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# Optimal dose of intravenous oxycodone for attenuating hemodynamic changes after endotracheal intubation in healthy patients
## A randomized controlled trial

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## Abstract

**Background:** Intravenous oxycodone has been used as an adjunct to anesthetic agents. This study aimed to assess the optimal dose of intravenous oxycodone for the attenuation of the hemodynamic responses to laryngoscopy and endotracheal intubation.

**Methods:** A prospective, randomized, double-blind study was conducted. Ninety-five patients were randomly divided into 5 groups based on the oxycodone dose: 0, 0.05, 0.1, 0.15, 0.2 mg/kg. After administering the assigned dose of intravenous oxycodone, anesthesia was induced with thiopental. Heart rate (HR) and blood pressure (BP) were measured at baseline, before intubation, and 1, 2, and 3 minutes after intubation. The percentage increase of BP was calculated as (highest BP after intubation – baseline BP)/baseline BP × 100 (%). The percentage increase of HR was calculated in same formula as above. Hypertension was defined as a 15% increase of systolic BP from baseline, and probit analysis was conducted.

**Results:** Hemodynamic data from 86 patients were analyzed. The percentage increase of mean arterial pressure after intubation in groups 0.05, 0.1, 0.15, and 0.2 was significantly different from that in the control ($P < 0.001$). For HR, the percentage increase was lower than control group when oxycodone was same or more than 0.1 mg/kg ($P < 0.05$). Using probit analysis, the 95% effective dose ($ED_{95}$) for preventing hypertension was 0.159 mg/kg (95% confidence interval [CI], 0.122–0.243). In addition, $ED_{50}$ was 0.020 mg/kg (95% CI, −0.037 to 0.049). However, oxycodone was not effective for maintaining the HR in our study dosage. There were no significant differences in the incidence of hypotension during induction between groups.

**Conclusions:** Using 0.1 mg/kg of intravenous oxycodone is sufficient to attenuate the increase of BP and HR during induction period in healthy patients. The $ED_{95}$, which was 0.159 mg/kg, can be useful to adjust the dosage of IV oxycodone for maintain stable BP during induction of general anesthesia.

**Abbreviations:** BP = blood pressure, DBP = diastolic blood pressure, HR = heart rate, IV = intravenous, MAP = mean arterial pressure, SBP = systolic blood pressure.

**Keywords:** hemodynamics, intubation, oxycodone

## 1. Introduction

Direct laryngoscopy and endotracheal intubation is the most painful and stimulating procedure for anesthesiologists. Endotracheal intubation is frequently associated with an increase of catecholamine and arterial blood pressure (BP).[1,2] This response to laryngoscopy and tracheal intubation may cause a fatal event like cerebral hemorrhage or cardiac failure to patients who have cardiovascular or cerebral disease. Therefore, to prevent the hemodynamic responses to laryngoscopy and tracheal intubation, adjuvant use of opioids, beta-adrenergic blocker like esmolol, or antihypertensive drug during the anesthetic induction phase is common.[3–6]

Oxycodone (14-hydroxy-7,8-dihydrocodeinone) is a semisynthetic opioid derived from the baine and has an agonistic activity on the mu, kappa, and delta receptors.[7] The oral form of oxycodone has been used to control cancer pain or chronic pain for about 100 years. The intravenous (IV) form of oxycodone was recently introduced and makes the control of acute pain in the operating room possible. Intravenous administration of oxycodone can help modifying hemodynamic response to laryngoscopy and intubation during induction phase and can be an adjuvant drug to inhalation agents during maintenance period of general anesthesia. The optimal dose of fentanyl[3] or

dexmedetomidine[8] for attenuating the hemodynamic changes during induction was investigated. However, the recommendations for the appropriate dosage of oxycodone, especially for intubation, are insufficient.

Therefore, we aimed to assess the optimal dose of IV oxycodone for the attenuation of the hemodynamic responses to laryngoscopy and endotracheal intubation.

