Effects of discontinuing angiotensin receptor blockers on perioperative hypotension in patients undergoing laparoscopic cholecystectomy

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Continuing angiotensin receptor blockers (ARBs) until the day of surgery remains controversial because of the risk of intraoperative hypotension. This study was aimed at evaluating the perioperative hemodynamic changes and postoperative complications associated with continuation or discontinuation of ARBs in patients undergoing laparoscopic cholecystectomy. A total of 283 patients with antihypertensive medication, including ARBs, were enrolled in this retrospective study. On the day of surgery, ARBs were continued in some patients (continuation group, n=111) and discontinued in other patients (discontinuation group, n=172). On the basis of the patients' electronic medical records, hemodynamic values (systolic blood pressure, mean arterial pressure, and heart rate) were compared before anesthesia (baseline), at 10 min after induction (post-induction), and on arrival at the post-anesthesia care unit (post-anesthesia). Vasoactive drug use, postoperative complications, and length of hospital stay were compared. The blood pressures and heart rates at baseline and post-induction were not significantly different between the groups. The number of patients who required ephedrine to correct intraoperative hypotension was significantly higher in the continuation group than in the discontinuation group (27.9% vs. 14.5%, $p=0.009$). The systolic blood pressure at post-anesthesia was significantly higher in the discontinuation group (159.9 ± 21.7 vs. 146.4 ± 20.9 , $p<0.001$). The postoperative complications and length of hospital stay were similar. Discontinuing ARBs may reduce the incidence of intraoperative hypotension requiring pharmacological intervention in patients undergoing laparoscopic cholecystectomy; however, possible occurrence of postoperative hypertension should be considered.

Keywords: Angiotensin receptor blockers; Antihypertensive agents; Laparoscopic cholecystectomy; Preoperative period; Renin-angiotensin system

INTRODUCTION

The renin-angiotensin-aldosterone system is responsible for regulating blood pressure levels and, as such, is an important target for the treatment of essential hypertension [1]. Nowadays, angiotensin receptor blockers (ARBs) are

used as first-line antihypertensive agents for patients with renal impairment, coronary disease, heart failure, or diabetes mellitus [2,3]. ARBs are also recommended as part of the anti-hypertensive regimen for poorly controlled hypertension with single-agent therapy [4].

Despite the wide use of ARBs, whether to continue or

discontinue these antihypertensive agents on the day of surgery remains controversial. Some clinicians discontinue ARBs before surgery because intraoperative hypotension followed by continuation of ARBs may be associated with major perioperative morbidity such as vascular events [5]. Conversely, other clinicians believe that continuation of ARBs may lower risks of perioperative mortality, morbidity, and complications (e.g., hypotension, cerebrovascular complications, and renal failure) [6,7]. Although numerous studies have investigated the potential advantage or disadvantage associated with continuation or discontinuation of ARBs in the perioperative period, the controversy is still unsolved. Even the well-known perioperative guidelines vary in the recommendations made regarding perioperative continuation or discontinuation of ARBs.

Laparoscopic surgery in reverse Trendelenburg position may result in significant intraoperative hemodynamic changes [8]. The combined effect of anesthesia, head-up tilt, and pneumoperitoneum may impair venous return and reduce cardiac output by up to 50%. At the same time, pneumoperitoneum using carbon dioxide increases systemic vascular resistance. This could be greater than the reduction in cardiac output, maintaining or even increasing systemic blood pressure. This complexed cardiovascular change may be affected by antihypertensive agents, especially ARBs. However, the effect of continuing or discontinuing ARBs on the hemodynamic changes in laparoscopic surgery in reverse Trendelenburg position has not been studied extensively.

