Clinical Research Article

Korean J Anesthesiol 2010 October 59(4): 256-259
DOI: 10.4097/kjae.2010.59.4.256

Does a single dose of intravenous nicardipine or nimodipine affect the bispectral index following rapid sequence intubation?

Jeong Jin Lee, Jie Ae Kim, Hyun Joo Ahn, Jin-Kyoung Kim, Mikyung Yang, Soo Joo Choi, Hyun-Soo Kim, and Soo Hyun Yang

Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Theoretically, L-type calcium channel blockers could modulate anesthetic effects. Nicardipine does not affect the bispectral index (BIS), but nimodipine, which can penetrate the blood-brain barrier, has not been studied. The aim of this study was to evaluate whether a single dose of intravenous nicardipine or nimodipine could affect BIS following rapid sequence intubation.

Methods: This study was done in a double-blind, randomized fashion. Anesthesia was induced with fentanyl 2 μg/kg, thiopental sodium 5 mg/kg, and 100% oxygen. After loss of consciousness, patients received rocuronium 1.0 mg/kg and either a bolus of 20 μg/kg nicardipine, nimodipine, or a comparable volume of normal saline (n = 20). Intubation was performed 1 min after study drug administration. BIS, mean blood pressure (MBP), and heart rate (HR) were measured before anesthetic induction, after loss of consciousness, before intubation, during intubation, and 1, 2 and 5 min after intubation.

Results: BIS dropped rapidly after induction but increased to 60 before intubation in all groups irrespective of study drug. In nimodipine, the increase in BIS during intubation was not significant compared to pre-intubation, in contrast to the other two groups, but there was no difference in BIS during intubation. HR significantly increased, but MBP just rose to pre-induction values after intubation in nicardipine and nimodipine groups. BIS, MBP, and HR following intubation increased in control group.

Conclusions: A single dose of intravenous nicardipine or nimodipine could attenuate blood pressure increases but not affect BIS increases in rapid sequence intubation. (Korean J Anesthesiol 2010; 59: 256-259)

Key Words: BIS, Intubation, Nicardipine, Nimodipine.

Received: March 4, 2010. Revised: 1st, April 28, 2010; 2nd, June 1, 2010. Accepted: June 14, 2010.

Corresponding author: Jie Ae Kim, M.D., Ph.D., Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea. Tel: 82-2-3410-0363, Fax: 82-2-3410-6626, E-mail: jakim0813@yahoo.com

Introduction

Theoretically, L-type calcium channel blockers (CCB) could influence anesthetic potency through modulating intracellular messenger function and post synaptic neuronal excitability, affecting secretion of neurotransmitters, or indirectly altering hemodynamics. L-type calcium channels exist in sensory neurons in the spinal cord and the brain [1,2]. L-type CCB potentiate the action of sedatives [3], opioids [4], and anesthetics [5] and several anesthetics act on L-currents in neurons [6-8]. However, CCB activity on anesthesia is still controversial [9,10]. If CCB is administered via a peripheral intravenous route, it needs to cross the blood-brain barrier (BBB) to show anesthetic effects. Nicardipine weakly crosses the BBB, whereas nimodipine crosses better [11].

Intubation causes a peripheral nociceptive response that can induce central arousal [12]. Endotracheal intubation can increase the bispectral index (BIS) and change hemodynamics [12,13]. We compared BIS and hemodynamic changes for nicardipine and nimodipine, which cross the BBB differently, after rapid sequence endotracheal intubation.

Materials and Methods

This study was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from each patient. We enrolled ASA physical status I patients who were scheduled for elective surgery under general anesthesia. Patients with a history of hypertension, diabetes mellitus, body weight >130% of ideal body weight, cardiovascular or cerebrovascular disease, and those receiving medications that affect cardiovascular and psychological function were excluded. The age range was from 18−60 years. Patients were randomly allocated into 3 groups using a computer-generated sequence (n = 20, each).