## 2. Materials and methods

This study was approved by the Chung-Ang University Hospital Institutional Review Board (C2014115 [1311], Seoul, Korea) and registered with ClinicalTrial.gov (NCT02484352). This manuscript adheres to the applicable Equator guidelines. Patients aged between 20 and 65 years who were scheduled to undergo elective orthopedic surgery under general anesthesia were included in the study. All patients were categorized as class 1 under the American Society of Anesthesiology's (ASA) physical status classification system. We excluded patients who were classified as ASA class 2 or higher, expected difficult intubation, and intubation attempt was more than once. Patients were randomly divided into 5 groups according to the received dose of IV oxycodone. The different doses of oxycodone were as follows: 0 (group 0), 0.05 (group 0.05), 0.1 (group 0.1), 0.15 (group 0.15), and 0.2 (group 0.2) mg/kg. The randomization was performed with Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA).

Both the patient and the anesthesiologist who performed the intubation and measured hemodynamic parameters were blinded to their assigned study groups. Another anesthesiologist prepared the drug by mixing the predetermined dose of oxycodone with normal saline and making it up to a total volume of 10 mL. After entrance to the operating room without premedication, the patient's electrocardiogram, pulse oximetry, and noninvasive BP were monitored. The baseline BP was recorded. If baseline systolic blood pressure (SBP) was higher than 150 mmHg, IV midazolam 1 to 3 mg was administered according to the patient's body weight and age for anxiolysis. When the patient's vital signs were stabilized and their SBP was lower than 140 mmHg, the assigned drug was administered intravenously. However, the patients who were treated with midazolam were excluded from the analysis. After obtaining baseline vital sign, we injected the assigned dose of oxycodone intravenously. Thiopental sodium 4 to 5 mg/kg was used for the induction of anesthesia. After confirming loss of consciousness, rocuronium bromide 0.6 mg/kg was administered to facilitate the endotracheal intubation. Mask ventilation was done for over 3 minutes with 100% $O_2$ and sevoflurane 3 vol% from the administration of rocuronium until the time of intubation. Intubation was performed by an experienced anesthesiologist more than 3 minutes after oxycodone injection and the position of the endotracheal tube was confirmed by auscultation. The mechanical ventilation was continued with $O_2$ and 50% nitrous oxide. The mechanical ventilation was set at a tidal volume of 10 mL/kg and a respiratory rate of 8 to 12 breaths per minute to maintain the end-tidal carbon dioxide between 30 and 35 cmH$_2$O. The BP and heart rate (HR) were recorded just before intubation, and at 1, 2, and 3 minutes after intubation. Hypotension was defined as a 20% decrease of BP from the baseline and ephedrine 5 mg or phenylephrine 25 to 50 μg was administered via the IV route, depending on HR, at the anesthesiologist's discretion.

The sequential changes of vital signs at 5 time points were recorded. Including baseline level, we recorded the highest HR, SBP, mean arterial pressure (MAP), and diastolic blood pressure (DBP) at preintubation, and at 1, 2, and 3 minutes after intubation. The differences between these values and the baseline HR, SBP, and MAP were obtained. The percentage increase of HR was calculated as (highest HR − baseline HR)/baseline HR × 100 (%). The percentage increases of SBP, MAP, and DBP were calculated in a similar manner and compared between groups.

We performed a one-way analysis of variance (ANOVA) to reveal the differences in the percentage increases of MAP among the 5 groups (oxycodone 0, 0.05, 0.1, 0.15, 0.2 mg/kg). Fifteen patients in each group were required with a power of 0.9 and a risk of 0.05 for a type-I error for the 2-tailed statistical analysis. After assuming a loss to follow-up rate of 20%, we included 19 patients in each group. The difference in percentage change of each dosage group was compared using one-way ANOVA and the comparison of 2 groups was done by Tukey post analysis. The changes of hemodynamic parameters in each group were compared using repeated measures ANOVA with Greenhous–Geisser correction and Bonferroni post-hoc analysis to find out the actual different groups. Probit analysis was used to derive the optimal dose of oxycodone for attenuating the hemodynamic responses to intubation. The incidence of use of vasopressors was also compared using a chi-square test. Results were considered to be statistically significant when the $P$ value was less than 0.05. SPSS 21.0 was used for the statistical analyses (SPSS Inc., IBM, Chicago, IL).

## 3. Results

A total of 95 patients were recruited but 9 were excluded (Fig. 1). One patient's data were missing and in another 2 patients, intubation was successful at second trial. There were 6 patients who were treated with midazolam due to baseline hypertension before administration of induction agents. IV midazolam was administered to 2 persons in group 0, 3 persons in group 0.05, and 1 for group 0.1. Therefore, data from 86 patients were analyzed. There were no significant differences in demographic data between the groups (Table 1).