This retrospective study was aimed at evaluating the hemodynamic changes and postoperative complications associated with continuation or discontinuation of ARBs in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

This study was approved by the institutional review board of our hospital, and informed consent was waived for the medical record review study. We selected the electronic medical records of patients who underwent elective laparoscopic cholecystectomy between May 1, 2010, and December 31, 2015. Adult patients (American Society of Anesthesiologists physical status II and III) with primary hypertension treated with pharmacological regimens, including ARBs,

were enrolled in this study. The exclusion criteria were as follows: unstable blood pressure in the preoperative period (systolic blood pressure [SBP] of <60 or >180 mmHg), prolonged or complicated surgery such as conversion to open cholecystectomy, severe anxiety before induction of anesthesia, massive intraoperative bleeding (>150 ml in 1 min), difficult airway (laryngoscopy grades III and IV), enrolment in other clinical trials at the time of surgery, and physical unfitness for the trial.

From the electronic medical records of the enrolled patients, we investigated the demographic characteristics; underlying disease; current medication, including antihypertensive regimen; postoperative complications; and length of hospital stay. Perioperative blood pressure and heart rate (HR) for every 5 min were extracted from the anesthesia and the post-anesthesia care unit (PACU) records.

For all the enrolled patients, general anesthesia was induced with propofol (1–2 mg/kg) and rocuronium (0.6–0.8 mg/kg), and subsequently maintained with desflurane, sevoflurane, or propofol. Remifentanyl was infused continuously during anesthesia. In accordance with our routine clinical practice, intraoperative hypotension (mean arterial pressure [MAP] of <60 mmHg) was treated with intravenous bolus of ephedrine 4–8 mg or intravenous fluid loading in most cases. Intraoperative hypertension (MAP of >100 mmHg) was treated with intravenous bolus of nicardipine 0.5–1 mg generally or esmolol 20–40 mg when combined with tachycardia. Vasoactive drug use and the amount of total intravenous fluid administered during anesthesia were also investigated.

All the enrolled patients were given ARBs until the day before surgery on the basis of the inclusion/exclusion criteria. On the day of surgery, however, some patients continued their ARB medication, while the others discontinued their ARB medication per the preference of the attending anesthesiologist. The patients were divided into continuation and discontinuation groups according to this difference. The SBP, MAP, and HR on arrival at the operating room (preoperative baseline), at 10 min after induction (post-induction time point), and on arrival at the PACU (post-anesthesia time point) were compared between the groups. The relative changes from baseline SBP, MAP, and HR at post-induction and post-anesthesia were also compared between the groups. In addition, vasoactive drug use,

amount of total intravenous fluid administered, and length of hospital stay were compared.

The Student *t* test was used for normally distributed continuous variables (e.g., hemodynamic variables), and the chi-square or Fisher exact test was used for categorical variables (e.g., vasoactive drug use). Data from each case were transferred into an Excel table (Microsoft Excel 2010; Microsoft Corp., Redmond, WA, USA), and statistical analyses were performed using SPSS (18.0; SPSS Inc., Chicago, IL, USA).

Table 1. Demographic data

	Continuation group (n=111)	Discontinuation group (n=172)	p value
Age (y)	62.7±11.3	64.5±11.7	0.192
BMI (kg/m ²)	24.8±3.1	25.0±3.6	0.642
Sex (male/female)	49/62	97/75	0.051
ASA physical status (II/III)	107/4	161/11	0.418
Underlying disease			
NSTEMI/UAP	7 (6.3%)	10 (5.8%)	0.865
Diabetes	28 (25.2%)	43 (25%)	0.966
Concurrent medication			
Beta blocker	13 (11.7%)	13 (7.6%)	0.293
Calcium channel blocker	49 (44.1%)	82 (47.7%)	0.626
Thiazide	38 (34.2%)	51 (29.7%)	0.434

Values are presented as mean±standard deviation or number only or number of patients (percentage). BMI: body mass index, ASA: American Society of Anesthesiologists, NSTEMI/UAP: non-ST-segment elevation myocardial infarction/unstable angina pectoris.

RESULTS

The study population consisted of 283 patients (111 in the continuation group and 172 in the discontinuation group, Fig. 1). The demographic characteristics of the two study groups are shown in Table 1. No significant differences were found in underlying diseases and concurrent antihypertensive medication.

