

# An Equivalence Trial Comparing Labetalol and Diltiazem in Controlling Emergence Hypertension after Supratentorial Tumor Surgery

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**Background:** Hypertension and tachycardia during emergence from anesthesia for craniotomy could increase risks of cerebral complications. Several anesthetic, sedative, and antihypertensive drugs have been suggested that may be successful at suppressing these unwanted hemodynamic consequences.

**Objective:** To study the equivalent efficacy and side effects of two antihypertensive drugs, diltiazem and labetalol.

**Material and Method:** A block randomized control trial was performed in 184 patients who developed emergence hypertensive response after craniotomy for supratentorial tumor removal. Systolic blood pressure (SBP) of each patient was suppressed by 2.5 mg of study drugs and repeated with fix dosage of 2.5 mg every two to three minutes to maintain SBP lower than 140 mmHg with a cumulative dose within 20 mg. Data regarding demographic, successful rate in controlling hypertension, drug dosage, and incidence of side effects were analyzed.

**Results:** The success rate of treatment of labetalol was equivalent to diltiazem (87.1% and 80.2% respectively) [ $p = 0.003$ , 95% CI = 6.88 (-2.06 to 15.8)]. There was no statistical significant difference on dosage of drugs used or incidence of side effect (hypotension, bradycardia, heart block, and bronchospasm). Median (minimum-maximum) dosage of labetalol and diltiazem were 10 mg (2.5-20 mg) and 10 mg (2.5-20 mg) respectively. The expense for labetalol was 1/6 of diltiazem.

**Conclusion:** Labetalol has equivalent efficacy to diltiazem. Both drugs used low median dosage giving low incidence of side-effects. Labetalol is a good alternative drug to control hypertensive response during emergence from anesthesia for post-craniotomy.

**Keywords:** Labetalol, Diltiazem, Emergence hypertension, Craniotomy

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Major cerebral complications such as intracranial hemorrhage (ICH), edema, and ischemia after intracranial surgery have been reported between 13 and 27.5%<sup>(1-3)</sup>. The causes of complication may come from surgery or from metabolic change during delayed emergence from anesthesia<sup>(1)</sup>. Rapid recovery and extubation is desirable to make an early diagnosis of surgical complications and avoid metabolic effects from anesthesia. On the other hand, rapid recovery that comes along with light anesthesia during emergence period is always with sudden hypertension and tachycardia<sup>(4-9)</sup>. The incidences of the cardiovascular change after neurosurgery from previous reports were between 54 and 91%<sup>(6,10-13)</sup>. Hypertension and tachycardia during emergence that are the result of

sympathetic release of norepinephrine are transient and subside after extubation<sup>(14-19)</sup>. Usually most of the patients tolerate well. However, for neurosurgical patients, the factors involved in emergence hypertensive response after craniotomy are likely different from those in other surgical procedures. Alteration of central autoregulation may result in a positive feedback loop that induces an exaggerate increase in blood pressure and stays for longer time<sup>(20,21)</sup>. Without prompt appropriate hemodynamic control of explosive hypertension during the impairment of cerebral pressure autoregulation from surgery and anesthesia may increase the tendency of ICH from disrupting the hemostatic plugs or develop vasogenic cerebral edema. Tachycardia may cause myocardial ischemia, which, combined with hypertension, may lead to congestive heart failure.

The ideal drug for attenuating these hypertension and tachycardia would be intravenous antihypertensive drugs with rapid onset, high efficacy

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for prompt management, and short duration. The duration must not be over the emergence period, which hypertensive may dramatically reduce to hypotension after stimuli subsides. The drug should have minimum or no effect on cerebral vasodilatation and reflex tachycardia. Cerebral vasodilatation may increase intracranial pressure (ICP) and increase the risks of uneven cerebral perfusion or intracranial steal effect leading to decrease cerebral blood flow (CBF) to affected area and brain damage<sup>(9,22)</sup>.