SBP and MAP were significantly increased from baseline level at 1 minute after intubation in group 0 ($P < 0.001$). SBP at 1 minute after intubation in group 0 was significantly different from groups 0.05, 0.1, 0.15, and 0.2 and MAP was higher than groups 0.1, 0.15, and 0.2 ($P < 0.05$). SBP and MAP were significantly decreased compared with the baseline measurement at 3 minutes after intubation in groups 0.1, 0.15, and 0.2. The HR after intubation was significantly higher than the baseline HR in all groups ($P < 0.001$). The HR stabilized after 3 minutes but still remained higher than the baseline in all groups ($P < 0.001$ in groups 0, 0.5, and 0.15 and $P < 0.05$ in groups 0.1 and 0.2) (Fig. 2).

The percentage increase of MAP within 3 minutes after intubation showed a significant difference across groups 0.05, 0.1, 0.15, and 0.2, compared with group 0 ($P < 0.001$). The percentage increase of HR in groups 0.1, 0.15, and 0.2 was significantly different from that in group 0 ($P < 0.05$) (Fig. 3).

Probit analysis was done to derive the optimal dose of oxycodone (Fig. 4). We found that 0.159 mg/kg (95% confidence interval [CI], 0.122–0.243) of IV oxycodone was needed to attenuate the hemodynamic response to intubation, which was defined as an increase in SBP of no more than 15% over the baseline level in 95% of the patients (ED$_{95}$). To achieve the same effect in 50% of the patients (ED$_{50}$), the required dose was 0.020 mg/kg (95% CI, −0.037 to 0.049). Similarly, for the MAP, the
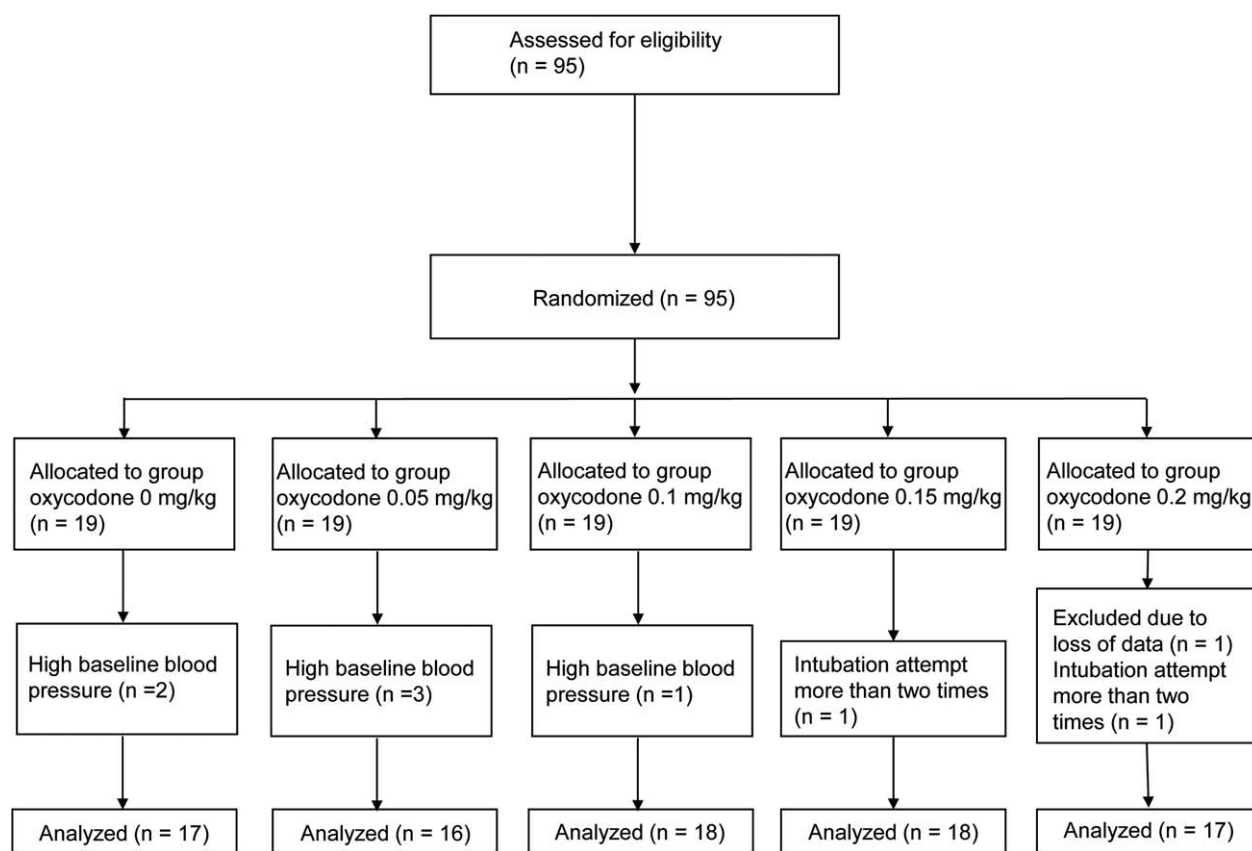
**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) diagram.