Compared with the discontinuation group, preoperative

Table 2. Comparison of blood pressure and heart rate on arrival at the operating room (baseline), at 10 min after induction (post-induction), and on arrival at the post-anesthesia care unit (post-anesthesia)

	Continuation group (n=111)	Discontinuation group (n=172)	p value
Systolic blood pressure (mmHg)			
Baseline	141.4±24.4	146.6±20.6	0.065
Post-induction	113.0±21.4	110.8±21.7	0.324
Post-anesthesia	146.4±20.9	159.9±21.7 ^a	<0.001
Mean arterial pressure (mmHg)			
Baseline	99.6±15.0	102.3±11.9	0.110
Post-induction	79.0±15.4	78.1±15.2	0.529
Post-anesthesia	107.7±14.8	111.9±16.9 ^a	0.032
Heart rate (beats/min)			
Baseline	71.7±13.3	70.3±12.3	0.607
Post-induction	66.1±12.9	63.4±12.2	0.123
Post-anesthesia	84.7±12.9	82.2±13.8	0.109

Values are presented as mean±standard deviation. ^aStatistically significant (p<0.05)

Fig. 1. Flowchart of the inclusion of patients in the retrospective analysis. ARB, angiotensin receptor blocker.

SBP was lower in the continuation group, but the difference was not significant ($p=0.065$; Table 2). Preoperative MAP and HR were similar between the groups. After induction of anesthesia, SBP, MAP, and HR decreased in most patients, and the values were not significantly different between the groups at 10 min after induction (post-induction). On arrival at the PACU (post-anesthesia), significantly higher SBP and MAP were observed in the discontinuation group than in the continuation group ($p<0.001$ for SBP and $p=0.032$ for MAP).

In comparison with the preoperative value (baseline), the relative decreases at post-induction were not significantly different between the continuation and discontinuation groups (-19.6% vs. -22.7% for SBP, -19.9% vs. -23.3% for MAP, and -6.6% vs. -8.6% for HR; Fig. 2). The relative increases at post-anesthesia were not also significantly different between the groups (5.8% vs. 9.9% for SBP, 10.0% vs. 10.4% for MAP, and 20.9% vs. 18.1% for HR).

The number of patients who required ephedrine to correct intraoperative hypotension was significantly higher in the continuation group than in the discontinuation group (Table 3). In three patients in the continuation group, the cumulative ephedrine dose exceeded 10 mg (12, 16, and 20 mg). One of the patients needed dopamine infusion for hypotension, which was not corrected with ephedrine. None of the patients in the discontinuation group required >10 mg of ephedrine or other vasopressors. Intraoperative use of nicardipine/esmolol required to correct hypertension or tachycardia was similar in both groups. The amount of

intraoperative fluid administered was also similar between the continuation and discontinuation groups (811 ± 326 mL vs. 842 ± 507 mL, $p=0.568$).

No severe complication required intensive care or was related to the hospital mortality that occurred in both groups. In the continuation group, one patient with a history of coronary artery bypass graft complained of chest pain after surgery; however, no abnormal findings were detected on echocardiography, and the symptom resolved spontaneously. In the discontinuation group, pulmonary thromboembolism was diagnosed in one patient after surgery and treated appropriately without any complication. The other patient in the discontinuation group showed persistent postoperative hypotension, which was corrected by adjusting the doses of the beta-blocker and thiazide in the ward. No significant difference in the length of postoperative hospital stay as found between the continuation and discontinuation groups (3.25 d vs. 3.26 d, $p=0.972$).