Most antihypertensive drugs have drawback because of their adverse effects. Nicardipine, one of calcium channel antagonist that had been used widely for attenuating the emergence hypertensive response have adverse effects on cerebral vasodilatation and reflex tachycardia<sup>(21,23)</sup>. Recently, diltiazem and labetalol have been advocated to replace nicardipine for suppressing hypertension from postoperative craniotomy. These two antihypertensive drugs are different in mechanism of action, but their pharmacological effects are similar. Diltiazem, a calcium channel blocker is well established for suppressing hypertension without reflex tachycardia<sup>(16,22-27)</sup>. Labetalol, a selective  $\alpha_1$ -adrenergic antagonist and non-selective  $\beta_1$ - and  $\beta_2$ -adrenergic antagonist has been used successfully<sup>(14,17,28-30)</sup>. If labetalol had equivalent efficacy to diltiazem, we could have another choice of intravenous hypertensive drug that specifically counteracts physiologic change suspected to increase catecholamine secretion during emergence from anesthesia, after craniotomy<sup>(14,15,18,19)</sup>. Lower cost of labetalol is another potential benefit, which is meaningful for the developing country.

### Material and Method

The present study was approved by the Institutional Review Board of Siriraj Medical School, Mahidol University, and all subjects provided informed consents (Clinical Trials Gov. ID: Net 01408524).

Patients aged 18 years and over that underwent elective craniotomy for supratentorial tumor removal between February 2010 and November 2012 were enrolled in the study. The exclusion criteria were the patients who had underlined cardiac problems (bradycardia, heart rate less than 60 BPM, second or third degree heart block), history of severe asthma, chronic obstructive pulmonary disease (COPD), or allergic to investigated drugs and those who were planned to remain intubated after craniotomy.

A block randomized-control trial of diltiazem or labetalol in sealed envelope technique was performed.

All patients had no pre-anesthetic medication. Anesthesia was induced with thiopental (5 mg/kg) or propofol (1-2 mg/kg) and fentanyl (1-2 mcg/kg), facilitated intubation by vecuronium (0.5 mg/kg). Patients were monitored with electrocardiogram (ECG), pulse oximetry, end-tidal CO<sub>2</sub>, temperature, non-invasive blood pressure (NIBP), and intra-arterial blood pressure through an indwelling catheter placed before or immediately after induction of anesthesia. Anesthesia was maintained with isoflurane (0.5-1.2%) in air/O<sub>2</sub> (1:1 LPM), fentanyl infusion (2-10 mcg/kg/hour), and vecuronium (1-2 mcg/kg/hour). Ventilation was controlled to maintain PaCO<sub>2</sub> between 30 and 35 mmHg. The heart rate (HR), systolic blood pressure (SBP), mean arterial blood pressure (MAP), diastolic blood pressure (DBP), and O<sub>2</sub> saturation were recorded every five minutes.

Fentanyl infusion was withheld at 45 to 60 minutes before the end of operation, isoflurane was gradually withdrawn to 0.2 to 0.6% at the time of dural closure. During this period of dural closure, if SBP was higher than 140 mmHg, patients were subsequently randomized to receive 2.5 mg standard preparation (1 mg/ml) of either diltiazem or labetalol and repeated every two to three minutes to maintain SBP less than 140 mmHg. At the conclusion of the operation, the neuromuscular blockade was reversed with 2.5 mg neostigmine and 1.2 mg atropine. Patients were extubated under appropriate condition and transferred to intensive care unit (ICU) with O<sub>2</sub> supplement.

The amount of drugs was recorded along with their side effects. If serious side effects such as bradycardia (HR <50 BPM), hypotension (MAP <60 mmHg), or bronchospasm would occur, the subject would be symptomatically treated.

Those whose hypertension did not respond to 20 mg of the study drugs were rescued by either nicardipine or additional dosage of labetalol or diltiazem, which was chosen by the attending anesthesiologist. In ICU, all monitoring parameters were continuously recorded every 15 minutes for another six hours. High blood pressure in ICU would be treated by routine ICU regiment or traditional antihypertensive drugs, according to the attending physician.

