ORIGINAL ARTICLE

# Midazolam is more likely to cause hypotension than etomidate in emergency department rapid sequence intubation

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**Objective:** To compare the haemodynamic effect of low dose midazolam and etomidate as induction agent in emergency department rapid sequence intubation.
**Methods:** A prospective observational study in two phases. In phase one, midazolam 2–4 mg was used as induction agent and in phase two, etomidate 0.2–0.3 mg/kg was used. The haemodynamic data were recorded before and after intubation for comparison. Changes in mean systolic blood pressure were analysed with SPSS software.
**Results:** A 10% decrease in mean systolic blood pressure was observed in the midazolam group ($p = 0.001$) while there was no significant change in the etomidate group. Some 19.5% of patients had hypotension after being given midazolam while only 3.6% with etomidate ($p = 0.002$). Patients older than 70 tended to have more hypotension episodes but the difference was not statistically significant.
**Conclusions:** Midazolam, even in low dose, was more likely than etomidate to cause significant hypotension when used as an induction agent for rapid sequence intubation. Etomidate is a better alternative.

Rapid sequence intubation (RSI) is a procedure commonly performed by doctors working in the emergency department in many parts of the world. It had been shown that the procedure could significantly reduce intubation related complications especially trauma to the airway and aspiration when compared with intubation without sedation and paralysis.[1 2] However, by reviewing the recent publications we discovered a change in the pattern of complications. Accompanying the drastic decrease of airway trauma and aspiration, hypotension has become the most commonly encountered complication.[3–5] After reviewing local data, we have found the same problem.[6] The issue has not been properly investigated in previous studies and some might believe that acutely ill patients were haemodynamically compromised and prone to develop hypotension. The occurrence of hypotension is associated with significant mortality and morbidity in critically ill patients[7–8] and we should not overlook its potential hazards. Midazolam was the most commonly used induction agent for many years locally and we suspected that it was probably responsible for hypotension. Other common induction agents, for example, thiopentone and propofol are known to cause hypotension as well. We therefore investigated whether etomidate is a better choice than midazolam as an induction agent in terms of haemodynamic stability. We were unable to find any studies directly comparing these two drugs as induction agent in RSI in our review of the literature.

## METHODS

This was a prospective observational study carried out in an emergency department of an urban district hospital. All non-cardiac arrest patients that needed emergency intubation in the emergency department were eligible to be recruited in the study and patients with either midazolam or etomidate as induction agent for RSI were included. The study period was divided into two phases. Phase one lasted for 11 months during which midazolam was the most commonly used induction agent while etomidate was not yet available in our department. Phase two lasted for another 12 months when etomidate was made available and was encouraged to be used as the first choice. Besides the change in the induction agent, the remaining part of emergency RSI protocol was unchanged throughout the period.

Data collected included the use of pre-medications, induction agents, and muscle relaxants, the dose of each drug, the blood pressure and the pulse rate just before intubation and within five minutes after intubation. The blood pressure was measured non-invasively using the conventional cuff over upper arm with electronic sphygmomanometer. The measurement was carried out at every one to three minutes interval according to clinical need. Other useful information included initial diagnoses of the patients, concurrent use of other medication, oxygen saturation by pulse oximeter, occurrence of other complications, and final outcome of the patients. Hypotension was defined as a decrease in systolic blood pressure (SBP) below 90 mm Hg or a decrease of more than 20% within five minute after intubation compared with the SBP just before intubation. If the SBP before intubation was below 90 mm Hg, the case was not counted as concurrent fluid and inotrope resuscitation might affect the blood pressure and the changes in haemodynamic parameters cannot be attributable to the effect of induction agents alone.

The data collected were processed with SPSS software. The occurrence of hypotension and the change in mean SBP between the two groups was compared. The concurrent use of other medications was also analysed to avoid bias attributable to confounding factors. Student's $t$ test was used to compare means and $\chi^2$ test was used for categorical variables.

## RESULTS

A total of 160 cases were collected in the two phases with 77 receiving midazolam and 83 receiving etomidate. Although

**Abbreviations:** RSI, rapid sequence intubation; SBP, systolic blood pressure

**Table 1** Patient characteristics of midazolam and etomidate groups

| | Midazolam | Etomidate |
|---|---|---|
| Total number | 77 | 83 |
| Male:female | 42:35 (1:0.83) | 49:34 (1:0.69) |
| Mean age | 63.3 | 65.9 |
| Trauma cases | 3 | 5 |
| Stroke cases | 25 | 28 |
| Acute pulmonary oedema cases | 14 | 12 |
| Respiratory failure cases | 11 | 8 |
| Unspecified coma cases | 15 | 16 |
| Convulsion cases | 1 | 5 |
| Initial mean SBP (mm Hg) | 165 | 159 |
| Lignocaine (lidocaine) used as pre-medication* | 30 | 18 |
| Fentanyl used as pre-medication | 16 | 24 |

*There were significantly more patients in the midazolam group who had received lignocaine (lidocaine). However, use of lignocaine did not significantly affect blood pressure (p value of Fisher's exact test was 0.445).

there was no randomisation, the two groups were comparable from the beginning (table 1). There was no significant difference between their mean age, initial diagnoses, and mean initial SBP.