No premedication was administered. All patients were monitored with noninvasive blood pressure, electrocardiogram, temperature, and peripheral oxygen saturation. BIS was monitored using an Aspect A-1000 EEG monitor, version 3.12 (Aspect Medical Systems, Natick, USA). Baseline values of BIS and vital signs were recorded before induction of anesthesia. Rapid sequence intubation was designed to increase BIS in the control group. Under monitoring, intravenous fentanyl 2 μg/kg was given and anesthesia was induced with thiopental sodium 5 mg/kg and 100% oxygen. After loss of consciousness, patients received rocuronium 1.0 mg/kg and at the same time either a bolus of nicardipine 20 μg/kg, nimodipine 20 μg/kg, or a comparable volume of normal saline. One minute after study drug administration, the trachea was intubated with a direct laryngoscope by a second-year anesthesia resident. Only one attempt was allowed for tracheal intubation. Intubation was accomplished within 30 sec in all cases. After intubation, ventilation was controlled with 1 vol% sevoflurane in 100% oxygen for 5 min. End-tidal carbon dioxide concentration was maintained between 35−40 mmHg throughout the study. Mean blood pressure (MBP), heart rate (HR), and BIS value were recorded before induction of anesthesia (B0), after loss of consciousness (B1), before intubation, during intubation (L0), 1, 2 and 5 min after intubation (L1, 2, and L5). We allocated 16 patients to each group to detect a 5-point increase in BIS after intubation, with $\alpha = 0.05$ and $\beta = 0.2$ [14]. To compensate for drop out, we targeted 20 patients in each group. Data are presented as mean ± SD. SPSS version 12.5 (SPSS Inc, Chicago, IL) was used for analysis.

Statistical analysis was performed using the chi-square test or one-way analysis of variance followed by the Tukey test. One-way analysis of variance for repeated measures followed by multiple comparisons was performed for time-dependent variables. $P < 0.05$ was considered statistically significant.

Results

A total of 63 patients were included in the study. Two patients in the nicardipine group and one patient in the control group were excluded from the study due to difficult intubation. No differences were observed in demographic data, baseline hemodynamics, and BIS values before induction of anesthesia (Table 1).

BIS values rapidly fell after induction of anesthesia (B1) and then increased up to 60 just before intubation in all groups. Nicardipine or nimodipine injection did not affect BIS values 1 min after drug injection. BIS values significantly increased by 7-8 after intubation in controls compared to baseline (B2) ($P < 0.05$, Table 2). Nicardipine injection did not block the increase in BIS following intubation. In the nimodipine group, the increase in BIS during intubation (L0) was not significantly different than baseline (B2), in contrast to the other two groups. However, there was no difference in BIS during intubation (L0) in any group (P = 0.09 vs. control) (Table 2).

MBP fell before intubation in all groups (B2), with larger

Table 1. Characteristics of Patients

	Control group (n = 20)	Nicardipine group (n = 20)	Nimodipine group (n = 20)
Sex (M/F)	9/11	7/13	8/12
Age (yr)	45.1 ± 10.2	43.7 ± 9.3	43.6 ± 11.0
Weight (kg)	57.3 ± 10.7	56.5 ± 12.0	58.0 ± 13.1
Height (cm)	160.1 ± 10.8	159.4 ± 10.1	161.1 ± 11.4

Values are mean ± SD and the number of patients. There were no statistical differences among groups.

changes in the nimodipine group ($P < 0.05$ compared to controls). Intubation increased MBP in controls, but the MBP at 1 or 2 min after intubation (L1, 2) in nimodipine or nicardipine group was similar to before anesthetic induction ($P < 0.05$ compared to control group) (Table 3).

HR significantly rose 1 min after intubation and remained elevated in the control group ($P < 0.05$ compared to pre-induction value). HR rose at 1 min after administration of nicardipine or nimodipine, and remained elevated until 5 min after intubation in the nicardipine or nimodipine group. The nicardipine group showed the highest HR during intubation and 2 min after intubation (L0 and L2) (Table 3).

Discussion

Here, a single dose of intravenous nicardipine or nimodipine blocked blood pressure increases after rapid sequence endotracheal intubation, but did not change BIS increases. CCB may modify anesthetic effects. Dihydropyridine CCB and nitrendipine potentiate the anesthetic effects of benzodiazepine, and Bay K 8644 (an L-type calcium channel activator) reduced the anesthetic potency of midazolam [3]. Verapamil decreased the MAC of halothane in dogs [15], and intrathecally administered L-type calcium channel blockers produce antinociceptive effects in rats [16]. Intravenous nicardipine and diltiazem did not affect BIS under general anesthesia in hypertensive patients [17]. Intravenous nicardipine did not affect anesthetic depth in response to endotracheal intubation [13,18]. Generally, passage of nicardipine across the BBB is limited, whereas nimodipine is relatively permeable to the BBB. L-type CCB are more effective anesthetics when used via the intrathecal or epidural route than intravenously. Intravenously administered nimodipine enhanced the analgesic effect of epidural morphine and epidural nimodipine alone produced brief but intense analgesia [19].

We found that intravenous nimodipine could block the increase in BIS during intubation, but the BIS differences of 4−5 before and during intubation were not sufficient to show any statistical or clinical significance compared to controls. Nicardipine has a rapid onset of action of 1−2 min. Nicardipine 15−30 μg/kg is usually used at 1 min prior to intubation to reduce the hemodynamic response associated with endotracheal intubation. We chose a 20 μg/kg single dose of nicardipine and nimodipine. Other administration routes such as continuous intravenous or intrathecal administration may increase the interactions with anesthetics.

Changes of BIS values after stimulation are caused by direct effects on neuronal function [20] or by indirectly affecting cerebral blood flow [21,22]. Intubation releases central and peripheral catecholamine and increases BIS, MBP, and HR [12,23]. In general, peripheral catecholamine does not cross the BBB. High MBP raises cerebral blood flow and might open the BBB to improve drug effects [24-26]. Peripherally administered nicardipine or nimodipine blocked the increase in MBP associated with endotracheal intubation, but failed to block the increase in BIS, implying little indirect action on BIS through affecting hemodynamics or blocking movement of peripheral catecholamine.

Intravenous epinephrine can influence BIS [27]. In BIS 50,

Table 2. Changes in Bispectral Index (BIS) in Response to Intubation

	Control group (n = 20)	Nicardipine group (n = 20)	Nimodipine group (n = 20)
Before induction	97 ± 1*	97 ± 1*	96 ± 1*
After loss of consciousness (B1)	40 ± 10*	39 ± 9*	39 ± 10*
Before intubation (B2)	60 ± 7	59 ± 9	60 ± 8
L 0	67 ± 9*	64 ± 5*	63 ± 5
L 1	68 ± 9*	66 ± 5*	64 ± 2*
L 2	67 ± 8*	66 ± 4*	65 ± 3*
L 5	68 ± 3*	67 ± 4*	64 ± 3*

Data are presented as mean ± SD (n = 20, each group). L0: during intubation, L1, L2, L5: 1, 2, 5 min after intubation. *$P < 0.05$ compared to before intubation (B2).

Table 3. Changes in Mean Blood Pressure (MBP) and Heart Rate (HR) in Response to Intubation