Primary outcome was the response rate of successfully controlled SBP lower than 140 mmHg, with a total accumulation dose of diltiazem or labetalol within 20 mg.

Secondary outcome was concerned about the incidence of side effects during the first six hours

in ICU, and the length of ICU admission. The total accumulative dosage, minimum (min), maximum (max), and median dosage in milligram were considered, and the optimal dosage of each drug for Thai patient was estimated.

### Statistic

Sample size was calculated by assuming the response rate of standard treatment of diltiazem in approximately 95%. The difference in response from labetalol was not greater than 8% by accepting 5% Type I Error, 20% Type II Error, and power of 0.8 by nQuery Advisory calculation. The calculation of minimum sample size of each group randomization yielded 92.

All analyzed were performed by using the program SPSS 17.0. Demographic data and perioperative hemodynamic data were analyzed by Chi-square test and Man-Whitney U test. The non-inferiority was determined by Z test. A *p*-value <0.05 was considered statistical significance.

### Results

Two hundred thirty two patients who underwent supratentorial tumor removal were enrolled in the present study. One hundred eighty four of the 232 patients (79.31%) developed SBP more than 140 mmHg during emergence. Fifty-five of 184 patients (29.89%) were known to have underlying hypertension and 129 patients (70.10%) were normotensive. Ninety-one patients were in diltiazem group and 93 patients in labetalol group. No patient was dropped off from the study (Fig. 1). There was no statistical difference in demographic data (age, sex, body mass index (BMI), operative time, fentanyl dosage, fluid management, and total blood loss) between the two groups (Table 1). The average SBP, MAP, and HR were not different in any time period including pre-operation, pre-treatment, post-treatment, and in ICU (Fig. 2).

The successful rate of controlling SBP lower than 140 mmHg in diltiazem group was 73 of 91 patients (80.2%), and 81 of 93 patients (87.1%) in labetalol group. The median (min-max) dosage requirement of both drugs were 10 mg (2.5-20 mg) and 10 mg (2.5-20 mg) respectively. No statistical difference in the rates of success and dosage used in milligrams. Thus, the study demonstrated the equivalent efficacy of labetalol to diltiazem in controlling blood pressure during emergence from anesthesia for craniotomy [*p* = 0.003, 95% CI = 6.88 (-2.06 to 15.8)] (Table 2).

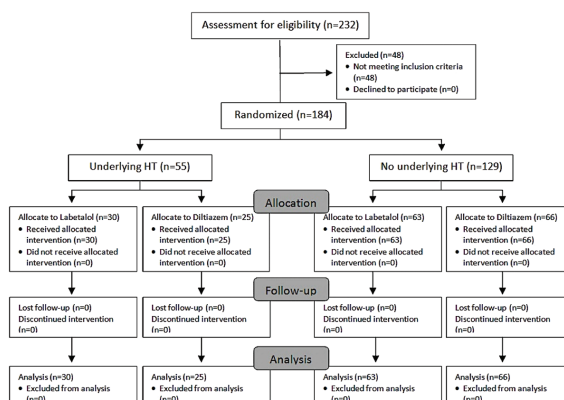
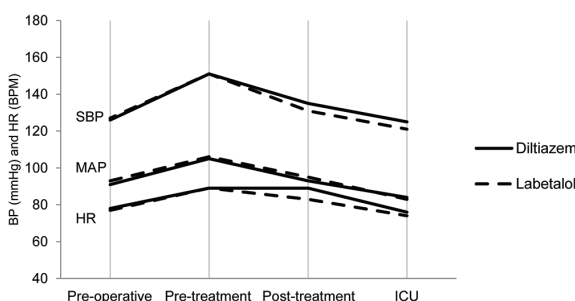


Fig. 1 Diagram describing patient enrollment.



SBP = systolic blood pressure; MAP = mean arterial pressure; HR = heart rate

Fig. 2 The average hemodynamic of the patients during the study period (SBP, MAP, and HR).

Whereas 154 of 184 patients (83.7%) were successfully controlled SBP with total cumulative doses within 20 mg. The others 30 patients (16.3%) who failed to respond were rescued by either nicardipine 0.4 to 2.0 mg or additional dose of diltiazem 10 mg or labetalol 5 to 25 mg.