$ED_{95}$ of oxycodone for prevention of increase of MAP more than 15% from baseline was 0.219 mg/kg (95% CI, 0.171–0.335) and the $ED_{50}$ was 0.054 mg/kg (95% CI, 0.001–0.083). Oxycodone was not found to be effective for maintaining the HR at less than 115% of the baseline value. The $ED_{50}$ for preventing an increase of HR to more than 20% over the baseline level was far more than our experimental dose.

There were 3 patients who showed hypotension in 3 different groups (groups 0.05, 0.1, and 0.15) but there was no significant difference in the incidence of hypotension between the groups.

## 4. Discussion

We demonstrated that the use of IV oxycodone, even at dosages higher than 0.1 mg/kg, led to an attenuation of the percentage increase in HR and MAP during endotracheal intubation using thiopental in healthy patients. The $ED_{95}$ to avoid hypertension,

which was defined as an increase in SBP of more than 15% over the baseline, was 0.165 mg/kg. This result can be used to guide the adequate administration of IV oxycodone to avoid hypertension during intubation.

Previous studies have evaluated the optimal dose of fentanyl for attenuating the hemodynamic response during induction and intubation. Sawano et al[3] found that 2 μg/kg fentanyl without hypertension and 4 μg/kg fentanyl with hypertension was sufficient to minimize the change in HR and BP. Furthermore, 5 μg/kg fentanyl was suggested to completely abolish the hemodynamic responses to tracheal intubation in another study.[9] However, there have not been enough trials to determine the optimal dose of IV oxycodone to minimize the changes in HR and BP after intubation.

In addition, there have been a few investigations to find out the equianalgesic dose ratio of oxycodone to fentanyl. The equianalgesic dose ratio of morphine to oxycodone was known.

**Table 1**

Demographic data and adverse effects.

| | Group 0 (n=17) | Group 0.05 (n=16) | Group 0.1 (n=18) | Group 0.15 (n=18) | Group 0.2 (n=17) |
|---|---|---|---|---|---|
| Gender (F/M) | 3/12 | 9/7 | 7/11 | 7/11 | 9/8 |
| Age, yr | 37.4±10.1 | 38.0±13.2 | 34.5±14.4 | 34.6±11.6 | 38.1±13.3 |
| Height, cm | 170.9±9.9 | 165.5±7.3 | 166.9±9.6 | 169.5±8.7 | 166.8±8.3 |
| Weight, kg | 68.9±10.9 | 61.7±9.9 | 65.5±11.9 | 68.8±11.8 | 64.8±10.0 |
| Incidence of hypotension | 0 | 1 | 1 | 1 | 0 |