	Before induction	B1	B2	L0	L1	L2	L5
Control							
MBP (mmHg)	87.2 ± 10.5	84.3 ± 12.1	76.1 ± 11.5*	89.5 ± 20.1	113.6 ± 19.2*	114.5 ± 12.1*	103.4 ± 19.3*
HR (bpm)	85.1 ± 21.3	85.2 ± 17.5	88.3 ± 11.1	90.2 ± 19.1	113.1 ± 23.3*	103.5 ± 26.0*	99.2 ± 24.1
Nicardipine							
MBP (mmHg)	92.2 ± 14.4	85.5 ± 10.5	74.5 ± 18.4*	70.6 ± 21.5*,†	93.6 ± 19.5†	97.5 ± 20.2	90.5 ± 17.4
HR (bpm)	82.5 ± 18.4	81.4 ± 13.7	95.0 ± 13.2	112.1 ± 24.5*,†	126.2 ± 22.1*	123.6 ± 25.4*,†	115.5 ± 24.3*
Nimodipine							
MBP (mmHg)	88.5 ± 16.4	83.2 ± 17.4	65.3 ± 22.7*,†	70.4 ± 21.5*,†	90.7 ± 13.5†	89.7 ± 13.5†	89.8 ± 19.0
HR (bpm)	87.5 ± 17.1	89.5 ± 19.4	102.2 ± 14.4	103.6 ± 18.2*	123.4 ± 11.9*	120.4 ± 12.5*	111.4 ± 16.1*

Data are presented as mean ± SD (n = 20, each group). B1: after loss of consciousness, B2: before intubation, L0: during intubation, L1, L2, L5: 1, 2, 5 min after intubation. *$P < 0.05$ versus before induction. †$P < 0.05$ compared to control group.

the BIS value did not change in response to intravenous epinephrine, but the BIS 70 value rose after epinephrine treatment [27]. Esmolol can blunt the increase in BIS after endotracheal intubation during sevoflurane anesthesia but not desflurane anesthesia [28], probably via the sympathetic stimulation of desflurane. The same stimulation induces different BIS responses according to the underlying conditions. We evaluated the effects of nicardipine and nimodipine on BIS in rapid sequence intubation, which might increase BIS values. However, nicardipine and nimodipine did not affect pre-intubation BIS values in the range of 57–60.

In conclusion, a single dose of intravenous nicardipine or nimodipine decreased the blood pressure response to endotracheal intubation, but did not affect the BIS increase. These results suggest that a single dose of intravenous nicardipine or nimodipine can blunt the hemodynamic response associated with endotracheal intubation but does not affect anesthetic depth in rapid sequence intubation.

