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# ผลของการใช้ยาอิโตมิเดทเป็นยานำสลบในการใส่ท่อช่วยหายใจแบบฉุกเฉินต่อการเกิดภาวะความดันโลหิตต่ำหลังการใส่ท่อช่วยหายใจในผู้ป่วยสูงอายุ

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# Effect of Etomidate Used as Induction Drug for Emergency Intubation on Post Intubation Hypotension in Elderly Patients

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Received: 18 March 2024 /Review: 19 March 2024 / Revised: 14 May 2024 /
Accepted:15 May 2024

## บทคัดย่อ

**หลักการและวัตถุประสงค์:** การใส่ท่อช่วยหายใจแบบฉุกเฉินเป็นการรักษาเพื่อช่วยชีวิตที่พบได้บ่อยในห้องฉุกเฉิน ในปัจจุบันการทำหัตถการดังกล่าวด้วยวิธีการใส่ท่อช่วยหายใจชนิดรวดเร็วถือเป็นวิธีมาตรฐาน ซึ่งยานำสลบที่มักถูกนำมาใช้คือยาอิโตมิเดท เนื่องจากมีผลต่อระบบไหลเวียนโลหิตค่อนข้างน้อยและมีระยะเวลาในการออกฤทธิ์สั้น อย่างไรก็ตามปัจจุบันมีการศึกษาเกี่ยวกับผลข้างเคียงของยาอิโตมิเดทในกลุ่มผู้ป่วยสูงอายุค่อนข้างจำกัด วัตถุประสงค์ของการศึกษานี้จึงต้องการศึกษาผลของการใช้ยาอิโตมิเดทในการใส่ท่อช่วยหายใจแบบฉุกเฉินในผู้สูงอายุต่อการเกิดภาวะความดันโลหิตต่ำหลังใส่ท่อช่วยหายใจ

**วิธีการศึกษา:** การศึกษานี้เป็นการศึกษาแบบย้อนหลังในผู้ป่วยสูงอายุที่ได้รับการใส่ท่อช่วยหายใจแบบฉุกเฉินในห้องฉุกเฉิน ผู้ป่วยถูกแบ่งเป็นกลุ่มที่ได้รับยาอิโตมิเดท และกลุ่มที่ไม่ได้รับยาอิโตมิเดทตามชนิดของยาที่ใช้ในการนำสลบ โดยผลลัพธ์หลักของงานวิจัยคือการเกิดภาวะความดันโลหิตต่ำหลังใส่ท่อช่วยหายใจ และผลลัพธ์รองคือการเริ่มหรือการเพิ่มปริมาณยาตีบหลอดเลือดที่ใช้ภายใน 24 ชั่วโมง การเริ่มการใช้ยาไฮโดรคอร์ติโซนภายใน 24 ชั่วโมง และการเสียชีวิตในโรงพยาบาล

**ผลการศึกษา:** มีผู้ป่วยในการศึกษาทั้งสิ้น 231 ราย โดยแบ่งเป็นกลุ่มผู้ป่วยในกลุ่มที่ได้รับยาอิโตมิเดท 118 และ 113 รายในกลุ่มที่ไม่ได้รับยาอิโตมิเดท มีผู้ป่วย 29 รายในผู้ป่วยกลุ่มที่ได้รับยาอิโตมิเดทและ 18 รายในกลุ่มที่ไม่ได้รับยาอิโตมิเดทเกิดภาวะความดันโลหิตต่ำหลังใส่ท่อช่วยหายใจ จากการวิเคราะห์โดยการถดถอยโลจีสติกไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติของการใช้ยาอิโตมิเดทและการเกิดภาวะความดันโลหิตต่ำหลังใส่ท่อช่วยหายใจในผู้สูงอายุ adjusted odds ratio (AOR) 2.10 (0.94-2.71) p=0.070 อย่างไรก็ตามพบว่าการใช้ยาอิโตมิเดทมีความสัมพันธ์กับการเริ่มหรือการเพิ่มปริมาณยาตีบหลอดเลือดที่ใช้ภายใน 24 ชั่วโมง การเริ่มการใช้ยาไฮโดรคอร์ติโซน (hydrocortisone) ภายใน 24 ชั่วโมง และการเสียชีวิตในโรงพยาบาล

