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A comparison of continuation of one-quarter dose and full-dose ACEIs /ARBs effect on incidence of intraoperative hypotension in patients undergoing non-cardiac surgery, a randomized controlled study

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Abstract
Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angioensin II receptor blockers (ARBs) are commonly prescribed to treat hypertension in general surgical patients. However, the patients who continued ACEIs/ARBs preoperatively increased incidence of postinduction hypotension. Due to there was dose-related efficacy for lowering blood pressure of ACEIs/ARBs. Our objective was to compare the incidence of hypotension in patients who received continuation of one-quarter dose or full dose of ACEIs/ARBs on the morning of surgery.
Method: After IRB approval, a prospective randomized-control study consisted of 40 patients who received ACEIs/ARBs were scheduled for non-cardiac surgery. Patients were randomized into two groups, continued full dose (FD) group who continued the same dose ACEIs/ARBs and one-quarter dose (QD) group who received a quarter dose of their own ACEIs or ARBs on the morning of surgery. The baseline and intraoperative blood pressures were measured.
Results: Twenty-seven patients (67.5%) had been treated with ARBs. Either means of baseline or preinduction blood pressure in two groups was not significant difference. Four patients (20%) in QD group had episode of hypotension whereas ten patients (50%) in FD group. The incidence of hypotension in FD group had significantly higher than that of QD group (p=0.047). However, the incidences of intraoperative hypertension of QD and FD group were 55% and 30%, respectively. There was not significant difference between two groups.
Conclusions: The continuation of one-quarter dose ACEIs/ARBs in patients undergoing non-cardiac surgery was associated with a lower incidence of intraoperative hypotension compared with full-dose of medications.
Keywords: Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, intraoperative hypotension, intraoperative hypertension, Hypertension/ therapy, perioperative care

Introduction

Following the practice guideline from eighth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC8), prescription of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been increased for first-line treatment of hypertension.(1) As a result, anesthesiologists have seen many patients who have used these agents to treat hypertension in preanesthetic assessment as well. Apart from antihypertensive effect of ACEIs/ARBs, the current evidences found more advantages on end-organ protective effects and also attenuated the risk of acute myocardial infarction, atrial fibrillation or acute stroke.(2-4) Consequently, the perioperative guidelines for non-cardiac surgery from American heart association suggested continuing ACEIs/ARB to the day of surgery.(5) However, continuation or discontinuation of ACEIs/ARBs on preoperative period has remained inconclusive management. Due to there were some earlier studies found that continuing ACEIs/ARBs until the day of surgery was more likely to develop intraoperative hypotension in patients undergoing general anesthesia (6-9), whereas the recent studies showed no association between continuation of ACEIs/ARBs and increased risk of intraoperative hypotension.(10, 11) Moreover, there was a concerning of discontinuation that

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if ACEIs/ARBs were withhold in hypertensive patients, the perioperative hypertension might be increased. In prior study, the patients who discontinued ACEIs/ARBs preoperatively required more intraoperative antihypertensive treatment to control hypertension.(12) The survey of anesthesiologists in current management of preoperative ACEIs/ARBs, there were remained inconsistencies of their management among practitioners.(13) Mostly, the reason of discontinuation of preoperative ACEIs/ARBs was concern of intraoperative hemodynamic unstable after general anesthesia.

Owing to there was previous study that showed the dose-related arterial blood pressure lowering efficacy of ACEIs and ARBs. The study reported that reducing ACEIs/ARBs to one-quarter of recommended dose achieved a blood pressure lowering effect 60-70% of that attained by recommended dose.(14) Hence, we hypothesized that the incidence of intraoperative hypotension should be decreased along with the reducing dose of these antihypertensive medications.

Methods

The study was approved by institutional review board (ID 036028) and was registered in Thai Clinical Trial Registry (TCTR20210305002). Patients were recruited from February 2017 to January 2018, at Ramathibodi hospital. Eligible patients included adult patients older than 18 years, ASA physical status II to III, receiving ACEIs or ARBs for hypertension at least 3 months, who were undergoing elective open gynecologic surgery or lower abdominal colectomy under general anesthesia with endotracheal intubation with direct laryngoscope. Exclusion included patients who took ACEIs/ARBs only in the evening, patients who have poorly controlled hypertension and have history of end-organ damage such as stroke, myocardial infarction, congestive heart failure, and end staged renal disease.

