Guest Editorial

Induction agents for emergency airway management in critically ill patients

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Emergency airway management (EAM) in critically ill patients is an important component of patient care that can significantly impact patient outcomes. An international observational study evaluating tracheal intubation (TI) practice in critically ill patients (INTUBE) reported that 45% of critically ill patients develop a major peri-intubation adverse event, of which cardiovascular complications are the most common.[1] EAM in these patients involves anatomic, logistical, and physiological challenges or a combination of these.[2] The presence of a physiologically difficult airway, wherein the patients' physiological derangements predispose them to a higher risk of complications during TI and initiation of positive pressure ventilation [3], is common in these situations. The combination of sympatholysis due to anaesthesia induction drugs, increased intrathoracic pressure when converting with positive pressure ventilation, and the amelioration of the hypoxaemia- and hypercarbia-associated sympathetic drive all predispose these at-risk patients to haemodynamic collapse with TI. It has been reported that the choice of induction agent may be a modifiable cause of patient morbidity and mortality.[4]

The induction drugs currently used for TI in critically ill patients include propofol, etomidate, ketamine, benzodiazepines, and admixture drugs such as 'ketofol' (a combination of ketamine and propofol) and 'propadate' (a combination of propofol and etomidate). