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Original contribution

Prevention of atrial fibrillation after cardiac surgery using low-dose landiolol: A systematic review and meta-analysis

Takahiko Tamura, MD, PhD, Tomoaki Yatabe, MD, PhD *, Masataka Yokoyama, MD, PhD

Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku City, Kochi 783-8505, Japan

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ABSTRACT

Study objective: Atrial fibrillation (AF) is associated with mortality after cardiac surgery. Several studies have reported that landiolol might help to prevent postoperative AF. The objective of this study was to investigate whether low-dose landiolol is useful in terms of balance of benefit and risk.
Design: We conducted a meta-analysis after systematically searching the PubMed, the Cochrane library and the ICHUSHI to identify randomized, controlled trials investigating the preventive effect of landiolol on incidence of AF after cardiac surgery.
Patients: Six randomized trial with 571 patients were included.
Measurements: The primary outcome was incidence of AF after surgery, while secondary outcomes were mortality and complications.
Main results: Incidence of AF within 1 week after surgery was significantly lower in the landiolol group than in the control group (odds ratio, 0.27; 95% confidence interval, 0.18–0.42; $p < 0.001$). Three of the 6 studies reported data regarding in-hospital mortality and complications, showing no significant differences between groups (0.7 vs 3.0%; OR, 0.45; 95% CI, 0.07–2.74; $p = 0.39$; and 4.5 vs 9.7%; OR, 0.45; 95% CI, 0.16–1.23; $p = 0.12$, respectively).
Conclusions: Our systematic review revealed that low-dose landiolol might help to prevent AF after cardiac surgery and further large trials are needed to evaluate safety because mortality and morbidity rate were very low in included studies.

1. Introduction

Atrial fibrillation (AF) is one of the most common complications occurring after cardiac surgery [1]. Postoperative AF is associated with increased risks of embolic diseases, such as cerebral infarction, mortality, and medical care expenditures [2,3]. In addition, AF leads to decreased stroke volumes due to decreased left ventricular end-diastolic volumes. Therefore, maintaining sinus rhythms in patients who have undergone cardiac surgery is important.

Conventionally, calcium channel antagonists and digitalis are used to prevent postoperative AF. However, although calcium channel antagonists are effective against AF, they are frequently associated with adverse reactions, such as bradycardia [4]. Furthermore, a meta-analysis reported that digitalis was ineffective when used to prevent paroxysmal AF [5]. The American College of Cardiology Foundation/American Heart Association practice guideline for coronary artery bypass grafting recommends the use of perioperative beta-blockers to reduce the incidence of AF [6]. However, most evidence regarding the effect of beta-blockers on reducing AF is based on the use of traditional beta-blockers, such as metoprolol and propranolol [6,7]. On the other hand, several studies have reported that a low-dose, ultra-short-acting beta-blocker (specifically, landiolol), might help prevent AF after cardiac surgery [8,9]. Previous meta-analyses revealed that landiolol significantly reduced the incidence of AF after cardiac surgery, without increasing the risk of major complications, such as bradycardia [10,11]. In addition, landiolol might be more suitable for cardiac surgery patients, compared with other beta-blockers, because landiolol induces a less potent negative inotropic effect than esmolol [12]. However, these systematic reviews did not include studies written in Japanese, despite landiolol being widely used in Japan, increasing the likelihood of outcomes being reported in Japanese only. Furthermore, these reviews included studies involving both placebos and diltiazem in the control group. We believe that a direct comparison between landiolol and placebo is important for correctly evaluating the efficacy and risk of landiolol therapy. Previous systematic reviews also did not report the mortality effects of landiolol. Therefore, we conducted this systematic review, including studies written in Japanese, to investigate whether low-dose

* Corresponding author.
E-mail address: yatabe@kochi-u.ac.jp (T. Yatabe).

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landiolol is able to prevent AF and mortality after cardiac surgery, compared with placebo.

2. Materials and methods

2.1. Search strategy

We conducted a systematic review that conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [13]. To identify randomized controlled trials investigating the preventive effects of landiolol on the incidence of AF after cardiac surgery, a search was conducted in PubMed and the Cochrane library through June 7, 2017, using the following search terms: [random OR randomized] AND [short-acting beta-blocker OR landiolol]. We also searched articles in ICHUSHI Web (the largest database of Japanese medical journals, containing approximately 10 million manuscripts from 6000 journals) using the same terms, in Japanese characters.

2.2. Study selection

We included studies that fulfilled the following criteria: (1) randomized controlled trial (RCT); (2) full-text publication in English or Japanese; (3) included adult patients who underwent cardiac surgery; (4) included comparisons of intra- and/or postoperative low-dose landiolol (maximum dose, 10 μg/kg/min) and placebo (saline); and (5) included outcome measures of postoperative AF incidence, mortality (in-hospital or 90-day), and/or incidence of landiolol-related complications, such as severe bradycardia.

