Preventative Effects of Bisoprolol Transdermal Patches on Postoperative Atrial Fibrillation in High-risk Patients undergoing Non-cardiac Surgery: A subanalysis of the MAMACARI Study

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Abstract

Background: Perioperative atrial fibrillation (POAF) after non-cardiac surgery is a risk factor for cardiovascular events including stroke and death. The aim of this subanalysis of the MAMACARI study, a multicenter randomized control study on the effectiveness of a bisoprolol transdermal patch for prevention of perioperative myocardial injury in high-risk patients undergoing non-cardiac surgery, was to identify the predictors of POAF after non-cardiac surgery in high-risk patients and to determine changes in blood pressure and heart rate during bisoprolol patch administration in the perioperative period.

Methods and Results: Patients aged over 60 years with hypertension and a high revised cardiac risk index (≥2) who were scheduled to undergo non-cardiac surgery were randomly assigned to a bisoprolol patch group (n=120) or a control group (n=120). We divided the patients into two groups: patients with POAF (POAF group; n=16) and patients without POAF (non-POAF group; n=206). Multivariate analysis showed that bisoprolol patch therapy (OR: 0.30, 95% CI: 0.092-0.978) and surgery time of 250 minutes or more (OR: 4.99, 95% CI: 1.37-18.2) were independently associated with POAF. Although systolic blood pressure did not differ significantly between the two groups throughout the perioperative period, treatment with a bisoprolol patch significantly reduced heart rate throughout the perioperative period compared with that in the control group.

Conclusions: Low dose of a bisoprolol patch in the perioperative period was effective for prevention of POAF after non-cardiac surgery in high-risk patients, while long surgery time was an independent risk factor for POAF. It is expected that low dose of a bisoprolol patch can prevent POAF without causing hypotension.

Introduction

It has been reported that postoperative atrial fibrillation (POAF) occurred in 5-15% of patients who underwent non-cardiac surgery [1, 2]. Recent studies have revealed that patients with POAF after non-cardiac surgery have significantly increased risks of stroke, myocardial infarction and death [3, 4]. Therefore, prevention of POAF after non-cardiac surgery is needed.

We previously reported the results of the MAMACARI study, a multicenter, prospective randomized controlled study that was carried out to investigate the effectiveness of bisoprolol transdermal patches for prevention of perioperative myocardial injury in high-risk patients undergoing non-cardiac surgery [5]. In that study, patients aged >60 years with hypertension and a high revised cardiac risk index (≥2) who were scheduled to undergo non-cardiac surgery were randomly assigned to a bisoprolol patch or control group. POAF after non-cardiac surgery occurred in 10.9% of the patients in the control group. Several studies have been carried out to identify possible risk factors for POAF after non-cardiac surgery [6-8], and advanced age and male sex were reported to be predictors of POAF. However, predictors of POAF after non-cardiac surgery in those high-risk patients remain unknown.

A bisoprolol patch, a newly developed form of a beta-blocker in Japan, was designed to deliver bisoprolol through the skin to produce stable blood concentrations. However, it is uncertain whether the use of a bisoprolol path is effective for prevention of POAF. In the MAMACARI study, we showed that the use of bisoprolol patches in the perioperative period is safe for high-risk patients undergoing non-cardiac surgery. However, it is not clear whether bisoprolol patches cause significant changes in blood pressure and heart rate in the perioperative period.

The aim of this subanalysis of the MAMACARI study was to identify the predictors of POAF in high-risk patients undergoing non-cardiac surgery and to determine changes in blood pressure and heart rate during bisoprolol patch administration in the perioperative period.

