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ORIGINAL ARTICLE

Effects of landiolol on systemic and cerebral hemodynamics and recovery from anesthesia in patients undergoing craniotomy

Masahiko Kawaguchi · Yoshitaka Kawaraguchi · Yuri Yamamoto · Hironobu Hayashi · Ryuichi Abe · Satoki Inoue · Hiroyuki Nakase · Hitoshi Furuya

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Abstract
Purpose Maintenance of systemic and cerebral hemodynamics and quick recovery from anesthesia are required for craniotomy. We conducted a prospective randomized study to investigate the effects of continuous infusion of landiolol on hemodynamic responses to various stimuli, changes in systemic and cerebral hemodynamics during anesthesia, and recovery from anesthesia in patients undergoing craniotomy.
Methods Thirty patients undergoing elective craniotomy were randomly divided into two groups: a landiolol group and a control (saline) group. Landiolol was administered as an infusion rate of 0.125 mg/kg/min for 1 min, followed by an infusion at 0.01–0.04 mg/kg/min until 6 h after the end of anesthesia. Maximal values of heart rate (HR) and systolic blood pressure (SBP) in response to tracheal intubation, pin fixation, the beginning of operation, and extubation were compared between groups. Tissue oxygen index (TOI), mean arterial pressure (MAP), cardiac index (CI), and stroke volume index (SVI) before, during, and at the end of operation were compared between groups. Total doses of fentanyl, interval for the recovery from anesthesia, and incidence of postoperative nausea and vomiting (PONV) were also compared.
Results Maximal values of HR at intubation and pin fixation and of HR and SBP at extubation were significantly less in the landiolol group compared with those in the control group. TOI, MAP, CI, and SVI were similar between groups during anesthesia. Total doses of fentanyl were significantly less in the landiolol group than in the control group. Interval for recovery from anesthesia and incidence of PONV were similar between groups.
Conclusion This study indicates that continuous infusion of landiolol suppressed hyperdynamic responses to stimuli during anesthesia while maintaining arterial blood pressure and cerebral oxygen balance during craniotomy. Although landiolol infusion did not affect recovery from anesthesia and incidence of PONV, it reduced intraoperative requirement of fentanyl.

Keywords Beta blocker · Landiolol · Craniotomy · Near-infrared spectroscopy

M. Kawaguchi (✉) · Y. Kawaraguchi · Y. Yamamoto · H. Hayashi · R. Abe · S. Inoue · H. Furuya
Department of Anesthesiology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 623-8522, Japan
e-mail: drjkawa@naramed-u.ac.jp

H. Nakase
Department of Neurosurgery, Nara Medical University, Nara, Japan

Introduction

In patients undergoing craniotomy, maintenance of systemic and cerebral hemodynamics is essential. An increase in blood pressure in response to stimuli during anesthesia may increase intracranial pressure and/or occasionally induce intracranial hemorrhage [1]. Tachycardia, as well as an increase in blood pressure, in response to stimuli during anesthesia may also increase cardiac oxygen consumption and subsequently result in an increase of cardiac morbidity [2]. In contrast, a reduction in blood pressure may reduce cerebral blood flow and cerebral oxygen balance, which may aggravate cerebral injury. Furthermore, quick recovery from anesthesia is required to perform neurological assessment early after neurosurgical procedures [3]. For these purposes, adjunctive agents may be supplemented during anesthesia for craniotomy.

Landiolol, an ultra-short-acting, highly selective β-1 receptor antagonist, is being widely used in Japan. This drug is rapidly hydrolyzed to an inactive form by both carboxylesterase in the liver and pseudocholinesterase in plasma, leading to an elimination half-time of approximately 4 min. Landiolol has a higher cardioselectivity ($\beta1/\beta2 = 255$) than esmolol ($\beta1/\beta2 = 33$) and less suppressive effects on blood pressure compared with other β-blocking agents, so that it has been effectively and safely used for treating and preventing tachycardia in patients during general anesthesia [4–10]. Furthermore, recent evidence indicates that continuous infusion of landiolol reduces anesthetic requirement in surgical patients under general anesthesia [11].