2.3. Data abstraction and quality assessment

Two reviewers (TT and TY) independently abstracted the data and assessed the methodologic quality of the eligible studies; disagreements were resolved via consensus, after discussion. The data abstracted from each study included the first author's name, year of publication, country, number of study sites, number of patients, patient ages, type of operation, landiolol dose, and timing and duration of landiolol infusion. Methodologic quality was evaluated using the Cochrane risk of bias assessment tool, which assesses randomization, allocation concealment, blinding of study participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other potential sources of bias [14].

2.4. Outcome measures

For the analyses, we defined the primary outcome as the incidence of postoperative AF, defined as new AF occurrences within 1 week of surgery. Secondary outcomes included in-hospital or 90-day mortality, overall complications, myocardial infarctions, strokes, and duration of hospitalization.

2.5. Statistical analysis

We performed the meta-analysis using Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Comparative odds ratios (ORs) were reported with their associated 95% confidence intervals (CIs). We selected the random effects model because this model incorporates statistical heterogeneity [15]. Statistical heterogeneity was determined by assessing I^2 values [14], which were interpreted as follows: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity, and 75–100%, represents considerable heterogeneity [14]. We assessed publication bias using funnel plots.

2.6. Subgroup analyses

We conducted subgroup analyses according to type of surgery (with or without cardiopulmonary bypass), timing of landiolol administration (intra- or postoperative), and risk of bias (low or high). In addition, we also performed an additional analysis using the fixed model (Supplementary material).

3. Results

The primary database (PubMed, Cochrane, and ICHUSHI) searches resulted in 449 articles; 423 were excluded after the title and abstract review. After the full-text review, 6 articles were finally included in this systematic review [8,9,16–19] (Fig. 1). These studies included a total of 571 patients; all of the studies were performed in Japan. Table 1 shows the list of excluded studies. Eight studies, written in Japanese, were excluded because the subjects in 5 studies demonstrated tachycardia or atrial fibrillation/flutter, 2 studies were not RCTs, and the control patients in 1 study received combined landiolol and olprinone. Therefore, none of RCTs, written in Japanese, met our inclusion criteria.

The characteristics of the included studies are summarized in Table 2. Each study included 60–140 patients, ranging in age from 67 to 71 years. Four of the 6 studies involved patients who underwent cardiac surgery involving cardiopulmonary bypass [10,16–18]. In these 6 studies, the initial landiolol dose range was 2–10 μg/kg/min, with infusion durations of 48–72 h. In 4 studies, the landiolol infusion began during surgery [8,9,17,18], whereas it began postoperatively in 2 studies [16,19]. The primary outcome measure was the incidence of AF during the first 7 postoperative days (PODs) in 5 studies [8,9,17–19] and during the first 3 PODs in the remaining study [16]. In 3 studies, patients were considered to have AF if it continued for at least 5 min [8,17,18], 10 min in 2 studies [9,19], and 1 min in 1 study [16].

The risk of bias in each study is shown in Fig. 2. Three studies were classified as having high risks of bias, 2 studies had unclear risks of bias, and one had a low risk of bias. In the 3 studies with high risks of

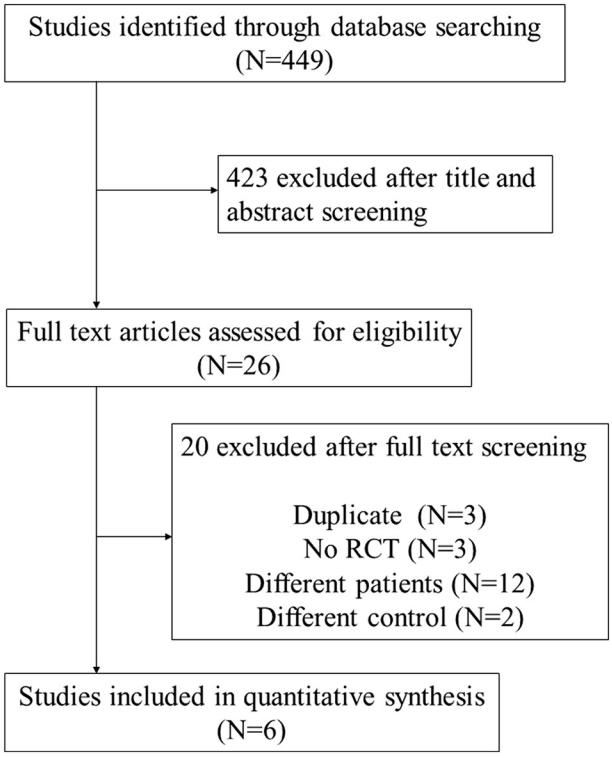

Fig. 1. Flowchart of literature selection. No RCT: this study was not randomized controlled trial.