Data are expressed as mean±SD except sex and incidence of hypotension (number of patients).
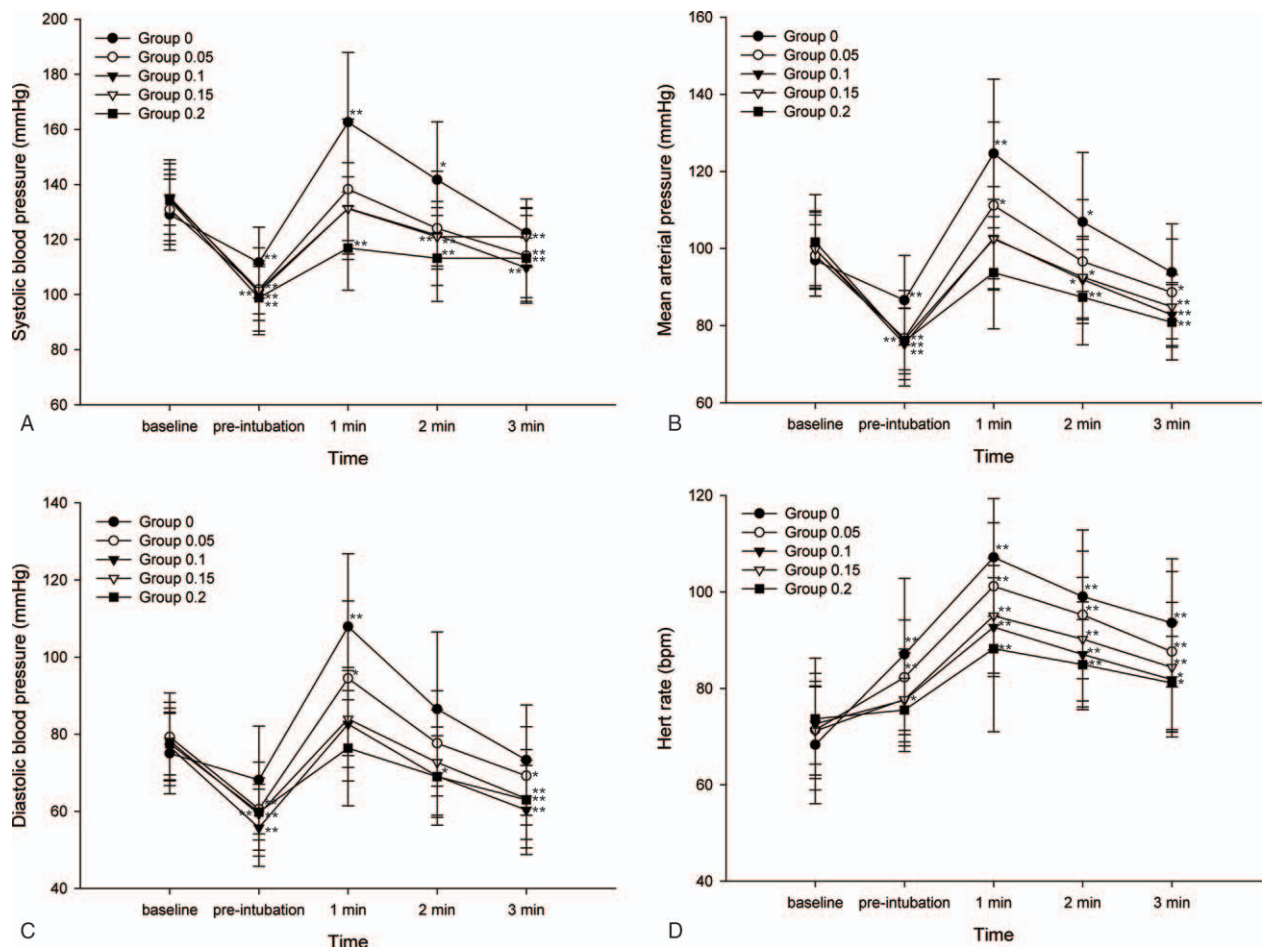
**Figure 2.** Sequential changes of hemodynamic parameters (A) systolic blood pressure, (B) mean arterial pressure, (C) diastolic blood pressure, (D) heart rate. $^{*}P < 0.05$ compared with baseline values, $^{**}P < 0.01$ compared with baseline values.

For the IV use of oxycodone and morphine, the equianalgesic dose ratio of morphine to oxycodone was found to vary from 0.7:1 to 1:1.[10,11] In a study comparing IV oxycodone and IV fentanyl, the authors compared the conversion ratios of both drugs to morphine,[12] and suggested a potency ratio of 1:100.[13] In this study by Koch et al,[13] oxycodone showed better analgesia but also more side effects. Comparing 2 μg/kg fentanyl from Sawano's study with our data, 0.159 mg/kg for ED$_{95}$, the equianalgesic ratio between oxycodone and fentanyl is 1:82.5. This result indicates that a lower dose of oxycodone is sufficient for use during induction of general anesthesia than previously known (1:100).[13] However, Koch et al used opioids to control postoperative acute pain rather than hemodynamic response after intubation which makes the comparison of the equianalgesic ratio to be not appropriate.

Regarding the HR, previous studies using IV fentanyl showed various results. In patients without hypertension, 2 μg/kg of fentanyl could abolish the increase of both HR and MAP. However, 4 μg/kg fentanyl was needed to achieve stabilization of HR and MAP in patients with hypertension.[3] Hosalli et al[9] found no statistically significant difference in the mean HR between a fentanyl 3 μg/kg group and a 5 μg/kg group in healthy patients without hypertension. There was another study that evaluated hemodynamic response to intubation using alfentanil, esmolol, and their combination.[4] Patients who were premedi-

cated with 0.1 mg/kg oxycodone 60 minutes before anesthesia was enrolled in this study of Korpinen et al.[4] Both 15 and 30 μg/kg alfentanil prevented the increase of arterial pressure but only 30 μg/kg prevented that of the HR. Putting previous studies together, we need more dose of opioid to prevent increase of HR than BP during induction phase. In our study, IV oxycodone at the highest studied dosage of 0.2 mg/kg could not abolish the sequential increase of HR from baseline level within 3 minutes after intubation. However, the percentage increase of HR was significantly lower than the group without oxycodone when more than 0.1 mg/kg IV oxycodone was used. We concluded that a higher dose of oxycodone is required to completely prevent an absolute increase in HR, but lower doses are still able to mitigate the percentage increase in HR during induction. In addition, to avoid the side effects of high dose opioid like postoperative respiratory depression, we can consider combined use of beta-adrenergic blocker with opioid to prevent tachycardia after intubation.

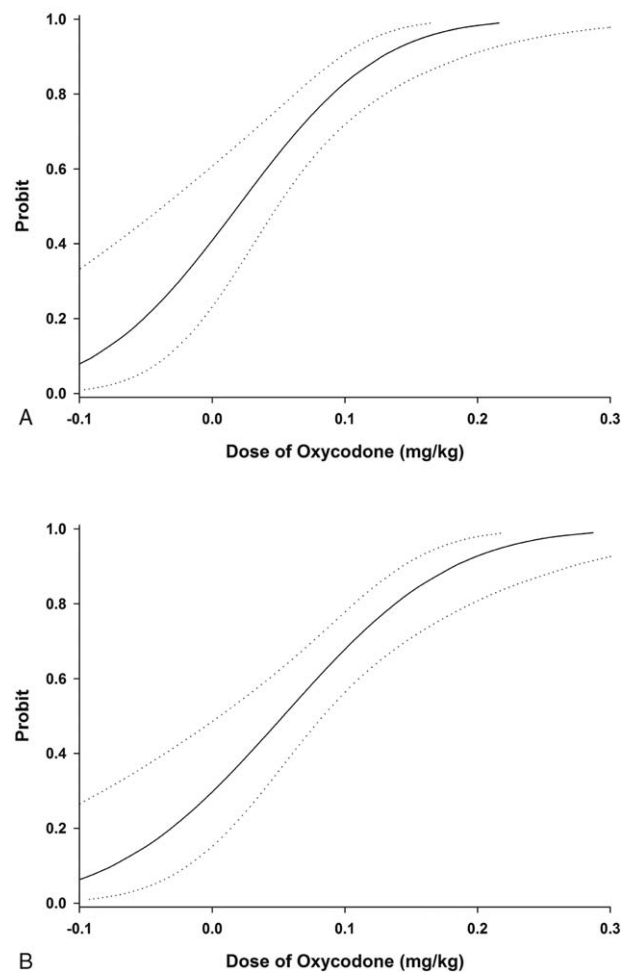We used thiopental in this study because, in our pilot study, we found that a small dose of IV oxycodone induced hypotension when used in conjunction with 2 mg/kg propofol during the induction of general anesthesia. Therefore, the optimal oxycodone dose of 0.165 mg/kg only applies to usage with thiopental. Further trials are needed to determine the optimal dosage for use with other induction agents.
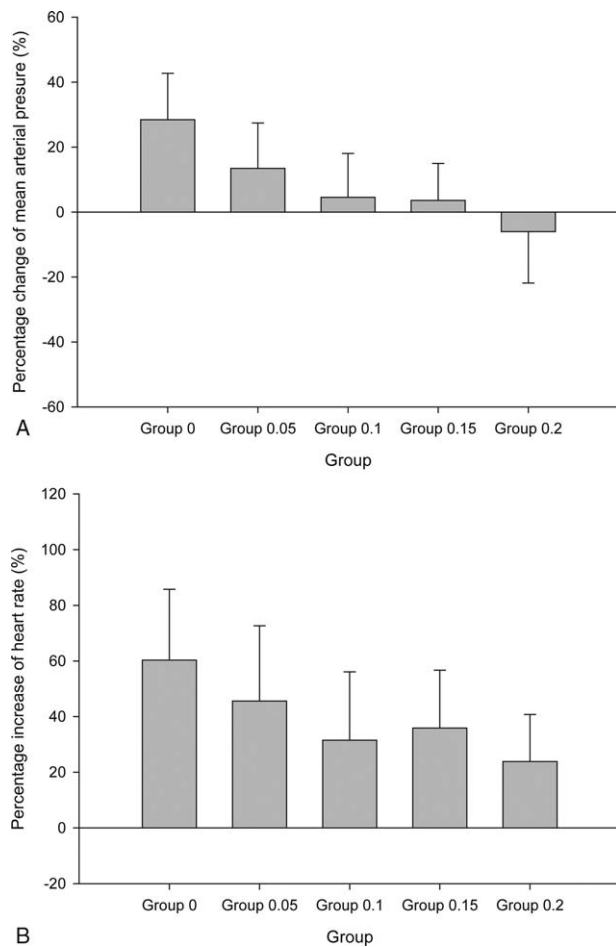
**Figure 3.** Comparison of the percentage change of (A) mean arterial pressure and (B) heart rate according to the dosage of oxycodone. $^*P < 0.05$ compared with group 0.