All of the patients received preanesthetic assessment by anesthesiology residents on the day before surgery. Informed consent was obtained then patient' medications were identified. The patients were randomly assigned into two groups by sealed envelopes which were continuation one-quarter dose group (QD group) or full dose of ACEIs/ARBs (FD group). In QD group, the anesthesiology residents prepared the patients' ACEI or ARB to one-quarter of daily regular dose. All patients were received their ACEI or ARB which depended on their study group and the usual dose of all other antihypertensive medications except diuretics 2 hours before operation with 30 mL of clear fluid. The baseline preoperative blood pressures were obtained from the average of three times measurements at ward after rest for 15 minutes on the day before surgery.

Anesthesia protocol

All patients were given sedative agents either midazolam or lorazepam the night before surgery. At operative theater, all patients were monitored with Philips IntelliVue MP30 including non-invasive arterial blood pressures, ECG, and pulse oxymetry. All of patients were conducted general anesthesia starting with fentanyl 1.5 mcg/kg, then propofol 1.5-2 mg/kg following by atracurium of 0.5 mg/kg then facemask ventilation for 3 minutes. The patients who were intubated with endotracheal tube by direct laryngoscopy then were maintained with 1-1.2 MAC of sevoflurane with 50% mixture of nitrous and oxygen. Amount of balanced salt solution fluid in first hour was calculated from the maintenance fluid and half of total volume deficit fluid which was given with constant rate. For definition of hypertensive events, systolic blood pressure values were more than 140 mmHg in stage 1 and were more than 160 mmHg in stage 2 of hypertension. If patients' blood pressures were more than 180 mmHg which were treated with intravenous nicardipine except for preinduction blood pressure. Hypotension events defined as patients' systolic blood pressures less than 85 mmHg which were treated with intravenous 6 mg of ephedrine. When the event of hypotension was last long over three consecutive times of blood pressure measurements even received the treatment with ephedrine, those episodes were defined as persistent hypotension. The blood pressures were recorded before an induction of anesthesia, and after intubation at 2.5-minutes intervals to one hour of operation. The number of hypotension episodes or hypertension episodes was recorded. Attending anesthesiologists who treated the patients' blood pressures and the nurse anesthetists who record blood pressures had not known the study group of their patients.

The calculation of sample size was based on the previous study which reported that 100 % of patient continuing ACEIs until the day of surgery had hypotensive episodes.(15) As summing that 10% drop of participants would drop out, 20 patients would be needed in each group to detect $\alpha = 0.05$ and power of 80 %. All data were analyzed by SPSS version 20.0 software (IBM Co., Armonk, NY., USA). Categorical variables were presented as frequencies and percentages; differences between groups were assessed by Pearson chi-square test or Fisher exact test. Continuous variables were reported as means and standard deviations or median and interquartile range; differences between groups were assessed by student's t-test or Mann-Whitney U test. Normality of the variables were examined by using the

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Kolmogorov-Smirnov test. Comparison of hemodynamic variables between baseline and each time points were analyzed by paired t-test. A two-tailed P-value < 0.05 was denoted statistical significance.

Results

Fifty-two patients who meet inclusion criteria were recruited in this prospective randomized control trial study. Twelve patients were excluded from the study as shown in Figure 1. The forty eligible patients were randomized in two groups; twenty patients in each group. Overall, thirty-four patients (85%) were female. Mostly, twenty-seven patients (67.5%) and thirteen patients (32.5%) preoperatively received ARBs and ACEIs, respectively. Only 14 patients (35%) were prescribed a combination of ACEIs or ARBs with other antihypertensive agents. Majority of operations was a gynecologic surgery. The patients' demographic data were shown in table 1.