Methods

Study design

The design of the MAMACARI study (UMIN000016908) has been described elsewhere [5]. The principal study was a multicenter, prospective randomized controlled, open-label study conducted from November 2014 to February 2019. That study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Density, and Pharmaceutical Sciences and other hospitals. The study was approved by the local medical ethics committee (application number of Ethical Committee of Okayama University m07015; Effects of Bisoprolol Transdermal Patches for Prevention of Perioperative Myocardial Injury in High-risk Patients Undergoing Non-cardiac Surgery: MAMACARI study) and all patients provided written informed consent. This trial was conducted in compliance with the Declaration of Helsinki.

Participants

The protocol of the study was described previously [5]. Patients were eligible for the study if they were aged ≥60 years, had hypertension and a revised cardiac risk index (RCRI) of ≥2, and were scheduled to undergo elective non-cardiac surgery under general anesthesia. RCRI is determined by assigning one scoring point for each of the following six criteria: high-risk

type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/dL [9]. A total of 240 patients were registered and randomly assigned to a bisoprolol group or a control group. Intention to treat analysis was conducted for 222 patients. Patients receiving beta blockers were excluded from the enrollment criteria and were not included in this study. Similarly, cases in which the oral medication was switched to a patch were not included. In this trial, administration of 4 mg/day of bisoprolol in a patch form was started 7 days before surgery and was continued until 7 days after surgery. If the initiation dose of the bisoprolol patch was not tolerated, the dose was reduced to 2 mg/day and administration was stopped if this lower dose was not tolerated. The median bisoprolol dose used was 2 mg in the bisoprolol patch group. According to the protocol, the bisoprolol patch was discontinued on the 8th day after surgery, but in cases in which it was clinically necessary to continue administration of bisoprolol by the patch after the 8th day, administration could be continued at the discretion of the attending physician.

Definition of POAF

POAF was defined as onset of atrial fibrillation (AF) that occurred within 30 days after surgery [3]. Patients with paroxysmal AF were included in this study, but those with chronic AF were excluded. In this study, ECG monitoring was performed for several days after surgery. After the ECG monitoring was discontinued, arrhythmia was detected on the basis of the patient's symptoms and vital signs.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables are presented as frequency or proportion (%). Differences between the two groups were evaluated using the chi-square test for categorical variables and Student's t-test for continuous variables. Associations of variables were assessed by Pearson's correlation coefficients. Changes in systolic blood pressure and heart rate within POD 3 from registration were evaluated using analysis of covariance (ANCOVA), and the adjusted mean and 95% CI for each group were calculated. The independent relationship between POAF and use of a bisoprolol patch was assessed by multivariate logistic regression analysis, adjusting for variables at baseline with a p value of < 0.05 in univariate analysis (bisoprolol patch, surgery time). $P < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS 27.0 for Windows (IBM, Armonk, NY, USA).

Results

Flow diagram of patients in this study

The MAMACARI study started in November 2014 and ended in February 2019, and five institutions in Japan were involved in the study [5]. A total of 240 patients undergoing non-cardiac surgery were randomly assigned to a bisoprolol patch group or a control group. The flow diagram of patients in this study is shown in Fig. 1. A few patients were excluded because of cancellation or postponement of surgery for various reasons. Intention to treat analysis was performed for 112 patients in the bisoprolol patch group and 110 patients in the control group. POAF occurred in 4 patients in the bisoprolol patch group and in 12 patients in the control group. We summarized the details of the 16 cases of POAF in Supplementary Table 1. Occurrence of POAF in the bisoprolol patch group was significantly

lower than that in the control group (bisoprolol group: 3.6% vs control group: 10.9%; P=0.035) (Fig. 2A).

Characteristics of patients and predictors of POAF

Characteristics of the patients are shown in Table 1. Eleven patients underwent thoracic surgery including lobectomy. Thirteen patients underwent non-cardiac surgery with surgery time of more than 250 minutes, and the majority of patients with POAF had longer surgery (P=0.009). Bisoprolol patch treatment was performed for a significantly larger proportional of patients in the non-POAF group than in the POAF group (P=0.040). There was no left atrial dilation in either group. In the POAF group, 6 patients (38%) had a history of PAF, while 5 patients (2%) in the non-POAF group had a history of PAF. There was a clear significant difference (P <0.001) between the two groups. Of the 11 patients with a history of PAF, 4 were in the bisoprolol patch group and 7 were in the control group, and there was no statistically significant difference (P = 0.34).