We hypothesized that the use of landiolol during craniotomy may blunt the hemodynamic responses to stimuli without reducing blood pressure and cerebral oxygen balance and may reduce anesthetic requirements, resulting in a quicker recovery. This study was therefore conducted to evaluate the effects of continuous infusion of landiolol on hemodynamic responses to various stimuli, changes in systemic and cerebral hemodynamics under steady state conditions during anesthesia, and recovery from anesthesia.

Methods

After institutional approval and informed consent, 30 patients undergoing craniotomy were included in this study. Patients who had cardiac failure, severe bronchial asthma, diabetic ketoacidosis, bradycardia (<50 bpm), renal failure, severe liver failure, severe obesity (body mass index > 35 kg/m^2), immunocompromised, or who were pregnant were excluded. Patients were randomly allocated to one of two groups: the control (C) or landiolol (L) group using the envelope method. The envelope was to be opened before induction of anesthesia.

Patients had no premedication for anesthesia. Patients on antihypertensive drugs except angiotensin receptor blockers had them preoperatively. After recording of blood pressure, heart rate (HR), and oxygen saturation, continuous infusion of landiolol was started at a loading dose (0.125 mg/kg/min) for 1 min, followed by 0.04 mg/kg/min. In the C group, saline was administered. Five minutes after the commencement of landiolol or saline infusion, anesthesia was inducted with IV injection of 2 mg/kg of propofol, 2 μg/kg of fentanyl, 20 μg/kg of droperidol, and 0.15 mg/kg of vecuronium. Anesthesia was maintained with sevoflurane in 40% of oxygen and fentanyl. The concentration of sevoflurane was controlled to keep bispectral index (BIS, A-2000, Nihon Koden, Tokyo, Japan) between 40 and 60. A bolus of 2 μg/kg of fentanyl was administered before pinning for the stereotactic frame, and 1 μg/kg of fentanyl was injected additionally with an interval of at least 5 min when systolic blood pressure (SBP) was raised to >140 mmHg. Nicardipine was administered when blood pressure did not decrease regardless of fentanyl administration. After induction of anesthesia, the landiolol dosage was adjusted to 0.01–0.04 mg/kg/min to keep HR between 60 and 80 bpm (landiolol doses were fixed at 0.04 mg/kg/min from induction of anesthesia to tracheal intubation and from the end of the operation to tracheal extubation). In the L group, landiolol infusion was discontinued at 6 h after the end of anesthesia.

Routine monitoring for all patients included electrocardiogram, noninvasive arterial blood pressure, intra-arterial catheter for arterial blood pressure, pulse oximetry, end-tidal concentrations of carbon dioxide and sevoflurane, BIS, and a rectal temperature. Additionally, cardiac output (CO), cardiac index (CI), stroke volume (SV), and stroke volume index (SVI) were measured by FloTrac system (Edwards Lifesciences, Irvine, CA, USA). Tissue oxygen index (TOI) was also measured by the NIRO200 (Hamamatsu Photonics, Hamamatsu, Japan) at the opposite side to the operation. However, TOI data was only available after positioning of patients (no control data in awake).

In regard to emergence from anesthesia, intervals from discontinuation of sevoflurane to eyes opening and to tracheal extubation, and Aldrete score at 3, 10, and 30 min after the tracheal extubation, were evaluated [12]. The patients were considered to have normal recovery scores (Aldrete score ≥ 9) when able to move extremities spontaneously or on command, to breathe and cough, having systolic arterial pressure values within 20 mmHg of preanesthetic levels, alert or arousable to quiet voice, and able to maintain saturation of peripheral oxygen (SpO_2) >90% with supplementary O_2 administration through a face mask. Regarding wound pain, visual analog scale (VAS) at 30 min and 2 h after tracheal extubation and the following morning, and necessity of administration of analgesic drug (flurbiprofen) until 24 h after the operation, were assessed. The incidence of postoperative nausea and vomiting (PONV) until 24 h after operation was also evaluated. The presence of PONV was defined as at least one episode of nausea or vomiting or retching, or any combination of these emetic symptoms.