References

1. Ricci A, Sabbatini M, Tomassoni D, Mignini F, Petrelli C, Amenta F. Neuronal populations of rat cerebral cortex and hippocampus expressed a higher density of L-type Ca2+ channel than corresponding cerebral vessels. Clin Exp Hypertens 2002; 24: 715-26.
2. Verma D, Gupta YK, Parashar A, Ray SB. Differential expression of L- and N-type voltage-sensitive calcium channels in the spinal cord of morphine+nimodipine treated rats. Brain Res 2009; 1249: 128-34.
3. Dolin SJ, Patch TL, Rabbani M, Taberner PV, Little HJ. Differential interactions between benzodiazepines and the dihydropyridines, nitrendipine and Bay K 8644. Neuropharmacology 1991; 30: 217-24.
4. Omote K, Sonoda H, Kawamata M, Iwasaki H, Namiki A. Potentiation of antinociceptive effects of morphine by calcium-channel blockers at the level of the spinal cord. Anesthesiology 1993; 79: 746-52.
5. Dolin SJ, Little HJ. Effects of nitrendipine on nitrous oxide anesthesia, tolerance, and physical dependence. Anesthesiology 1989; 70: 91-7.
6. Hirota K, Lambert DG. I.v. anaesthetic agents inhibit dihydropyridine binding to L-type voltage-sensitive Ca2+ channels in rat cerebrocortical membranes. Br J Anaesth 1996; 77: 248-53.
7. Olcese R, Usai C, Maestrone E, Nobile M. The general anesthetic propofol inhibits transmembrane calcium current in chick sensory neurons. Anesth Analg 1994; 78: 955-60.
8. Herrington J, Stern RC, Evers AS, Lingle CJ. Halothane inhibits two components of calcium current in clonal (GH3) pituitary cells. J Neurosci 1991; 11: 2226-40.
9. Zarauza R, Sáez-Fernández AN, Iribarren MJ, Carrascosa F, Adame M, Fidalgo I, et al. A comparative study with oral nifedipine, intravenous nimodipine, and magnesium sulfate in postoperative analgesia. Anesth Analg 2000; 91: 938-43.
10. Casey G, Nortcliffe SA, Sharpe P, Buggy DJ. Perioperative nimodipine and postoperative analgesia. Anesth Analg 2006; 102: 504-8.
11. Shibuya T, Watanabe Y. Central effect of Ca2+ channel blockers; multiple sites of action. Nippon Yakurigaku Zasshi 1992; 100: 239-47.
12. Sie MY, Goh PK, Chan L, Ong SY. Bispectral index during modified rapid sequence induction using thiopentone or propofol and rocuronium. Anaesth Intensive Care 2004; 32: 28-30.
13. Kim JH, Lee YS, Kim WY, Kim HJ, Chang MS, Park JY, et al. Effect of nicardipine on haemodynamic and Bispectral Index changes following endotracheal intubation. J Int Med Res 2007; 35: 52-8.
14. Coppens MJ, Versichelen LF, Mortier EP, Struys MM. Do we need inhaled anaesthetics to blunt arousal, haemodynamic responses to intubation after i.v. induction with propofol, remifentanil, rocuronium? Br J Anaesth 2006; 97: 835-41.
15. Maze M, Mason DM Jr, Kates RE. Verapamil decreases MAC for halothane in dogs. Anesthesiology 1983; 59: 327-9.
16. Hara K, Saito Y, Kirihara Y, Sakura S, Kosaka Y. Antinociceptive effects of intrathecal L-type calcium channel blockers on visceral and somatic stimuli in the rat. Anesth Analg 1998; 87: 382-7.
17. Hirota K, Kabara S, Kushikata T, Kitayama M, Ishihara H, Matsuki A. Effects of nicardipine and diltiazem on the bispectral index and 95% spectral edge frequency. Eur J Anaesthesiol 2003; 20: 809-12.
18. Miyazaki M, Kadoi Y, Takashi S, Sawano Y, Shimada H. Comparative effects of propofol, landiolol, and nicardipine on hemodynamic and bispectral index responses to endotracheal intubation: a prospective, randomized, double-blinded study. J Clin Anesth 2008; 20: 257-62.
19. Filos KS, Goudas LC, Patroni O, Tassoudis V. Analgesia with epidural nimodipine. Lancet 1993; 342: 1047.
20. Todd MM. EEGs, EEG processing, and the bispectral index. Anesthesiology 1998; 89: 815-7.
21. Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. Anesthesiology 1986; 64: 551-9.
22. Schlünzen L, Cold GE, Rasmussen M, Vafaee MS. Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission tomography. Acta Anaesthesiol Scand 2006; 50: 306-12.
23. Kayhan Z, Aldemir D, Mutlu H, Oğüş E. Which is responsible for the haemodynamic response due to laryngoscopy and endotracheal intubation? catecholamines, vasopressin or angiotensin? Eur J Anaesthesiol 2005; 22: 780-5.
24. Tuor UI, Edvinsson L, McCulloch J. Catecholamines and the relationship between cerebral blood flow and glucose use. Am J Physiol 1986; 251: H824-33.
25. Myburgh JA, Upton RN, Grant C, Martinez A. The cerebrovascular effects of adrenaline, noradrenaline and dopamine infusions under propofol and isoflurane anaesthesia in sheep. Anaesth Intensive Care 2002; 30: 725-33.
26. Ogoh S. Autonomic control of cerebral circulation: exercise. Med Sci Sports Exerc 2008; 40: 2046-54.
27. Shin HW, Ban YJ, Lee HW, Lim HJ, Yoon SM, Chang SH. Arousal with iv epinephrine depends on the depth of anesthesia. Can J Anaesth 2004; 51: 880-5.
28. Choi SH, Kim CS, Kim JH, Kim BS, Kim EM, Min KT. A single dose of esmolol blunts the increase in bispectral index to tracheal intubation during sevoflurane but not desflurane anesthesia. J Neurosurg Anesthesiol 2009; 21: 214-7.