The dose of midazolam given ranged from 2 mg to 4 mg as a bolus while the dose of etomidate was 0.2 mg–0.3 mg/kg. A decrease in mean SBP within five minutes after intubation by around 10% was observed in the midazolam group. There was no statistically significant decrease in mean SBP in the etomidate group (table 2). In the midazolam group, 15 of 77 (19.5%) patients had hypotension according to our definition. On the other hand, only 3 of 83 patients in etomidate group had hypotension and the difference was statistically significant. For the midazolam group, patients younger than 70 were found less likely to develop hypotension than older patients, although the difference is not statistically significant (table 3).

For the three patients with hypotension in the etomidate group, one had received 20 mg diazepam intravenously for status epilepticus during intubation and it might have contributed to hypotension. Another patient was found hypotensive because of inappropriately high tidal volume in the ventilator setting and the blood pressure returned to normal after correction of the setting. The cause of hypotension in the remaining case was unknown.

Among all 18 patients who suffered hypotension episodes, six of them had received fluid bolus to achieve a reasonable perfusion pressure and none of them need vasopressors. There were no data available on the occurrence of hypoxic end organ damage.

Pre-medications such as lignocaine and fentanyl were often used before intubation and muscle relaxants such as suxamethonium or vecuronium were also given in RSI. Further statistical analysis was carried out to investigate the impact of pre-medications and the use of muscle relaxants on the blood pressure. The results showed that the choice of pre-medication and the use of muscle relaxant did not significantly affect the mean SBP.

**Table 2** Change in mean systolic blood pressure after intubation

| | Midazolam | Etomidate |
|---|---|---|
| Number of cases | 77 | 83 |
| Number with hypotension (%) | 15 (19.5%) | 3 (3.6%) |
| Initial mean SBP (mm Hg) | 164.75 | 159.05 |
| Post-intubation mean SBP (mm Hg) | 149.81 | 157.41 |
| Difference in blood pressure | −14.95 | −1.64 |
| p Value of paired sample *t* test (two tailed) | 0.001 | 0.649 |

**Table 3** Incidence of hypotension

| | Midazolam | Etomidate |
|---|---|---|
| Number of cases | 77 | 83 |
| Age <70 | 38 | NA |
| Age ⩾70 | 39 | NA |
| Hypotension (%) | 15 (19.5%)* | 3 (3.6%)* |
| Age <70 with hypotension (%) | 5 (13.2%)† | NA |
| Age >70 with hypotension (%) | 10 (25.6%)† | NA |

*Significant difference Fisher's exact test p = 0.002 (two tailed).
†Difference is not statistically significant.

## DISCUSSION

Midazolam has been a popular sedation agent since the 1980s as it is short acting and has comparatively few side effects. It has become a popular agent for induction for RSI locally as emergency department doctors are familiar with it and feel more confident in its use. With the accumulation of experience, doctors found out that the recommended dose (0.2–0.3 mg/kg) of midazolam may cause significant hypotension. Previous study has shown that it is associated with a dose related hypotension.[9] As a result, a low dose of midazolam (less than 5 mg bolus) was commonly used in Hong Kong and other part of the world for induction in RSI. Inadequate anaesthesia is a potential problem with such a low dose but no occurrence of awareness during intubation was reported in this study. However, even with such a low dose, we have shown that midazolam could still cause hypotension nearly 20% of patients. The incidence of hypotension for patients older than 70 doubled the younger age group. The difference was statistically not significant probably because of small sample size. We still believe that elderly patients are more prone to develop hypotension with midazolam.

In this study, we aimed to persuade local doctors to change their practice by proving midazolam can cause hypotension even in low dose. At the same time, we have suggested an alternative, which is etomidate, a well researched agent commonly used in other parts of the world.[10 11] As hypotension has been one of the most common complications for RSI in the emergency department, by selecting etomidate instead of midazolam as induction agent one could reduce the complication rate significantly.

Our study had several limitations. The main limitation of this study was the use of non-random samples. Although the patients' characteristics including age, initial blood pressure, and initial diagnoses were well matched, there was difference in intervention. Lignocaine had gone out of favour and was less used in phase two of the study. Lignocaine was used to prevent increase in blood pressure and intracranial pressure during laryngoscopy and intubation. There was no literature suggesting lignocaine can cause a significant decrease in blood pressure in RSI. In our data analysis, the use of lignocaine did not significantly affect blood pressure. The other limitation was that the study was in two phases. However, apart from the increase use of etomidate and decrease use of lignocaine, the RSI protocol had not changed during the study period.

In conclusion, midazolam, even in low dose, was more likely than etomidate to cause significant hypotension when used as an induction agent for RSI. Etomidate is a better alternative.

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