Table 1. Demographic data

	Diltiazem (n = 91)	Labetalol (n = 93)	<i>p</i> -value
Age (year)	50±13	48±12	0.22
Male	34 (37%)	27 (29%)	0.23
BMI	25±4	25±5	0.79
Operative time (hour)	4±1	4±1	0.12
Fentanyl (mcg)	218±64	208±60	0.10
Crystalloid (ml)	2,420±994	2,376±1,068	0.66
Colloid	38 (42%)	38 (41%)	0.92
Blood	18 (20%)	22 (24%)	0.48
Total blood loss (ml)	645±680	541±493	0.23

BMI = body mass index

Values are mean ± SD or number (proportion)

**Table 2.** Successful rate of controlling SBP <140 mmHg and median (min-max) dosage of the studied drugs

Treatment	Diltiazem (n = 91)	Labetalol (n = 93)	Total (n = 184)
Successful rate (SBP <140 mmHg)	73 (80.2%)	81 (87.1%)	154 (83.7%)
Median of dosage (mg) (min-max)	10 (2.5-20)	10 (2.5-20)	

SBP = systolic blood pressure

During the first six hours of ICU admission, 11 patients (15%) in the diltiazem group, and 13 patients (16%) in the labetalol group developed hypotension (MAP <60 mmHg). In addition, six patients (8.2%) in the diltiazem group and seven patients (6.6%) in the labetalol group developed bradycardia (HR <50 BPM). These side effects responded well to small bolus doses of ephedrine, norepinephrine, or atropine. There was no statistically significant difference of postoperative outcome between the two groups concerning the incidence of hypotension, bradycardia, heart blocks, bronchospasm, and the length of ICU admission (Table 3).

In the subgroup analysis of 55 patients previously diagnosed as having hypertension, the successful rate of controlling SBP with diltiazem were 15 of 25 patients (60%) with median dosage of 10 mg (2.5-20 mg). Whereas 25 of 30 patients (83%) were successfully controlled by labetalol with the median dosage of 10 mg (2.5-20 mg). Thus the successful rate of treatment with labetalol was superior to diltiazem [ $p = 0.04$ , 95% CI = 23.33 (3.71 to 42.5)] with no significant difference in median dosage ( $p = 0.54$ ).

On the other hand, for those 129 non-hypertensive patients, the successful rate of treatment was 58 from 66 patients (88%) for diltiazem with median dosage of 10 mg (2.5-20 mg) and successful rate of treatment with labetalol was 56 out of 63 patients (89%) with median dosage 7.5 mg (2.5-20 mg). Through statistical analysis, the successful rate in non-hypertensive patients for controlling blood pressure was also equivalent [ $p = 0.55$ , 95% CI = -1.01 (-8.27 to 10.29)] with no significant difference in median dosage ( $p = 0.085$ ).

Labetalol seem to be superior to diltiazem in hypertensive patients (Fig. 3). The summary of 95% confidence interval of non-inferiority test is shown in Fig. 4.

## Discussion

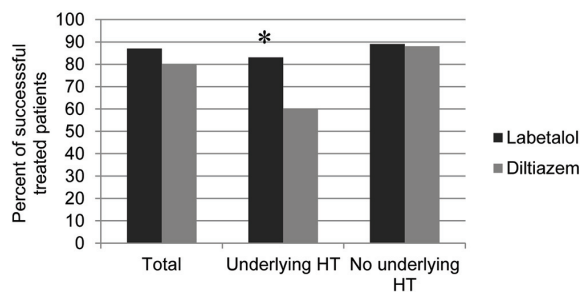
The present study demonstrated equivalent efficacy of labetalol to diltiazem in controlling blood pressure of the patients during emergence from anesthesia for supratentorial craniotomy. The result of

