Comparative Prophylactic and Therapeutic Effects of Intravenous Labetalol 0.4 mg/kg and Nicardipine 20 μg/kg on Hypertensive Responses to Endotracheal Intubation in Patients Undergoing Elective Surgeries With General Anesthesia: A Prospective, Randomized, Double-Blind Study

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ABSTRACT

Background: Laryngoscopy and tracheal intubation (LTI) after induction of general anesthesia often cause hypertension and tachycardia. Labetalol and nicardipine have been used to prevent and treat acute cardiovascular responses to LTI.

Objective: The goal of this study was to compare the preventive and therapeutic effects of labetalol 0.4 mg/kg IV and nicardipine 20 μg/kg IV on hypertensive responses to LTI during induction of general anesthesia.

Methods: Patients undergoing general anesthesia were randomly allocated to 4 groups. In part I (prevention), 80 patients were randomized to receive either 0.4 mg/kg of labetalol (n = 40) or 20 μg/kg of nicardipine (n = 40) 4 minutes before LTI. In part II (treatment), patients were randomized to receive 0.4 mg/kg of labetalol (n = 40) or 20 μg/kg of nicardipine (n = 40) after LTI if hypertension occurred. The number of additional study drug doses required by patients with hypertension (parts I and II) and time to return to normotension (part II) were recorded. Mean arterial pressure and heart rate were monitored, and rate–pressure product was calculated. Adverse events were also monitored.

Results: A total of 130 patients (72 patients in part I and 58 patients in part II) were included in the analysis. In parts I and II, the number of patients who required additional doses of the study drug because of persistent hypertension was lower in the nicardipine groups than in the labetalol groups ($P < 0.05$). Mean arterial pressure was lower and heart rate was significantly higher over time in the nicardipine groups compared with the labetalol groups ($P < 0.05$) in parts I and II. In part II, time to return to normotension was shorter in the nicardipine treatment group than in the labetalol treatment group (61 [21] vs 130 [46] seconds; $P = 0.01$). No statistical differences were observed in the incidence of adverse events except for tachycardia in part I (2 cases in the labetalol prevention group vs 18 cases in the nicardipine prevention group; $P = 0.01$).

Conclusions: Patients who received nicardipine were less likely to require additional doses for either the prevention or treatment of hypertensive responses to LTI and responded to the study drug more rapidly than patients who received labetalol for the treatment of hypertensive responses to LTI. However, labetalol was associated with a lower incidence of tachycardia and less of an increase in rate–pressure product when used for the prevention of hypertension during LTI. ClinicalTrials.gov identifier: NCT01041066. (*Clin Ther*. 2012;34:593–604)

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Key words: hypertensive response, labetalol, laryngoscopy, nicardipine, tracheal intubation.

INTRODUCTION

Laryngoscopy and tracheal intubation (LTI), a method of securing the airway during induction of general anesthesia and critical care, causes sympathoadrenal stimulation and increases plasma catecholamine concentrations.[1] LTI has frequently been associated with significant hypertension and tachycardia during induction of anesthesia,[1] which is particularly dangerous to patients with preexisting cardiovascular or cerebrovascular disease.[2] Controlling blood pressure (BP) and heart rate (HR) responses to LTI is critical for decreasing the incidence of severe adverse events.

A wide variety of antihypertensive drugs and/or techniques have been used for the prevention of acute cardiovascular responses to LTI. During induction of general anesthesia, increasing the depth of anesthesia with opioids[3] and administration of intravenous and/or volatile[4] anesthetic agents have been shown to attenuate the hemodynamic response to LTI. However, deepening anesthesia may also cause bradycardia and/or hypotension. Other methods include the administration of antihypertensive agents such as esmolol,[5,6] labetalol,[7–11] verapamil,[12] diltiazem,[13] and nicardipine.[6,13–16]

The ideal pharmacologic agent for the management of hypertension during LTI would be immediately effective, short-acting, reliable, titratable, and without significant adverse effects. As a combined α_1- and nonselective β-adrenergic blocker, labetalol can be used to treat hypertension caused by hyperadrenergic activity, including during LTI.[14] The drug takes effect within 2 to 5 minutes and reaches a peak effect at 4 to 15 minutes.[15] Acting as a cerebral vasodilator, nicardipine is a dihydropyridine calcium channel blocker that increases stroke volume and coronary blood flow without changing intracranial volume or pressure.[14]

Previous studies have established the efficacy and tolerability of labetalol[7–11] and nicardipine[13,16–18] for the prevention of detrimental cardiovascular changes during LTI. We searched PubMed from January 1895 to December 2009 using the terms: *nicardipine, labetalol, hypertension,* and *intubation* but no study that compared the use of labetalol and nicardipine for the prevention and treatment of adverse cardiovascular response during LTI was found. Therefore, we designed and conducted a prospective, randomized study to compare the prophylactic and therapeutic efficacy of a single bolus administration of 0.4 mg/kg of labetalol and 20 μg/kg of nicardipine, using the dosage from previous studies,[7,18] for hypertensive responses to LTI. In a series of 2 studies, patients received 1 of 2 drugs before (part I) and after (part II) LTI to assess the cardiovascular effects in terms of prevention (part I) and treatment (part II) of hypertension associated with LTI.

PATIENTS AND METHODS

Study Design

The institutional research and ethics committee of Seoul National University Bundang Hospital (Seongnam-si, Kyonggi-do, South Korea) and Boramae Medical Center (Seoul, South Korea) approved the study protocol. Patients provided written informed consent during the preoperative visit and screening procedures. This study consisted of 2 parts that were performed simultaneously. The study was conducted at Seoul National University Bundang Hospital and Boramae Medical Center.

Inclusion and Exclusion Criteria

A total of 160 normotensive Korean patients (American Society of Anesthesiologists classification I), aged 20 to 65 years and scheduled for elective surgery under general anesthesia, were enrolled in this randomized, prospective study. A priori exclusion criteria included diabetes mellitus, hypertension with antihypertensive medication, heart failure or coronary artery disease, second- or third-degree atrioventricular block or bradycardia (<45 beats/min), and baseline BP outside the 100/50– to 140/90–mm Hg range. Additional exclusion criteria were history of asthma or chronic obstructive pulmonary disease, hepatic or renal dysfunction, allergy or other contraindications to study medications, and patients with anticipated difficult intubation (Mallampati class III and IV).[1]

Study Part I

Study part I comprised the comparison between labetalol and nicardipine for the prevention of hypertension after LTI. The anesthesiologist responsible for study coordination assigned a study inclusion number to each patient and randomized patients to receive either labetalol (group PL; n = 40) or nicardipine (group PN; n=40) using the sealed envelope method. The syringes of labetalol and nicardipine were labeled with the patient's inclusion number and prepared by a nurse