Multivariate analysis showed that bisoprolol patch therapy (OR: 0.30, 95% CI: 0.09-0.98) and surgery time of 250 minutes or more (OR: 4.99, 95% CI: 1.37-18.24) were independently associated with POAF (Table 2).

Changes in blood pressure and heart rate in patients with a bisoprolol patch

Changes in systolic blood pressure and heart rate during the perioperative period are shown in Fig. 2B and C. There was no significant difference in systolic blood pressure between the two groups during the perioperative period. On the other hand, heart rate was increased after surgery in the control group, but it was not increased after surgery in the bisoprolol

group. Treatment with a bisoprolol patch significantly reduced heart rate throughout the perioperative period compared with that in the control group.

Discussion

Two major new findings were obtained in the present study. First, bisoprolol patch therapy was found to be associated with reduction in the risk of POAF after non-cardiac surgery in high-risk patients. To our knowledge, this is the first report on the efficacy of bisoprolol patch therapy for prevention of POAF in non-cardiac surgery. Second, treatment with a bisoprolol patch did not reduce systolic blood pressure, but it significantly reduced heart rate throughout the perioperative period compared with that in the control group. It is expected that the use of a bisoprolol patch can prevent POAF without causing hypotension.

POAF is caused by the combination of multiple mechanisms and factors. The stress of surgery increases heart rate and release of catecholamines. Clinical circumstances such as hypovolemia, intraoperative hypotension, anemia, trauma, and pain can also affect sympathetic activity [2]. Therefore, beta-blockers would be effective for prevention of POAF. However, there are several problems about using beta-blockers in the perioperative period. In the POISE trial, which showed that beta-blockers significantly reduced the incidence of perioperative myocardial infarction, clinically significant new POAF was found in 2.2% of the patients in the metoprolol group and in 2.9% of the patients in the placebo group (HR: 0.76, 95% CI: 0.58-0.99) [10]. These results suggest that preoperative metoprolol administration may prevent the development of POAF. However, compared to the placebo group, perioperative beta-blockade was also found to significantly increase the risk of stroke, clinically significant hypotension and bradycardia. Furthermore, the metoprolol group had a significantly higher risk of mortality. The problem with this trial was that administration of a

relatively high dose of long-acting metoprolol just before surgery, without titration, caused serious hypotension and stroke. The advantages and disadvantages of administering beta-blockers in the perioperative period need to be recognized. To overcome the limitations of previous studies on perioperative beta-blockers, several points including the trial design and the dosage and route of administration require consideration. A bisoprolol transdermal patch, a newly developed form of a beta-blocker in Japan, is designed to deliver the drug through the skin. The use of a bisoprolol transdermal patch has several benefits. First, it enables stabilization of blood concentrations of bisoprolol, making hemodynamic instability less likely. Sairaku et al. reported that administration of bisoprolol through the transdermal route resulted in a more constant blood level and was less likely to cause a spike concentration than was administration through the oral route [11]. Second, a bisoprolol patch can be used in patients with gastrointestinal disease who are undergoing abdominal surgery, for whom perioperative oral treatment would be difficult. Third, a bisoprolol transdermal patch can be safely and effectively used in patients with atrial fibrillation and heart failure. Momomura et al. suggest that a bisoprolol patch can be used safely by switching from oral bisoprolol in patients with chronic heart failure [12]. Yamashita et al. reported that 4 and 8 mg/day of bisoprolol patch treatment had heart rate-reducing effects similar to those of bisoprolol oral formulation at doses of 2.5 mg and 5 mg in patients with persistent or permanent atrial fibrillation, respectively, and that the incidence of adverse events did not differ between the bisoprolol patch and oral formulation groups [13]. However, there have been few studies on the safety of bisoprolol patch treatment in patients undergoing non-cardiac surgery in which perioperative changes in blood pressure and heart rate were monitored. We monitored perioperative changes in blood pressure and heart rate and we found that the use of a bisoprolol patch is safe. In this study, a bisoprolol

patch reduced only heart rate without reducing systolic blood pressure, which is a risk factor of stroke.