The primary endpoint was hemodynamic response to various stimuli during anesthesia, and events for stimuli, tracheal intubation, pin fixation, the beginning of operation, and extubation were included. At each event, maximal values for systolic and diastolic blood pressure and HR were evaluated. The secondary endpoints were systemic and cerebral hemodynamics under steady state conditions, requirement of anesthetic agents, intervals for recovery,

Table 1 Demographic variables

	Group C (control) ($n = 15$)	Group L (landiolol) ($n = 15$)	P value
Age (years)	59 ± 8	60 ± 10	0.7791
Sex (F/M)	6/9	8/7	0.4642
Height (cm)	162 ± 7	159 ± 7	0.1742
Weight (kg)	60 ± 9	58 ± 9	0.5313
Hypertension (yes)	6 (40%)	7 (47%)	0.7125
Diabetes (yes)	2 (13%)	0 (0%)	0.1432
Hyperlipidemia (yes)	5 (33%)	4 (27%)	0.903
Supra/infratentorial	14/1	14/1	>0.9999
Disease			
Brain tumor	8	9	0.6167
Aneurysm	6	6	
AVM	1	0	

Data are expressed as mean ± standard deviation or number (%)

AVM arteriovenous malformation

and incidence of PONV. As systemic and cerebral hemodynamics under steady sate conditions, TOI, mean arterial pressure (MAP), and CO, CI, SV, SVI 10 min before the beginning of operation, at the time of clipping, or removal of lesion under microscopy and 10 min before the end of operation were compared between groups.

Statistical analysis

Sample sizes were determined based on data in our previous and preliminary studies. We assumed it was clinically important if an increase in HR and SBP in response to stimuli were reduced by 15%. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.8, 15 patients were required for each comparison. Parametric data are expressed as mean ± standard deviation (SD), and nonparametric data are expressed as median (25th–75th). Unpaired t test or Mann–Whitney U test was used for between-group comparisons. Categorical data were compared using Fisher's exact test. Systemic and cerebral hemodynamic data were evaluated using the two-way analysis of variance with repeated measures, followed by Fisher's least significant difference (LSD) post hoc test. P values <0.05 are considered statistically significant.

Results

Patient's demographic variables of the patients are shown in Table 1. There were no statistically significant differences in demographic variables between groups. Table 2 shows intraoperative variables. There were no statistically significant differences in operation and anesthesia time; end-tidal concentration of sevoflurane; BIS values; total amount of infusion; total blood loss; urinary output; durations of bradycardia (HR < 50 bpm) and hypotension (SBP < 90 mmHg); total doses of ephedrine, nicardipine, and methoxamine; and intervals from the end of operation to eye opening and extubation between groups. Total doses of fentanyl were significantly less in the L group compared with those in the C group. A bolus of landiolol was administered in five patients in the C group. Total doses of landiolol were significantly higher in the L group compared with those in the C group.

Table 3 shows maximal values of SBP, diastolic blood pressure (DBP), and HR before anesthesia and immediately after intubation, pin fixation, beginning of operation, and extubation. Before anesthesia, values of SBP, DBP, and HR were similar between groups. SBP values immediately after extubation were significantly lower in the L group compared with those in the C group, whereas SBP at the other time points were similar between groups. DBP values at all time points were similar between groups. HR values immediately after intubation, pin fixation, and extubation were significantly lower in the L group compared with those in the group, whereas HR values immediately after beginning of operation were similar between groups.

Figure 1 shows the values of TOI, MAP, CI, and SVI 10 min before the beginning of operation, at the time of clipping or removal of lesion under microscopy, and 10 min before the end of operation. There were no statistical differences in values of TOI, MAP, CI, and SVI between groups. At the same time points, there were no statistical differences in values of SBP, DBP, HR, CO, SV, and temperature (data are not shown). Table 4 shows blood gas data before and at the end of operation. There were no statistically significant differences in values of pH, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), partial pressure of oxygen in arterial blood (PaO_2), arterial oxygen saturation (SaO_2), and hemoglobin between groups.

