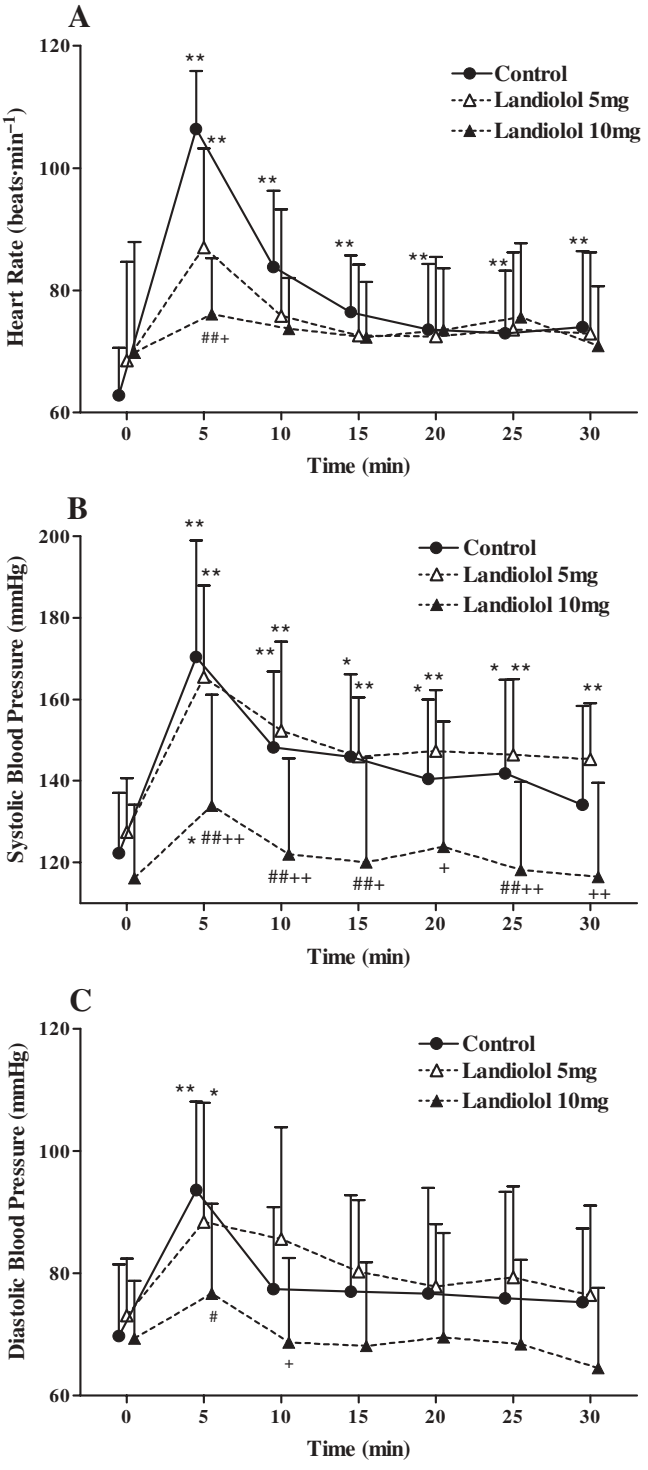

Fig. 1. Hemodynamic changes after epinephrine infiltration. **A** Heart rate. **B** Systolic blood pressure. **C** Diastolic blood pressure. *$P < 0.05$; **$P < 0.01$ vs time 0 min; $^{\#}P < 0.05$; $^{\#\#}P < 0.01$ vs control group; $^{+}P < 0.05$, $^{++}P < 0.01$ vs landiolol 5 mg group

Table 2. Numbers of rescue treatments

Group	No treatment	Nicardipine	Diltiazem	Sevoflurane
Control	0/12	2/12	4/12	10/12
Landiolol 5 mg	6/12*	3/12	3/12	2/12*
Landiolol 10 mg	9/12*	3/12	0/12	0/12*

* $P < 0.01$ vs Control

Results

The patient demographic data are shown in Table 1. There are no significant differences among the groups.

Epinephrine infiltration significantly increased blood pressure and heart rate. Both 5 and 10 mg of landiolol significantly antagonized epinephrine-increased heart rates, but the increase in blood pressure was significantly attenuated by only 10 mg of landiolol (Fig. 1).

The number of patients given either Ca blockers or sevoflurane in the control group was significantly higher than that in the landiolol groups (Table 2).

No arrhythmias were observed following epinephrine infiltration in any group.

Discussion

Epinephrine application often causes adverse reactions, such as hypertension, tachycardia, and arrhythmia [1–4]. In the present study, blood pressure and heart rate increased significantly after epinephrine infiltration in the control group. More importantly, although landiolol 5 mg attenuated only epinephrine-increased heart rates, landiolol 10 mg significantly did both hemodynamic variables. Epinephrine activates both α- and β-adrenoceptors to increase heart rate and blood pressure [10]. However, since 10 mg of landiolol, a β_1-blocker, significantly attenuated epinephrine-induced hypertension and tachycardia, the present data suggest that epinephrine-induced hyperdynamics may be mediated predominantly via β_1-adrenoceptors.

In the present study, landiolol 10 mg attenuated epinephrine-induced hyperdynamics more potently than landiolol 5 mg. Similarly, Kitamura et al. [8] studied the effects of 0.1, 0.25, and 0.5 $mg \cdot kg^{-1}$ of landiolol on tracheal intubation-induced tachycardia and hypertension, and found that 0.25 $mg \cdot kg^{-1}$ (about 12.5 mg) could be appropriate as 0.1 $mg \cdot kg^{-1}$ (about 5 mg) was insufficient to prevent hypertension, and 0.5 $mg \cdot kg^{-1}$ induced hypotension. In addition, although bolus administration of landiolol 5 mg was recommended for the treatment of tachyarrhythmia during anesthesia [11], Nishina et al. [12] suggested that 5 mg may be insufficient to attenuate tachycardia during manipulation of pheochromocytoma. It has been reported that increases in plasma epinephrine by manipulation of pheochromocytoma may be about 34- and 17-fold from baseline in patients undergoing transabdominal adrenalectomy and laparoscopic adrenalectomy, respectively [13]. In the present study, the increase in plasma epinephrine after infiltration of epinephrine (total dose about 100–120 μg) around the uterus would be similar to that by manipulation of pheochromocytoma as Low et al. [9] reported that plasma epinephrine concentration increased 18-fold from baseline after infiltration of epinephrine (total dose, 75 μg) into the cervix of the uterus in patients undergoing cervical cone biopsy. Therefore, landiolol 10 mg would be more suitable to prevent tachycardia and hypertension induced by local administration of epinephrine than landiolol 5 mg.

Although no arrhythmias were observed following epinephrine infiltration in the present study, the worst adverse reaction to epinephrine is a life-threatening arrhythmia [2–4]. In addition, since it has been reported that β_1-adrenoceptors may be involved in the mechanism of epinephrine-induced arrhythmia [5], β_1-blockers could be effective for such arrhythmias [6] if they occur. Moreover, Takahashi et al. [14] reported that landiolol increased the dysrhythmogenic dose of epinephrine in dogs during halothane anesthesia. Therefore, landiolol may be the best agent to prevent or treat arrhythmia induced by local infiltration of epinephrine.

In conclusion, landiolol may be one of the best agents to prevent or treat adverse reactions such as tachycardia and hypertension induced by local administration of epinephrine in patients undergoing vaginal total hysterectomy.

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