**สรุป:** การศึกษานี้ไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติของการใช้ยาอิโตมิเดทและการเกิดภาวะความดันโลหิตต่ำหลังการใส่ท่อช่วยหายใจแต่พบว่ามีความสัมพันธ์กับการเริ่มหรือการเพิ่มปริมาณยาตีบหลอดเลือดที่ใช้ภายใน 24 ชั่วโมง การเริ่มการใช้ยาไฮโดรคอร์ติโซนภายใน 24 ชั่วโมง และการเสียชีวิตในโรงพยาบาลในผู้ป่วยสูงอายุ

**คำสำคัญ:** ผู้สูงอายุ, การใส่ท่อช่วยหายใจแบบฉุกเฉิน, ห้องฉุกเฉิน, อิโตมิเดท, ความดันโลหิตต่ำหลังใส่ท่อช่วยหายใจ

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## Abstract

**Background and Objective:** Emergency tracheal intubation is a common lifesaving treatment in the emergency department, rapid sequence intubation is the standard method for performing this procedure. Etomidate is an induction drug which is commonly used due to minimal hemodynamic disturbance and having a short duration; however, the evidence of adverse effects in elderly patients are limit. The objective of this study was to evaluate the effect of etomidate used as induction drug for emergency intubation in elderly patients and post intubation hypotension.

**Methods:** This was a retrospective study in elderly patients who were intubated in the emergency department. The enrolled patients were divided into etomidate used group and non-etomidate used group according to induction drugs used for intubation. The primary outcome was post intubation hypotension and secondary outcomes included the initiation or increased doses of vasopressors within 24 hours, the initiation of hydrocortisone within 24 hours and in hospital mortality.

**Results:** A total of 231 elderly patients were enrolled in this study, 118 patients were in etomidate used group and 113 patients were in non-etomidate used group. In etomidate used group, 29 patients developed post intubation hypotension and 18 patients in non-etomidate used group experienced post intubation hypotension. Multivariable logistic regression showed no statistically significant association of etomidate used and post intubation hypotension in elderly patients adjusted odds ratio (AOR) 2.10 (0.94-2.71) p=0.070. However, etomidate was associated with the initiation or increased doses of vasopressors within 24 hours, the initiation of hydrocortisone within 24 hours and in hospital mortality.

**Conclusions:** The study demonstrated that etomidate used was not significantly associated with post intubation hypotension but significantly associated with initiation or increased doses of vasopressors within 24 hours, initiation of hydrocortisone within 24 hours and in hospital mortality in elderly patients.

**Keywords:** elderly, emergency intubation, emergency department, etomidate, post intubation hypotension

## Introduction

Etomidate is a worldwide drug used for induction in rapid sequence intubation because of minimal hemodynamic disturbance and short duration.[1] However, the previous studies found that etomidate may induce hypotension, which varies in each patient depending on volume status, vascular tone, and sympathetic nervous system activation, and it associates to decrease arterial elastance (Ea) and transients disturb adrenal gland function via inhibition of 11 β-hydroxylase enzyme which results in hypotension.[2,3] Although, the latest clinical practice guideline suggests that there is no difference between etomidate and other induction agents for rapid sequence intubation on hypotension and mortality.[4] Some current clinical studies evaluated the effect of etomidate on hemodynamic status of patients, they found that etomidate was associated with higher incidence of clinical hypotension.[5,6] Moreover, there are growing evidence that etomidate was associated with initiation of vasopressor and higher risk of mortality.[6-8] Therefore, the use of etomidate as induction drug in emergency tracheal intubation is controversy.

The population aging society is rapidly increasing worldwide, the incidence of elderly patients who visit the emergency department and receive tracheal intubation is also annually increasing.[9] Hemodynamic status in elderly patients is commonly labile from increased systemic vascular resistance and decreased arterial compliance, dehydration, coronary arteriosclerosis, etc.[10] Therefore, anesthetic drugs used in these patients should be highly concerned. Post intubation hypotension is a common complication after emergency tracheal intubation and increase incidence in older patients.[9] Although, there is the suggestion to use etomidate with decreased doses of etomidate in elderly patients to prevent hypotension, there was limit of supported evidence.[11-13]

The aim of this study was to evaluate etomidate used as an induction agent for emergency intubation on post intubation hypotension in elderly patients.