Table 2 Intraoperative variables

	Group C (control) ($n = 15$)	Group L (landiolol) ($n = 15$)	P value
Operation time (min)	251 ± 108	228 ± 82	0.5170
Anesthesia time (min)	331 ± 126	309 ± 83	0.5670
Total doses of fentanyl (μg)	613 ± 155	393 ± 78	<0.0001
End-tidal sevoflurane (%)	1.5 ± 0.1	1.4 ± 0.1	0.2067
Bispectral index value	44 ± 7	45 ± 6	0.6735
Total amount of infusion (ml)	2379 ± 546	2022 ± 434	0.0575
Total blood loss (ml)	196 ± 176	210 ± 167	0.7642
Urinary output (ml)	1042 ± 449	985 ± 580	0.7642
Infusion rates of landiolol (μg/kg/min)	0 ± 0	14 ± 5	<0.0001
Total doses of landiolol (mg)	5 ± 9	446 ± 159	<0.001
Duration of HR < 50 bpm	15 ± 20	17 ± 20	0.7203
Duration of SBP < 90 mmHg	41 ± 50	61 ± 51	0.2956
Use of ephedrine (yes)	13 (87%)	13 (87%)	>0.9999
Total doses of ephedrine (mg)	9 ± 8	13 ± 9	0.3144
Use of nicardipine (yes)	9 (60%)	6 (40%)	0.2733
Total doses of nicardipine (mg)	1.3 ± 1.8	0.7 ± 1.1	0.5428
Use of methoxamine (yes)	2 (13%)	1 (7%)	0.5428
Total doses of methoxamine (mg)	0.7 ± 2.1	0.1 ± 0.3	0.2799
Interval from the end of operation			
To eye opening (min)	7.9 ± 2.0	8.5 ± 2.5	0.5257
To extubation (min)	9.5 ± 1.8	10.1 ± 3.9	0.5550

Data are expressed as mean ± standard deviation or number (%). A bolus of landiolol was administered in five patients in the C group

HR heart rate, *SBP* systolic blood pressure

Table 3 Hemodynamic responses to stimulus during anesthesia

	Group C (control) ($n = 15$)	Group L (landiolol) ($n = 15$)	P value
Systolic blood pressure			
Before anesthesia	150 ± 19	148 ± 19	0.8235
Immediately after intubation	141 ± 32	128 ± 26	0.2132
Immediately after pin fixation	115 ± 26	115 ± 28	0.9734
Immediately after beginning of op.	97 ± 16	90 ± 14	0.2354
Immediately after extubation	169 ± 22	144 ± 20	0.0028
Diastolic blood pressure			
Before anesthesia	85 ± 10	85 ± 11	0.9156
Immediately after intubation	87 ± 22	82 ± 19	0.5790
Immediately after pin fixation	68 ± 17	68 ± 19	>0.9999
Immediately after beginning of op.	51 ± 10	50 ± 9	0.7008
Immediately after extubation	57 ± 11	56 ± 7	0.7354
Heart rate			
Before anesthesia	70 ± 14	72 ± 11	0.7188
Immediately after intubation	96 ± 25	73 ± 10	0.0029
Immediately after pin fixation	74 ± 20	62 ± 12	0.0484
Immediately after beginning of op.	57 ± 11	56 ± 7	0.7354
Immediately after extubation	105 ± 15	85 ± 15	0.0012

Data are expressed as mean ± standard deviation. Maximal value was selected at each time point

Op. operation

Table 5 shows postoperative data. Aldrete score 3, 10, and 30 min after extubation, VAS scores 30 min and 2 h after the extubation, percentage of patients who required analgesic drugs until 2 and 24 h, and incidence of PONV until 24 h were similar between groups.