**Figure 4.** Probit analysis. (A) Probability of preventing hypertension in systolic blood pressure after intubation. The $ED_{95}$ of intravenous oxycodone for prevention of increase of systolic blood pressure more than 15% from baseline is 0.159 mg/kg (95% confidence interval [CI], 0.122–0.243 mg/kg) and $ED_{50}$ is 0.020 mg/kg (95% CI, −0.037 to 0.049). (B) Probability of preventing hypertension in mean arterial pressure after intubation. The oxycodone $ED_{95}$ is 0.219 mg/kg (95% CI, 0.171–0.335) and the $ED_{50}$ is 0.054 mg/kg (95% CI, 0.001–0.083). Hypertension was defined as an increase more than 15% over the baseline level. Probability of preventing an increase of HR more than 15% or 20% of the baseline value was not obtained.

The dosage of oxycodone did not show a significant impact on hypotension incidence within 3 minutes after intubation in our study. However, considering that the preparation of the surgical drape usually takes longer, the incidence of adverse hypotension in practice will be higher than our result. Therefore, the choice of oxycodone dose should be made with this in mind. In addition, the onset of effects of oxycodone was similar to that of fentanyl (2–3 minutes after IV injection). However, the duration of action was longer than that of fentanyl ($t_{1/2}$: 4 hours 52 minutes vs. 3 hours 39 minutes).[9] Therefore, after a short procedure, such as removal of metal after an internal fixation of an extremity fracture or tendon release, the effect of oxycodone may persist until the emergence period, stabilizing the hemodynamics in the meantime.

The present study had several limitations. First, the enrolled patients were all healthy (ASA class 1), without any serious underlying disease. As the hemodynamic response during induction of general anesthesia is different based on the presence of underlying factors, especially hypertension and age, the amount of opioid will need to be adjusted in these populations. Second, we used thiopental for initiation of general anesthesia. The hemodynamics will be different when using other induction agents, like propofol. Therefore, our results are not applicable to different protocols of induction for general anesthesia. However, by comparing the typical dosage of fentanyl with other induction agents, an adequate dose of oxycodone could also be determined

from our study. Lastly, we did not record any observations on the postoperative effects, such as the time of emergence or level of postoperative pain. For surgeries lasting less than 2 hours, the oxycodone administered during induction may affect the emergence profile.

In conclusion, the simultaneous administration of more than 0.1 mg/kg IV oxycodone during induction with thiopental in healthy patients showed satisfactory hemodynamic stability. The $ED_{95}$ of oxycodone to avoid endotracheal intubation induced hypertension was 0.159 mg/kg.

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