In the MAMACARI study, administration of 4 mg/day of bisoprolol in patch form was started 7 days before surgery and was continued until 7 days after surgery [5]. A 4-mg bisoprolol patch is equivalent to 2.5 mg of oral bisoprolol. If the initiation dose of the bisoprolol patch was not tolerated, the dose was reduced to 2 mg/day and administration was stopped if this lower dose was not tolerated. Eventually, the median dose of bisoprolol actually administered was 2 mg in the bisoprolol patch group. This study showed that this low dose (2 mg/day) might be sufficient for prevention of POAF. Further studies are needed to clarify the appropriate dose of a bisoprolol patch.

Prolonged operative time is associated with an increase in the risk of complications across various surgical specialties and procedure types [14]. This study also showed that surgery time of 250 minutes or more was independently associated with POAF after non-cardiac surgery in high-risk patients. Further study is needed to evaluate the effects of reducing operating time on the incidence of POAF.

There are several reports showing that withdrawal of beta-blockers after cardiac surgery results in sympathetic nerve activity, increasing the risk of atrial fibrillation [14]. In this study, no cases of POAF developed after discontinuation in the bisoprolol patch group. However, it is necessary to determine whether treatment with a bisoprolol patch should be continued or discontinued several days after surgery for each case, and after discontinuation of treatment with the bisoprolol patch, attention should be paid to tachyarrhythmia, especially atrial fibrillation.

Study limitations

This study has several limitations. First, because the study included only patients aged ≥ 60 years and with a high RCRI risk score who were scheduled to undergo non-cardiac surgery, the results cannot be applied to younger patients and to patients with lower RCRI risk scores. Second, this study was carried out for only 30 days after surgery, and we could not evaluate the long-term efficacy of a bisoprolol patch for preventing POAF. Third, in this study, POAF was defined as AF that developed within 30 days after surgery, with reference to previous literature [3]. However, it is clear that the AF detection rate decreases after the completion of ECG monitoring, especially after discharge from the hospital, which is one of the limitations of this study. One of the findings of this study was that most cases of POAF occurred 3 days after surgery, suggesting the importance of preventing AF in the early postoperative period. Further studies are required to determine the best method for preventing POAF.

Conclusion

In conclusion, low dose of a bisoprolol patch in the perioperative period is effective for prevention of POAF after non-cardiac surgery in high-risk patients. It is expected that low dose of a bisoprolol patch can prevent POAF without causing hypotension.

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Disclosures

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Appendix

MAMACARI investigators, in addition to the authors, are Kunihisa Kohno, Atsuyuki Watanabe, Masao Hayashi, Takuro Masuda, Hideki Fujio, Kunihiko Hatanaka, Toshiaki Kurasako, Naoki Mukohara, Hisatoshi Mori, Masatoshi Sugiyama, Takefumi Oka, Yoichiro Naito, Hidekuni Hidaka, Mitsuru Munemasa, Koji Kabutan and Hiromi Matsubara.

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Figure legends

Fig. 1. Study flow chart. POAF, postoperative atrial fibrillation.

Fig. 2. Incidence of POAF and changes of systolic blood pressure and heart rate in the perioperative period. A. Incidence of POAF (%) according to the study group. B and C. Systolic blood pressure (B) and heart rate (C) at baseline, 1 day before surgery, and on postoperative day (POD) 1 and POD 3. Data are expressed as means ± SD. POAF, postoperative atrial fibrillation.