Discussion

The results in this study show that a continuous infusion of landiolol attenuated the increase in HR immediately after intubation and pin fixation and the increase in both HR and

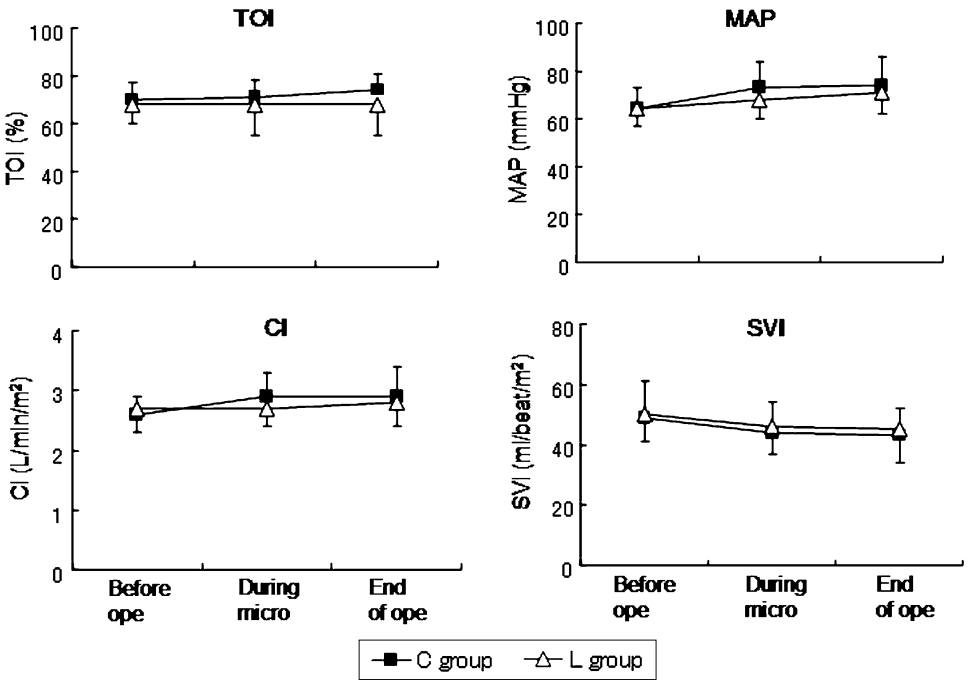

Fig. 1 Values of tissue oxygen index (TOI), mean arterial pressure (MAP), cardiac index (CI), and stroke volume index (SVI) 10 min before the beginning of operation (*before ope*), at the time of clipping or removal of lesion under microscopy (*during micro*), and 10 min before the end of operation (*end of ope*). There were no statistical differences in values of TOI, MAP, CI, and SVI between groups

Table 4 Blood gas data

	Group C (control) ($n = 15$)	Group L (landiolol) ($n = 15$)	*P* value
pH			
Before operation	7.42 ± 0.04	7.42 ± 0.02	0.5933
At the end of operation	7.45 ± 0.02	7.42 ± 0.04	0.0533
$PaCO_2$ (mmHg)			
Before operation	40 ± 5	39 ± 3	0.8356
At the end of operation	37 ± 4	39 ± 3	0.0862
PaO_2 (mmHg)			
Before operation	162 ± 33	149 ± 40	0.3289
At the end of operation	172 ± 28	172 ± 23	0.9604
SaO_2 (mmHg)			
Before operation	99 ± 1	99 ± 1	0.4705
At the end of operation	99 ± 1	100 ± 0.3	0.4974
Hemoglobin (g/dl)			
Before operation	12 ± 1	12 ± 1	0.9015
At the end of operation	11 ± 1	11 ± 1	0.9243

Data are expressed as mean ± standard deviation

$PaCO_2$ and *PaO_2* arterial partial pressure carbon dioxide and oxygen, respectively. *SaO_2* arterial oxygen saturation

SBP immediately after extubation, whereas TOI, MAP, CI, and SVI remained unchanged under steady state conditions in patients undergoing craniotomy. Although an infusion of landiolol did not affect the interval and quality of recovery from anesthesia, degree of postoperative pain, or incidence of PONV, it significantly reduced intraoperative requirement of fentanyl.