**Table 3.** Postoperative outcomes of 154 treated patients during the first 6 hours in ICU

Incidence	Diltiazem (n = 73)	Labetalol (n = 81)	p-value
Hypotension	11 (15.0%)	13 (16.0%)	1.00
Bradycardia	6 (8.2%)	7 (6.6%)	1.00
Bronchospasm	0	0	0
Heart block	0	0	0
ICU admission (hour), mean $\pm$ SD	25 $\pm$ 23	24 $\pm$ 18	0.60

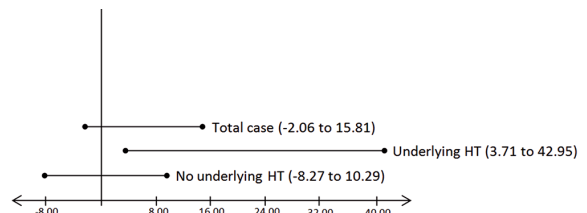
ICU = intensive care unit

our study showed that labetalol has efficacy equivalent to diltiazem in controlling emergence hypertensive response from postoperative supratentorial craniotomy ( $p = 0.003$ , 95% CI = 6.88) with the rate of successful treatment 87.1% and 80.2% respectively.



\*  $p$ -value <0.05

**Fig. 3** Efficacy of diltiazem and labetalol in controlling of emergence hypertensive response in all subjects and subgroup of hypertensive and normotensive patients.



**Fig. 4** The 95% confidence interval of non-inferiority test of the efficiency of labetalol compared to diltiazem in controlling emergence hypertension.



Diltiazem is a benzodiazepine derivative calcium channel antagonist whereas labetalol is a competitive selective  $\alpha_1$ -antagonists and competitive non-selective  $\beta_1$ - and  $\beta_2$ -antagonists. Both drugs have rapid onset within minutes and duration of a few hours, sufficient time for emergence period<sup>(17,22,24,31)</sup>. The onset and duration time are dose dependent<sup>(14,17)</sup>. Diltiazem is unlike nicardipine, as it has no effects on cerebral vasodilatation or reflex tachycardia. Besides, it has other beneficial effect on coronary circulation by improving myocardial oxygen utilization<sup>(22,32)</sup>.

Labetalol has longer onset and duration than diltiazem in clinical dose-range. This longer duration may offer advantages for controlling the hypertension in the postoperative period, but it also may cause hypotension after the stimuli is subsided. Labetalol does not cross blood brain barrier so it has no effect on cerebral vasodilatation or cerebrovascular dynamic (CBF) and ICP<sup>(17,28,29,33)</sup>. Systemic blood pressure is decreased by reducing peripheral vascular resistance through  $\alpha_1$ -antagonist. Reflex tachycardia is triggered by vasodilatation and abolished by  $\beta_1$ - and  $\beta_2$ -antagonists<sup>(14,30,34,35)</sup>.

The evidence of hypertensive response from our group was 79.3% consistent with previous reports (54-91%)<sup>(6,10-13)</sup>. The definition of hypertensive response after craniotomy has not yet been determined. We chose SBP higher than 140 mmHg based on 20% increase from SBP, which is suggested for practice in previously normotensive patients would be maintained (SBP <110 mmHg or MAP 70-80 mmHg)<sup>(29)</sup>. Our desired level of SBP higher than 140 mmHg for hypertensive response is similar to Tsutsui<sup>(27)</sup> and Kross et al<sup>(21)</sup> whereas the others selected SBP at 150 mmHg<sup>(6,17,23)</sup> or 160 mmHg<sup>(10,16)</sup>.

Our study used small fixed dose of 2.5 mg, approximate 0.05 mg/kg, and repeated every two to three minutes until SBP less than 140 mmHg. Our initial dosage was rather small the same as suggested by Tietjen et al<sup>(31)</sup>. In addition, we are aware that hypotension is as important as hypertension. Our regimen offered convenience and eliminated possible human error from the calculation the amount of drug given per kilogram of body weight, which may occur during emergence from anesthesia. We expected a rapid response and easy control SBP because we wanted to start management early when the SBP was higher than 140 mmHg. According to our regimen, we could reach recommended initial dose of 10 mg by our four fixed dosages within six minutes instead of the three minutes of previous studies. From careful titration with small

dosage, some of patients responded well with the first dosage of 2.5 mg. Thai patients may need only small cumulative dosage of both drugs to control effectively the hypertensive response of postoperative craniotomy with the median and range of cumulative drugs of 10 mg and 2.5 to 20 mg.