The hemodynamic variables in two groups were presented in table 2. Interestingly, one patient from each group had baseline systolic blood pressures more than 160 mmHg. Moreover, not only preinduction blood pressure but also the incidence of preinduction hypertension was no significant difference between two groups. During the intraoperative period, the hypotension episodes were significantly lesser in QD group than that of FD group. Interestingly, there was no the incidence of persistence hypotension in QD group, meanwhile that occurred in four patients of the FD group. All the hypotensive episodes of QD group occurred in first 15 minutes after induction of anesthesia and found only one episode without any recurrence. However, majority of the hypotensive episodes in FD group were found in first 30 minutes and only few patients found 30 minutes later. Lastly, there was no significant different in the incidence of both first stage and second stage intraoperative hypertension between two groups.

The values of systolic blood pressure in QD group were significantly lower than that of baseline from 10 to 40 minutes after induction. Surprisingly, the diastolic blood pressure in QD group showed no significant difference from baseline blood pressure for entire of study period. However, both intraoperative systolic blood pressure and diastolic blood pressure in FD group were significantly lower than baseline blood pressure at many time points as shown in Figure 2. In first hour of operation, amount of fluid administration in QD group and FD group were 457.5± 271.1 mL and 497.5± 213 mL, respectively. Amount of blood loss in both groups were 53.5± 17.6 and 60.3± 23.8, respectively. There were no statistically significant differences.

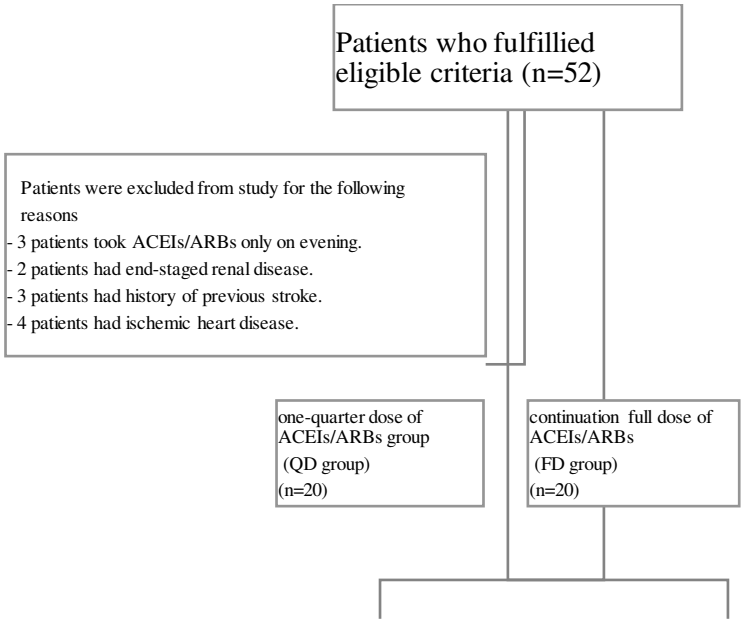

Figure 1. Patients enrollment flowchart

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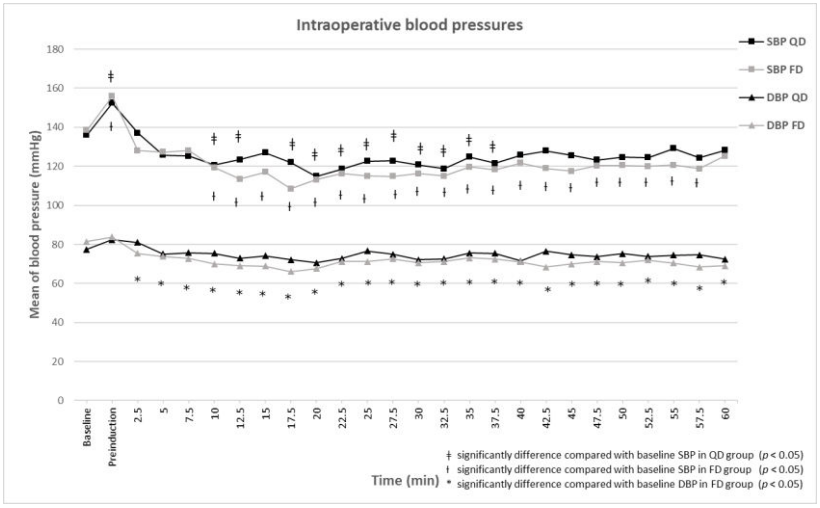