## Methods

### Study design and setting

This retrospective cohort study assessed the patients presented at the Department of Emergency Medicine (ED), Khon Kaen hospital – tertiary care hospital with in-patient capacity of 1,000 beds from 1st January 2021-31st October 2023. The study protocol was approved by the Institutional Review Board of Khon Kaen hospital under a waiver of informed consent with the approval number of KEXP67001.

### Participants and eligibility criteria

The patients who were intubated during admitted at the ED, Khon Kaen hospital were assessed for eligibility. The inclusion criteria were adults aged ≥60 years old, who were intubated in the emergency department. The exclusion criteria included incomplete data, and transferred to other hospitals.

### Data collection

The data were derived from the electronic database of Khon Kaen hospital. Patients with age ≥60 years old who developed respiratory failure and required intubation during admission at the ED, Khon Kaen hospital from 1st January 2021-31st October 2023 were screened and enrolled according to the eligibility.

Baseline characteristics data included sex, age, body mass index (BMI), comorbidities initial vital signs (heart rate, respiratory rate, oxygen saturation, non invasive blood pressure), indication for intubation, other analgosedation drugs used, paralytic drugs used, diagnosis, post intubation vital signs, post intubation hypotension, post intubation vasopressor used and post intubation corticosteroid used and in hospital mortality were collected. Patients were divided into etomidate used group and non-etomidate used group according to induction drugs used for intubation.

### Sample sizes calculation

According to the sample size estimation for cohort study formula[14]

$$N_{exposure} = \frac{\left[ z_1.\alpha_{/2}\sqrt{pq(1+1/r)} + z_1.\beta\sqrt{p1q1=p2q2/r} \right]^2}{Ip1-p2I}$$

p1 = P (outcome/exposure), q1=1-p1

p2 = P (outcome/unexposure), q2=1-p2

$\overline{p} = p1+p2r$ , $q = 1-p$

$r= N_{exposure}/ N_{unexposure}$

$\alpha$=The level of significance, 0.05

$\beta$= 0.2 (80%power)

From Mohr et al. study[1], post intubation hypotension of etomidate used was 49.5% and 68% in other drugs used, replaced p1=0.49 and p2=0.68, the sample size estimation of this study was 105 per group and we calculated missing data 10% therefore, the sample size of this study was 231.

### Outcomes

Primary outcome was post intubation hypotension. Secondary outcomes included the initiation or increased doses of vasopressors within 24 hours, the initiation of hydrocortisone and in hospital mortality.

### Operational definition

Post intubation hypotension was one of the followings criteria within 1 hour after intubation[15]

1. Systolic blood pressure <90 mmHg
2. A decrease in systolic blood pressure of ≥20% from the baseline
3. A decrease in mean arterial pressure to ≤65 mmHg
4. Treatment required for hypotension
5. Initiation or increased doses of vasopressor medication

### Statistical Analysis

All baseline variables were examined using descriptive statistic. Continuous variables were presented using either mean and standard deviation or median and range as appropriate. The t-test or Mann-Whitney U test was used to analyze the between group differences. Categorical variables were presented using frequent count and percentage and chi-square test was used to determine the baseline differences. The primary and secondary outcomes were analysed and presented as odds ratio (OR) and 95% confidence interval. The important demographic variables that influence the outcomes, ($p<0.2$) were included in multivariable analysis by using multiple logistic regression and were presented as adjusted odds ratio (AOR) and 95% confidence interval. Statistical significance determined as $p<0.05$. All data analysis were performed using STATA version 16.