Since diltiazem and labetalol are drugs used for symptomatic control of SBP, the optimal dosage and methods of administration are variable. Most of previous studies recommended initial dose of 0.2 to 0.25 mg/kg diltiazem or 10 to 12 mg IV in three minutes<sup>(16,22,24,27)</sup>, and 0.2 to 0.25 mg/kg labetalol or 10 to 12 mg IV in two minutes<sup>(14,17,30)</sup>, followed by IV infusion or increment stepwise in mg/kg until SBP response was obtained. The mean cumulative effective doses of diltiazem and labetalol for controlling hypertensive response were suggested to be 0.62 mg/kg (or 30 mg)<sup>(24)</sup> and 0.97 mg/kg (or 48 mg)<sup>(17)</sup> respectively.

In subgroup analysis, showing the effect of diltiazem and labetalol in different population, the successful rate of treatment by diltiazem and labetalol in normotensive patients through our regimen was satisfied with 88% and 89% respectively. For the patients who had history of hypertension, the successful rate of diltiazem seemed to be inferior to labetalol (60% vs. 83%,  $p = 0.04$ ). Patients with underlying hypertension may have more exaggerated cardiovascular response to sympathetic stimulation during the emergence periods than non-hypertensive patients. This was as we suspected that mechanism of action of labetalol,  $\alpha_1$ - and  $\beta$ -adrenergic blocker, which has more sympathetic inhibitory effect, would be more specific treatment than diltiazem. Careful titration of antihypertensive agent administering in chronic hypertensive was suggested to reduce complications. Lastly, combined antihypertensive drugs administration is more efficient than single therapy<sup>(31)</sup>.

There was no bronchospasm or heart block in our study. The advantage of reducing the amount of drugs used is to diminish the side effects and severity of hypotension and bradycardia. This dosage can be used safely, even in the hand of anesthesiologist who is not familiar with the drugs. This point is meaningful in the area lacks of neuro-anesthesiologist, but has to anesthetize for craniotomy surgery. Adverse effects of bronchoconstriction by  $\beta_2$ -antagonist may occurred, but never demonstrate in the dosage clinically used for controlling emergence hypertension<sup>(14,30)</sup>.

Our hospital pharmacy pays 6.4 Baht/mg for labetalol (Avexa<sup>®</sup>) and 36.5 Baht/mg for diltiazem

(Herbessor®). Thus, the overall cost of care would be decreased to 1/6, if labetalol was administered.

In conclusion, the efficacy of labetalol was equivalent to diltiazem in controlling emergence hypertensive response of postoperative craniotomy. Small amount of 2.5 mg/dose repeated every two to three minutes was sufficient to obtain appropriate SBP by average four dosages (10 mg) in six to nine minutes. With this low dose regimen, the side effects of each drug were minimal and easy to be corrected. Labetalol was a good alternative to diltiazem in attenuating high blood pressure response during emergence period of postoperative craniotomy.

#### **What is already known on this topic?**

Hypertension and tachycardia during emergence from anesthesia for craniotomy, could increase risks of cerebral complications. Several anesthetic, sedative, and antihypertensive drugs have been suggested to use with successful suppressing these unwanted hemodynamic consequences.

#### **What this study adds?**

The efficacy of labetalol was equivalent to diltiazem in controlling emergence hypertensive response of postoperative craniotomy. Small amount of 2.5 mg/dose repeated every two to three minutes was sufficient to obtain appropriate SBP.

#### **Acknowledgement**

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#### **Potential conflicts of interest**

The study had been funded from the Great Eastern Drug Co., Ltd. Bangkok, Thailand, which distribute labetalol (Avexa®). All authors declare no financial interests.