Landiolol has been shown to suppress hyperdynamic responses during laryngoscopy, tracheal intubation, emergence from anesthesia, and tracheal extubation [13–17]. Recently published meta-analysis involving seven randomized controlled trials with 325 patients demonstrated that landiolol administration at 0.125 mg/kg/min for 1 min following by 0.04 mg/kg/min effectively suppressed the increases in HR and BP following laryngoscopy and tracheal intubation [17]. HR weighted mean difference was −21.18 bpm with a 95% confident interval (CI) of −18.59 to −14.20, whereas SBP weighted mean difference was −16.26 mmHg with a 95% CI of −23.03 to −8.55. These results may contradict those in our study, in which HR but not SBP was attenuated by an infusion of landiolol during laryngoscopy and tracheal intubation. Reasons for the

Table 5 Postoperative data

	Group C (control) ($n = 15$)	Group L (landiolol) ($n = 15$)	P value
Aldrete score			
3 min after extubation	9 [9–10]	9 [9–10]	0.1985
10 min after extubation	10 [10–10]	10 [10–10]	0.1466
30 min after extubation	10 [10–10]	10 [10–10]	0.7557
Visual analog scale (VAS)			
2 h after extubation	20 [20–30]	20 [4–31]	0.6482
Next morning	15 [12–40]	19 [15–26]	0.9339
Use of analgesics			
Until 2 h	5 (33%)	4 (27%)	0.6903
Until 24 h	10 (67%)	9 (60%)	0.7046
PONV			
Until 24 h	6 (40%)	6 (40%)	>0.9999

Data are expressed as median [25th–75th], mean ± standard deviation, or number (%)

PONV Postoperative nausea and vomiting

contradictory results are unknown. However, the methodology we used might have affected the results. In our study, we only compared the maximal values immediately after intubation, but not percentage changes, between groups. In addition, fentanyl and droperidol were administered during the induction of anesthesia. These drugs might have blunted an increase in blood pressure after intubation, although SBP values tended to be higher in the C group than in the L group.

Regarding the effects of landiolol on hemodynamics during emergence from anesthesia and tracheal extubation, Shirasaka et al. [18] reported that continuous administration of landiolol at 0.03 or 0.04 mg/kg/min significantly attenuated an increase in HR but not MAP. Miyazaki et al. [19] demonstrated that landiolol infusion at 0.04 mg/kg/min partially prevented the increase in SBP and completely prevented the increase in HR associated with emergence from anesthesia in elderly patients with hypertension, whereas it brought a decrease in HR in elderly patients without hypertension. In our study, continuous infusion of landiolol significantly attenuated the increase in both HR and SBP during emergence from anesthesia and extubation in patients undergoing craniotomy. As the increases in HR and SBP are most marked during emergence from anesthesia and extubation in patients undergoing craniotomy, continuous infusion of landiolol may provide the greatest benefit during emergence from anesthesia and extubation. By suppressing the hyperdynamic response, an increase in intracranial pressure and development of intracranial hemorrhage may be prevented, although its efficacy remained undetermined.

Maintenance of cerebral perfusion pressure and cerebral blood flow is crucial to prevent cerebral injury during craniotomy. Because cerebral autoregulation can be disturbed in patients with intracranial lesions, reduction in blood pressure may reduce cerebral blood flow and subsequently worsen the cerebral injury during craniotomy. Most studies indicated that landiolol induced a significant HR reduction without reduction in arterial blood pressure and had less suppressive effects on blood pressure compared with another selective β1-blocker, esmolol [7–9.20]. Our results in patients undergoing craniotomy were consistent with those in the previous studies. Continuous infusion of landiolol did not reduce blood pressure under steady state conditions during anesthesia, although it attenuated the increase in SBP during emergence from anesthesia and extubation. In addition, we found that landiolol infusion did not affect TOI values during anesthesia, suggesting that cerebral oxygen balance may be maintained as long as blood pressure is maintained during craniotomy. However, as we did not measure cerebral blood flow, further study is required to clarify the effects of landiolol on cerebral blood flow and metabolism.