Figure.2 Intraoperative blood pressures SBP, systolic blood pressure; DBP diastolic blood pressur

Table.1 Baseline clinical and surgical characteristics of patients

	QD group N =20	FD group N=20	p value
Age (year)	64.20±7.8	61.25±8.3	0.198
BMI (kg/m^2)	26.20±4.5	25.5±5.3	0.858
Female	18 (90)	16 (80)	0.376
ASA physical status			
II	11 (55)	16 (80)	0.091
III	9 (45)	4 (20)	
ARBs			
Lorsatran	12 (60)	10 (50)	0.773
Irbesatran	2 (10)	3 (15)	
ACEIs			
Enalapril	4 (20)	6 (30)	
Lisinopril	2 (10)	1 (5)	
Other antihypertensive			
Beta adrenergic blockers	5 (25)	1 (5)	0.077
Calcium channel blockers	6 (30)	5 (25)	0.723
Diuretics	2 (10)	0 (0)	0.147
Comorbidities			
Chronic kidney disease	1 (5)	2 (10)	0.548
Dyslipidemia	5 (25)	4 (20)	0.705
Diabetes mellitus	4 (20)	3 (15)	0.677
Type of surgery			
Lower abdominal colectomy	7 (35)	9 (45)	0.518
Gynecology	13 (65)	11 (55)	

BMI; Body Mass Index, ASA; American Society of Anesthesiologists.
Continuous data were presented with mean±SD. Categorical data were presented with N(%).

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Table. 2 Perioperative blood pressures, incidence of hypotension and hypertension

	QD group N=20	FD group N=20	p value
Before induction			
Baseline preoperative SBP (mmHg)	135.9±14.7	138.5±9.9	0.525
Baseline preoperative DBP (mmHg)	77.4±9.6	81.5±7.2	0.141
Preinduction SBP (mmHg)	152.4±25.6	155.9 ±21.6	0.643
Preinduction DBP (mmHg)	82.4±11.6	83.8±12.7	0.730
Number of patients with preinduction hypertension	11 (55)	10 (50)	0.752
SBP > 160 mmHg	4 (20)	4 (20)	1.000
SBP > 180 mmHg			
After induction			
Total cases of hypotension	4 (20)	10 (50)	0.047
Cases of hypotension classified by time interval			
0-15 min	4 (20)	4 (20)	1.000
15-30 min	0	5 (25)	
30-45 min	0	1 (5)	
45-60 min	0	2 (10)	
Persistent hypotension	0	4 (20)	0.035
Total cases of hypertension	11(55)	6(30)	0.109
Cases of hypertension (SBP > 160 mmHg) classified by time interval			
0-15 min	9 (45)	5 (25)	0.185
15-30 min	2 (10)	1 (5)	0.548
30-45 min	4 (20)	2 (10)	0.376
45-60 min	3 (15)	2 (10)	0.633

SBP; systolic blood pressure, DBP; diastolic blood pressure. Continuous data were presented with mean± SD. Categorical data were presented with N(%).

Discussions

Since the previous studies showed that there were both risks and benefits from continuation ACEIs/ARBs, there is no practice guideline for appropriate use of these agents in perioperative setting. In our institute, the anesthesiologists usually decided to continued or discontinued these agents based on the balance between their organ-protective benefits or level of preoperative blood pressure and the risk of intraoperative hypotension. This present study demonstrated the consequences of decreasing the ACEIs/ARBs dose to one-quarter of usual dose on perioperative hemodynamic effects and found that the patients in QD group had a significant lower incidence of intraoperative hypotension than the patients in FD group. The intraoperative hypotension occurred rate was 20% and 50% in QD group and FD group, respectively. Our result in incidence of hypotension in QD group was reduced by 60% which corresponded to the effect of reducing dose of ACEIs in prior study.(14)