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การศึกษาเปรียบเทียบความเท่าเทียมของ *labetalol* และ *diltiazem* ในการควบคุมความดันโลหิตสูงช่วงพื่นจากการระงับความรู้สึกเพื่อการผ่าตัดเนื้องอกสมองบริเวณ *supratentorial*

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**ภูมิหลัง:** ภาวะความดันโลหิตสูงและภาวะหัวใจเต้นเร็วในช่วงพื่นจากการระงับความรู้สึกเพื่อการผ่าตัดสมองจะเพิ่มความเสี่ยงต่อภาวะแทรกซ้อนทางสมองหลังการผ่าตัด ปัจจุบันมีการใช้ยาหลายกลุ่มเพื่อควบคุมความดันเลือดให้อยู่ในเกณฑ์ที่เหมาะสม เช่น ยาระงับความรู้สึก ยากล่อมประสาท ยาลดความดันโลหิตสูง

**วัตถุประสงค์:** การศึกษานี้มีจุดมุ่งหมายเพื่อเปรียบเทียบความเท่าเทียมของ *labetalol* และ *diltiazem* ในการควบคุมความดันโลหิตสูงช่วงพื่นจากการระงับความรู้สึกเพื่อการผ่าตัดเนื้องอกสมองตลอดจนผลข้างเคียงจากยาที่อาจเกิดขึ้น

**วัสดุและวิธีการ:** ผู้ป่วยทั้งหมด 184 ราย ที่เกิดภาวะความดันโลหิตสูงกว่า 140 มม.ปรอท ในช่วงพื่นจากการระงับความรู้สึกเพื่อการผ่าตัดเนื้องอกสมองบริเวณ *supratentorial* จะได้รับการสุ่มเลือกโดยวิธี *block randomization* จากซองจดหมายปิดผนึก เพื่อเลือกให้ยาลดความดันโลหิตสูงระหว่าง *labetalol* หรือ *diltiazem* โดยผู้ฉีดยา ผู้บริหารยา และผู้ป่วยไม่ทราบว่าได้ยาชนิดใด ผู้บริหารยาจะให้ยาครั้งละ 2.5 มิลลิกรัม ทุก 2-3 นาที เพื่อควบคุมความดันให้ต่ำกว่า 140 มม.ปรอท โดยขนาดยารวมสูงสุดคือ 20 มิลลิกรัม ข้อมูลทั่วไปเกี่ยวกับผู้ป่วยและการผ่าตัด อัตราความสำเร็จในการควบคุมความดันโลหิต ตลอดจนขนาดของยาที่ใช้และอุบัติการณ์ของผลข้างเคียงจากยาจะถูกนำมาวิเคราะห์ผลทางสถิติ

**ผลการศึกษา:** อัตราความสำเร็จในการควบคุมความดันโลหิตสูงในกลุ่มที่ได้รับยา *labetalol* เทียบเท่ากับกลุ่มที่ได้รับยา *diltiazem* (87.1% และ 80.2%) [ $p = 0.003$ , 95% CI = 6.88 (-2.06 ถึง 15.8)] จากการศึกษาไม่พบความแตกต่างทางสถิติในขนาดของยาที่ใช้และอุบัติการณ์ของผลข้างเคียงจากยา ค่ากลางของขนาดยาที่ใช้เป็นมิลลิกรัม (ค่าต่ำสุด-ค่าสูงสุด) ในกลุ่ม *labetalol* คือ 10 (2.5-20) มิลลิกรัม และในกลุ่ม *diltiazem* คือ 10 (2.5-20) มิลลิกรัม พบว่าขนาดยารวมที่ใช้ในการควบคุมความดันโลหิตโดย *labetalol* คิดเป็น 1/6 ของ *diltiazem*

**สรุป:** *Labetalol* เทียบเคียงได้กับ *diltiazem* ในการควบคุมความดันโลหิตสูงช่วงพื่นจากการระงับความรู้สึกเพื่อการผ่าตัดเนื้องอกสมองบริเวณ *supratentorial* ทั้งในแง่ของประสิทธิภาพและผลข้างเคียงที่เกิดจากยา

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