Several reports address the effects of landiolol on requirements of anesthetic agents. Tanabe et al. [11] reported that a low dose of landiolol significantly reduced intraoperative sevoflurane requirement during sevoflurane/N_2O/fentanyl anesthesia in patients undergoing hip surgery. In contrast, Kurita et al. [21] demonstrated that landiolol did not alter the minimum alveolar anesthetic concentration of isoflurane in a swine model. Recently published randomized trial in patients with subarachnoid hemorrhage indicated that intraoperative requirement of fentanyl was significantly less in patients with landiolol infusion compared with those without landiolol [20]. In our study, intraoperative requirement of fentanyl was significantly less in the L group compared with that in the C group, whereas the requirement of sevoflurane was similar among groups. Mechanisms in which landiolol infusion significantly attenuated the requirement of fentanyl are unknown. An antinociceptive effect by landiolol or hemodynamic stability to noxious stimuli in the landiolol

group might have affected the usage of fentanyl by anesthesiologists. Further studies would be required to clarify the mechanisms responsible for the analgesic-sparing effect of landiolol. Although the requirement of fentanyl was reduced in the landiolol group, the interval for recovery from anesthesia, pain score, and incidence of PONV were not affected. This suggests that the efficacy of landiolol infusion during the recovery phase after extubation may be limited in patients undergoing craniotomy.

There are several limitations to merit comments in this study. First, the dose of landiolol was fixed at 0.04 mg/kg/min during intubation and extubation and was adjusted between 0.01–0.04 mg/kg/min during other periods. Higher doses of landiolol might have more suppressive effects on blood pressure. Second, anesthesia was maintained with sevoflurane and fentanyl; results may be different with different anesthetic regimes. Third, patients with impaired cardiac function were not; therefore, it is unclear whether landiolol can be safely administered without severe hypotension and impaired cerebral oxygen balance in such patients. Finally, cerebral oxygen balance was evaluated with TOI without control data in the awake state. If different methodologies, including jugular bulb venous saturation and other types of cerebral oximetry were used to assess cerebral oxygen balance, the results might be different. Further studies with more patients are required to clarify whether landiolol can be safely administered in patients undergoing craniotomy.

In conclusion, we investigated the effects of continuous infusion of landiolol on hemodynamic responses to various stimuli during anesthesia, changes in systemic and cerebral hemodynamics under steady state conditions, and recovery from anesthesia. Results indicated that continuous infusion of landiolol significantly suppressed an increase in HR in response to intubation and pin fixation and an increase in both HR and SBP in response to extubation, whereas it did not affect cardiac index, TOI, and the incidence of intraoperative hypotension during steady state conditions of anesthesia. Although the use of landiolol did not affect postoperative courses—including the time and quality of recovery, VAS, and the incidence of PONV—it significantly reduced intraoperative requirement of fentanyl. This suggests that continuous infusion of landiolol may be safely used without a detrimental effect on cerebral hemodynamics in patients undergoing elective craniotomy, although its influences on postoperative courses were limited. In particular, in patients in whom prevention of tachycardia is preferable to avoid perioperative cardiac morbidity, landiolol can be one candidate for use as an adjunctive agent to stabilize hemodynamic responses during anesthesia.