In this study, there were lower incidence of hypotension in FD group when compared with previous studies. From those studies, the incidences of hypotension in continue ACEIs/ARBs group have been vary from 60 -100%.(7, 15, 16) The explanation might be the variation of disease severity and comorbidity in patient populations, different stimuli from different surgery types, and definitions of hypotension. The pioneer studies in ACEIs continuation on the day of surgery, they showed that increased incidence of hypotension was likely in patients who underwent vascular surgery.(15) Inevitably, those patients had many cardiovascular diseases that might not be tolerate with general anesthesia leading to higher chance of hypotension. Our present study found that there was no event of persistent hypotension in QD group but that of FD group was 20%. According to study of Bertrand et

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al., reported no incidence of refractory hypotension in the patients who withdrawn ARBs in the morning surgery (7)

The induction dose of anesthetic agents may influence the hemodynamic in early phase after the induction. For this reason, we found the systolic blood pressures in QD group were significantly lesser than baseline blood pressure from 10 to 40 minutes since the induction of anesthesia had started. However, the last 20 minutes of observation, we found that the systolic blood pressure in QD group shown no significant difference from the baseline systolic blood pressure. The study of Comfere et al.(17) found that more frequent episodes of hypotension in first 30 minutes after induction which were resemble pattern of hemodynamic changes in this present study. Right after induction of general anesthesia, the sympathetic nerve system of the patients was abruptly reduced on cardiovascular system, especially on venous return and cardiac output.(18) However, when diminishing anesthetic effect on sympathetic nervous system and increasing volume load attributed to improve cardiovascular responses leading to higher up in blood pressures afterward. Immediate after intubation in first 10 minutes, the patients' blood pressures were not seen significant difference from baseline in both groups. According to hemodynamic responses after intubation studies,(19, 20) they demonstrated that the stimulus of endotracheal intubation affected on patient's blood pressure which would be intense in first 5-10 minutes. Interestingly, this present study found no significant alteration in diastolic blood pressure in QD group. Peck et al., reviewed the systolic blood pressures in patients receiving ACEIs were more significant reduction than diastolic blood pressures.(21) Therefore, the effect of one-quarter dose of ACEIs/ARBs on blood pressure could be vanished on diastolic blood pressure.

Among conflicting data on preoperative discontinuing or continuing ACEIs/ARBs, on the other hand, one of concerning aspects of discontinuation was loss of antihypertensive effect in poorly controlled or uncontrolled hypertensive patients. The incidence of perioperative hypertension might be increased or aggravated by perioperative surgical stresses. However, the recent study showed that patients in ambulatory surgery which were discontinued ACEIs/ARBs preoperatively, those patients did not increase in incidence of either pre- or postoperative hypertension compared with patients who continued ACEIs/ARBs preoperatively.(22) Our present study demonstrated one-quarter dose which gave the effect of lowing blood pressure about 60-70% of its full dose. This dose would not too strong or too week on controlling blood pressure. Subsequently, its residual effect of one-quarter was sufficient on antihypertensive treatment and also minimizing the incidence of intraoperative hypotension as well.

This study had some limitations. First of all, our populations had different types of surgery that might lead to the various degrees of surgical stimulations although this study included only open gynecologic surgery or lower abdominal colectomy. Secondly, there were few brands of ACEIs or ARBs which may have different durations of action, effect on blood pressure or pharmacology. However, those antihypertension medications had sufficiently long duration of action which would interact with initial phase anesthetics effect and surgical stress response. Lastly, we observed only an hour of intraoperative blood pressure which would not address the actual incidence of perioperative hypotension which might be higher than that of our study.

Conclusion

This prospective randomized study found an association between decreasing ACEIs/ARBs therapy in the morning of surgery to one-quarter dose and lowered incidence of intraoperative hypotension in chronic receiving ACEIs/ARBs therapy patients who undergoing non-cardiac surgery under general anesthesia. Additionally, by decreasing the usual dose to one-quarter did not increase the incidence of perioperative hypertension.

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