Table 3. Intraoperative use of intravenous vasoactive drugs

	Continuation group (n=111)	Discontinuation group (n=172)	p value
Vasopressor			
Ephedrine	31 (27.9%) ^a	25 (14.5%)	0.009
Antihypertensive drug			
Nicardipine	16 (14.4%)	19 (11.0%)	0.461
Esmolol	9 (8.1%)	7 (4.1%)	0.189

Values are presented as number of patients (percentage). ^aStatistically significant ($p<0.05$)

Fig. 2. Relative changes in (A) SBP, (B) MAP, and (C) HR from baseline to post-induction and post-anesthesia in the continuation (n=111) and discontinuation groups (n=172) groups. Values were measured on arrival at the operating room (baseline), at 10 min after induction (post-induction), and on arrival at the post-anesthesia care unit (post-anesthesia). No significant differences were found between groups in all the comparisons ($p<0.05$). SBP: systolic blood pressure, MAP: mean arterial pressure, HR: heart rate.

DISCUSSION

In the present retrospective study, blood pressure and HR before induction or at 10 min after induction were not significantly different between the patients who continued or discontinued taking ARBs on the day of surgery. However, intraoperative use of vasopressor was more frequent in the patients who continued using ARBs. On arrival at the PACU, blood pressure was significantly higher in the patients who discontinued using ARBs, although the relative changes from baseline were not significantly different between the patients who continued and those who discontinued using ARBs. Postoperative complications and length of hospital stay were also similar.

Unlike with most antihypertensive drugs such as calcium channel blockers and beta-blockers [4,9], continuing ARBs on the day of surgery has been controversial because of their mechanism of action. ARBs block angiotensin II receptor type 1, directly causing vasodilation, reducing vasopressin secretion, and reducing aldosterone production and secretion [10,11]. Furthermore, angiotensin II is known to contribute to the hemodynamic regulation during anesthesia [12]. Therefore, ARBs may produce the exaggerated hypotensive response to the induction of anesthesia and may increase the incidence and severity of intraoperative hypotension. Many studies have shown that maintenance of ARBs until the day of surgery may increase the probability of intraoperative hypotension [5,13–15]. In addition, a recent meta-analysis reported that discontinuing ARBs was associated with significantly less intraoperative hypotension [16].

Conversely, some studies have shown no association between preoperative administration of ARBs and intraoperative hypotension. Licker et al. [17] found no changes in hemodynamic parameters during cardiac surgery in patients receiving long-term angiotensin-converting enzyme inhibitor treatment. Likewise, our results showed that the continuation of ARBs did not result in hypotension requiring vasopressor before and after induction of anesthesia. However, our results also showed that the rates of intraoperative hypotension requiring administration of catecholamine (mostly ephedrine) significantly increased in the patients who continued using ARBs. Fortunately, untreated hypotension with routine pharmacological intervention was not observed in this study. On the other hand, the rates of intraoperative

hypertension requiring administration of nicardipine did not increase in the patients who discontinued using ARBs. Therefore, discontinuation of ARBs may reduce intraoperative hypotension requiring pharmacological intervention without significant intraoperative hypertension.

In contrast to the similar blood pressure between before and after induction of anesthesia, blood pressure after anesthesia showed a significant difference between the continuation and discontinuation groups in the present study. Although the relative changes from baseline were not significantly different between the groups, the SBP on arrival at the PACU was significantly higher in the discontinuation group than in the continuation group (159.9 ± 21.7 mmHg vs. 146.4 ± 20.9 mmHg, $p < 0.001$). Postoperative hypertension could be a serious clinical problem in a certain patient or surgery such as carotid endarterectomy. This possibility should be considered when deciding whether to discontinue ARBs before surgery.

This retrospective study had some limitations. First, although we could find the actual time of hypotension or hypertension requiring vasoactive drugs in the anesthetic records, the reason for the hemodynamic changes was not recorded. Therefore, surgery or other factors could be responsible for the hemodynamic changes. However, we tried to rule out such cases on the basis of the inclusion/exclusion criteria. Second, the exact durations of the preoperative ARB medication could not be collected in this study. Considering the individual variation, it may be another influencing factor for our results.

In conclusion, this retrospective study demonstrates that discontinuation of ARBs may reduce the incidence of intraoperative hypotension requiring pharmacological intervention in patients undergoing laparoscopic cholecystectomy; however, the possible occurrence of postoperative hypertension should be considered.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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