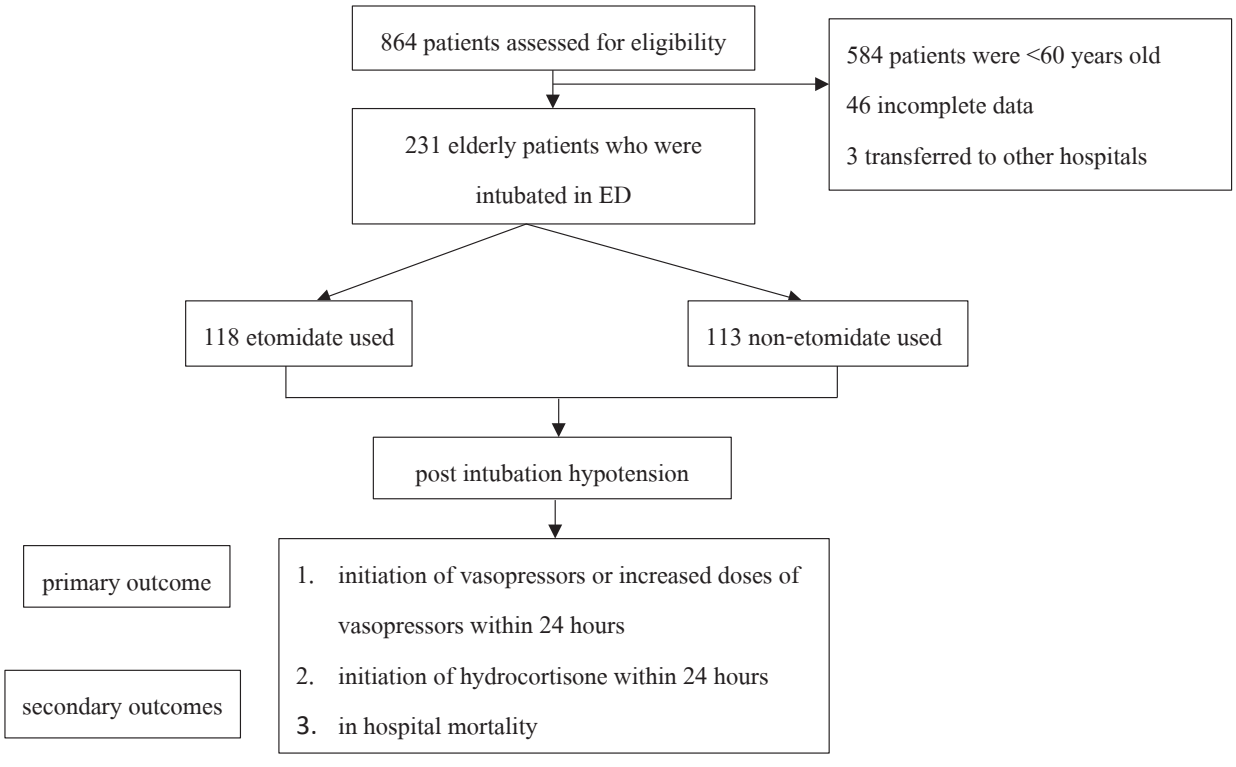


**Figure 1** Study flow

## Results

A total of 864 intubated patients were assessed for eligibility. Of these, 231 patients met the inclusion criteria and were enrolled in this study (Figure 1). One hundred and eighteen patients were assigned to etomidate used group and 113 were in non-etomidate used group according to type of induction drugs used. Mean age of patients was approximately 70 years old in both groups. The initial median blood pressure data (systolic blood pressure, diastolic blood pressure and mean arterial pressure) were statistically significant higher in non-etomidate used group, while median respiratory rate was higher in etomidate used group. Almost fifty percent of the patients were intubated due to hypoxia; 70 patients (30.3%) were in etomidate used group, and 38 patients (16.5%) were in non-etomidate used group. Propofol was the most common induction drug used in non-etomidate used group. Number of patients who received succinylcholine as paralytic drug used were significantly higher in etomidate used group; 59.32% and 28.32% in non-etomidate used group. Post intubation blood pressure data (systolic blood pressure, diastolic blood pressure and mean arterial pressure) were significantly higher in non-etomidate used group. Total number of patients who developed post intubation hypotension in this study were 47 of 231 patients, 29 patients in etomidate used group and 18 patients in non-etomidate used group (Table 1).