References

1. Basali A, Masche EJ, Kalfas I, Schbert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. Anesthesiology. 2000;93:48–54.
2. Slogoff S, Keats AS. Myocardial ischemia revisited. Anesthesiology. 2006;105:214–6.
3. Bruder NJ. Awakening management after neurosurgery for intracranial tumours. Curr Opin Anaesthesiol. 2002;15:477–82.
4. Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, Sakaki K, Hachiya K, Ichioka Y. Kawamura M: Development of a highly cardioselective ultra short-acting betablocker, ONO-1101. Chem Pharm Bull (Tokyo). 1992;40: 1462–9.
5. Muraki K, Nakagawa H, Nagano N, Henmi S, Kawasumi H, Nakahashi T, Imamizumi K, Tokuno T, Atsuki K, Imaizumi Y, Watanabe M. Effects of ONO-1101, a novel beta-antagonist, on action potential and membrane currents in cardiac muscle. J Pharmacol Exp Ther. 1996;278:555–63.
6. Sugiyama A, Takahara A, Hashimoto K. Electrophysiologic, cardiohemodynamic and beta-blocking actions of a new ultra-short-acting beta-blocker, ONO-1101, assessed by the in vivo canine model in comparison with esmolol. J Cardiovasc Pharmacol. 1999;34:70–7.
7. Harasawa R, Hayashi Y, Iwasaki M, Kamibayashi T, Mashimo T. Bolus administration of landiolol, a short-acting, selective beta1-blocker, to treat tachycardia during anesthesia: a dose-dependent study. J Cardiothorac Vasc Anesth. 2006;20(6):793–5.
8. Yamazaki A, Kinoshita H, Shimogai M, Fujii K, Nakahata K, Hironaka Y, Iranami H, Hatano Y. Landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure. Can J Anaesth. 2005;52(3):254–7.
9. Yoshida Y, Terajima K, Sato C, Akada S, Miyagi Y, Hongo T, Takeda T, Tanaka K, Sakamoto A. Clinical role and efficacy of landiolol in the intensive care unit. J Anesth. 2008;22:64–9.
10. Goto K, Shingu C, Miyamoto S, Miyakawa H, Noguchi T. The effect of landiolol on hemodynamics and left ventricular function in patients with coronary artery disease. J Clin Anesth. 2007;19(7):523–9.
11. Tanabe T, Fukusaki M, Fujinaga A, Ando Y, Yamashita K, Terao Y, Sumikawa K. Landiolol, a new ultra-short-acting beta1-blocker, reduces anaesthetic requirement during sevoflurane/N(2)O/fentanyl anaesthesia in surgical patients. Eur J Anaesthesiol. 2009;26(1):39–42.
12. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg. 1970;49:924–34.
13. Hasuo H, Tomiyasu S, Hojo M, Fujigaki T, Fukusaki M, Sumikawa K. Effect of ONO-1101, a novel short-acting β-blocker on hemodynamic response to isoflurane inhalation and tracheal intubation. J Anesth. 1998;12:115–8.
14. Kawaguchi M, Takamatsu I, Masui K, Kazama T. Effect of landiolol on bispectral index and spectral entropy responses to tracheal intubation during propofol anaesthesia. Br J Anaesth. 2008;101:273–8.
15. Goyagi T, Tanaka M, Nishikawa T. Landiolol attenuates the cardiovascular response to tracheal intubation. J Anesth. 2005;19:282–6.
16. Oda Y, Nishikawa K, Hase I, Asada A. The short-acting β1-adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. Anesth Analg. 2005;100:733–7.
17. Inoue S, Tanaka Y, Kawaguchi M, Furuya H. The efficacy of landiolol for suppressing the hyperdynamic response following laryngoscopy and tracheal intubation: a systemic review. Anaesth Intensive Care. 2009;37:893–902.

18. Shirasaka T, Iwasaki T, Hosokawa N, Komatsu M, Kasaba T, Takasaki M. Effects of landiolol on the cardiovascular response during tracheal extubation. J Anesth. 2008;22:322–5.
19. Miyazaki M, Kadoi Y, Saito S. Effects of landiolol, a short-acting beta-1 blocker, on hemodynamic variables during emergence from anesthesia and tracheal extubation in elderly patients with and without hypertension. J Anesth. 2009;23:483–8.
20. Kawaguchi M, Utada K, Yoshitani K, Uchino H, Takeda Y, Masui K, Sakabe T. Effects of a short-acting β1 receptor antagonist landiolol on hemodynamics and tissue injury markers in patients with subarachnoid hemorrhage undergoing intracranial aneurysm surgery. J Neurosurg Anesthesiol. 2010;22:21–31.
21. Kurita T, Takata K, Uraoka M, Morita K, Sato S. Landiolol, an ultra short-acting beta1-adrenoceptor antagonist, does not alter the minimum alveolar anesthetic concentration of isoflurane in a swine model. Anesth Analg. 2007;105(3):656–60.