From the univariate analysis, factors associated with post intubation hypotension ($p<0.2$) were male sex, hypertension, diabetes mellitus, intubation due to hemodynamic instability and mental status change, non paralytic drug used, first attempt success intubation, preintubation mean arterial pressure (MAP) <65mmHg, diagnosis of sepsis/septic shock and congestive heart failure (Table 2). In the multivariable logistic regression analysis that included all important data from univariate analysis, etomidate used was not statistically significant associated with post intubation hypotension in elderly patients, AOR 2.10 (0.94-2.17), $p=0.070$.

However, there were significant differences between etomidate used and non-etomidate used groups in the secondary outcomes. The analysis showed that etomidate used was significantly

associated with initiation or increased doses of vasopressors within 24 hours, AOR 3.03 (1.22-7.51), initiation of hydrocortisone within 24 hours, AOR 2.08 (1.78-5.52) and in hospital mortality AOR 2.99 (1.54-5.82) (Table 3).

**Table 1** Baseline characteristics of participants (n=231)

| Baseline characteristics | Etomidate used (n=118) | Non-Etomidate used (n=113) | p-value |
|---|---|---|---|
| Age, mean±SD, year | 72.70±8.18 | 71.90±7.72 | 0.445 |
| Male | 72 (61.02) | 63 (55.75) | 0.417 |
| **Comorbidities** | | | |
| Hypertension | 60 (50.85) | 60 (53.10) | 0.732 |
| Diabetes mellitus | 40 (33.90) | 42 (37.17) | 0.604 |
| Chronic kidney disease | 27 (22.88) | 18 (15.93) | 0.182 |
| Chronic obstructive pulmonary disease | 10 (8.47) | 15 (13.27) | 0.240 |
| Ischemic heart disease | 11 (9.32) | 10 (8.85) | 0.901 |
| Liver cirrhosis | 5 (4.24) | 2 (1.77) | 0.274 |
| Autoimmune disease | 3 (2.54) | 1 (0.88) | 0.334 |
| Malignancy | 4 (3.39) | 9 (7.96) | 0.132 |
| Others | 18 (15.25) | 21 (18.58) | 0.499 |
| Body mass index, median (IQR), $Kg/m^2$ | 20.44 (17.57-21.77) | 20.76 (18.75-23.03) | 0.044 |
| **Initial vital signs at ED** | | | |
| Systolic blood pressure, median (IQR), mmHg | 128.21 (103-150) | 152.85 (126-186) | <0.001 |
| Diastolic blood pressure, median (IQR), mmHg | 75.99 (59-89) | 88.73 (71-110) | <0.001 |
| Mean arterial pressure, median (IQR),mmHg | 92.48 (75-109) | 109.41 (94-133) | <0.001 |
| Heart rate, median (IQR), beat per minute | 106.10 (92-124) | 99.47 (84-118) | 0.151 |
| Respiratory rate, median (IQR), breath per minute | 30.89 (28-34) | 27.76 (22-34) | 0.003 |
| Oxygen saturation, median (IQR), % | 91.13 (88-99) | 86.42 (83-98) | 0.347 |
| **Indication for intubation** | | | |
| Cardiac arrest | 0 (0.00) | 5 (4.42) | 0.021 |
| Hypoxia | 70 (59.32) | 38 (33.63) | <0.001 |
| Hypercapnia | 5 (4.24) | 9 (7.96) | 0.235 |
| Hemodynamic instability | 34 (28.81) | 17 (15.04) | 0.012 |
| Alteration of consciousness | 7 (5.93) | 43 (38.05) | 0.001 |
| Others | 2 (1.69) | 4 (3.54) | 0.378 |
| **Attempts of intubation** | | | |
| 1 | 107 (90.68) | 86 (76.11) | 0.003 |
| 2 | 10 (8.47) | 17 (15.04) | 0.120 |
| ≥3 | 1 (0.85) | 10 (8.85) | 0.004 |

**Table 1** Baseline characteristics of participants (n=231) (cont.)

| Baseline characteristics | Etomidate used (n=118) | Non-Etomidate used (n=113) | p-value |
|---|---|---|---|
| **Type of non-etomidate induction drugs** | | | |
| Propofol | 0 (0.00) | 48 (42.28) | <0.001 |
| Ketamine | 0 (0.00) | 8 (7.08) | 0.003 |
| Midazolam | 0 (0.00) | 10 (8.85) | 0.004 |
| Benzodiazepine | 0 (0.00) | 9 (7.96) | 0.008 |
| None | 0 (0.00) | 25 (22.12) | 0.001 |
| **Paralytic drug used** | | | |
| None | 45 (38.14) | 80 (70.80) | <0.001 |
| Succinylcholine | 70 (59.32) | 32 (28.32) | <0.001 |
| Rocuronium | 3 (2.54) | 1 (0.88) | 0.334 |
| Other analgosedative drug used* | 34 (28.81) | 14 (12.39) | 0.002 |
| **Diagnosis** | | | |
| Pneumonia | 44 (37.29) | 13 (11.50) | <0.001 |
| Chronic obstructive pulmonary disease | 7 (5.93) | 13 (11.50) | 0.132 |
| Sepsis/septic shock | 36 (30.51) | 15 (13.27) | 0.002 |
| Acute stroke | 3 (2.54) | 31 (27.43) | <0.001 |
| Congestive heart failure | 19 (16.10) | 21 (18.58) | 0.618 |
| Traumatic brain injury | 0 (0.00) | 7 (6.19) | 0.006 |
| **Post intubation vital signs** | | | |
| Systolic blood pressure, median (IQR), mmHg | 129.67 (102-153) | 147.75 (128-167) | 0.003 |
| Diastolic blood pressure, median (IQR), mmHg | 78.65 (64-92) | 90.34 (72-103) | 0.001 |
| Mean arterial pressure, median (IQR), mmHg | 93.41 (77-111) | 108.03 (91-122) | 0.001 |
| Heart rate, median (IQR),beat per minute | 106.19 (90-119) | 103.43 (89-120) | 0.493 |
| Respiratory rate, median (IQR), breath per minute | 24.84 (24-26) | 23.63 (20-24) | 0.001 |
| Oxygen saturation, median (IQR), % | 100 (99-100) | 100 (99-100) | 0.185 |
| Post intubation hypotension | 29 (24.58) | 18 (15.93) | 0.103 |
| Initiation or increased doses of vasopressors within 24 hours | 42 (35.59) | 16 (14.16) | 0.001 |
| Initiation of hydrocortisone within 24 hours | 28 (23.73) | 11 (9.73) | 0.005 |
| Intensive care unit admission | 15 (2.71) | 32 (28.32) | 0.003 |
| In hospital mortality | 59 (50.00) | 38 (33.63) | 0.012 |

* Other analgesia or sedative drugs used not for induction

**Table 2** Factors associated with post intubation hypotension

| Variables | Crude odds ratio | 95%CI | p-value |
|---|---|---|---|
| Male | 2.14 | 1.06-4.33 | 0.027 |
| Underlying hypertension | 1.64 | 0.85-3.17 | 0.131 |
| Underlying diabetes mellitus | 1.62 | 0.84-3.12 | 0.145 |
| Indication of hemodynamic stability for intubation | 2.19 | 1.08-4.45 | 0.032 |
| Indication of altered mental status for intubation | 0.57 | 0.23-1.37 | 0.192 |
| Non paralytic drug used | 1.65 | 0.85-3.20 | 0.131 |
| Preintubation MAP<65 mmHg | 0.44 | 0.97-1.96 | 0.190 |
| First attempt success intubation | 0.48 | 0.22-1.04 | 0.071 |
| Sepsis/septic shock | 2.84 | 1.41-5.71 | 0.004 |
| Congestive heart failure | 0.43 | 0.16-1.16 | 0.007 |

**Table 3** Association of etomidate used and outcomes in elderly patients

| Outcomes | Etomidate used (n=118) | Non-Etomidate used (n=113) | Adjusted odds ratio (AOR) | 95%CI | p-value |
|---|---|---|---|---|---|
| **Primary outcome** | | | | | |
| - Post intubation hypotension | 29 (24.58) | 18 (15.93) | 2.10 | 0.94-2.71 | 0.070 |
| **Secondary outcomes** | | | | | |
| - Initiation or increased doses of vasopressors within 24 hours | 42 (35.59) | 16 (14.16) | 3.03 | 1.22-7.51 | 0.017 |
| - Initiation of hydrocortisone within 24 hours | 28 (23.73) | 11 (9.73) | 2.08 | 1.78-5.52 | 0.014 |
| - In hospital mortality | 59 (50.00) | 38 (33.63) | 2.99 | 1.54-5.82 | 0.001 |

## Discussion

In this study, we evaluated the post intubation hypotension in elderly patients after emergency tracheal intubation between etomidate used and non-etomidate used groups. The results showed that etomidate used was not statistically significant associated with the development of post intubation hypotension. Conversely, etomidate used was significantly associated with initiation or increased doses of vasopressors within 24 hours, initiation of hydrocortisone within 24 hours and in hospital mortality.

Emergency tracheal intubation is a lifesaving treatment, a common strategy to manage this procedure is rapid sequence intubation (RSI), which is a technique of administration of induction drugs rapidly follow by neuromuscular blocking agents to facilitate the success of intubation.[16] Although, the latest practice guideline for RSI, there was the best practice statement and ungraded quality of evidence.[4] The current evidence mentioned that etomidate used had adverse events to be concerned including hypotension and mortality.[5-8,17] Moreover, the current knowledge of adverse effect of etomidate used in elderly patients were limit.

This study showed similar results to a previous observational study that there was no association of peri intubation hypotension incidence between ketamine and etomidate in the ED patients. Additionally, they found that increasing age was the factor associated with peri intubation hypotension.[18]

The result of our study was distinct from one observational study that ketamine was associated with peri intubation hypotension when compared to etomidate. However, mean age of patients in that study was about 49 years old which was lower than our study and most of our patients in non-etomidate used group received propofol as induction drug.[19]

The induction drugs in rapid sequence intubation were the sedative drugs that effect to decreased catecholamine release, suppressed cardiac contractility, decreased vascular tone, suppressed adrenal gland function which affected on hemodynamic status of patients. Emergency tracheal intubation may increase probability of hypotension due to sympathetic activity dependent, predisposing hypovolemia, and positive pressure ventilation, especially in elderly patients. Therefore, induction drug which minimized hemodynamic alteration should be selected. Even though we did not find significant association of etomidate used and post intubation hypotension, the secondary outcomes of our study found that etomidate used associated with the initiation or increased doses of vasopressors, initiation of hydrocortisone and in hospital mortality.

From current knowledge, etomidate reversible suppressed adrenal gland function via inhibition of 11 β-hydroxylase enzyme for 24-48 hours[20], therefore the intermediate adverse effects and mortality should be concerned and be careful to use in elderly patients.

The strength of our study was the evaluation of adverse effects of etomidate used as an induction agent that quite limits current data in elderly patients.

There were a few limitations in this study. First, it was a retrospective study that lacks some data such as cardiac function and volume status of patients, amount of intravenous fluid administration during intubation that affected the outcomes. Second, the adrenal gland suppression from etomidate is dose dependent that our study did not show etomidate dose in milligram per kilogram in each patient, however the guideline for etomidate used in our department is 0.3 milligram per kilogram (actual weight) of patients. Therefore, we assumed that all of patients received the same doses of etomidate. Third, there were several types of induction drugs in non- etomidate group which propofol was the most common drug used that provided limitation to interpret the effects of etomidate to individual drugs. Fourth, although multivariable logistic regression was used to adjust, some confounders such as type and amount of induction drugs used in each patients, severity of illness, management in hospital ward may remain, the future propensity match or randomized controlled study should be considered.

## Conclusion

The study demonstrated that etomidate used was not significantly associated with post intubation hypotension but significantly associated with initiation or increased doses of vasopressors within 24 hours, initiation of hydrocortisone within 24 hours and in hospital mortality in elderly patients.

## Acknowledgement

I would like to thank department of information and communication technology, Khon Kaen hospital or all resources offered and data accessing.

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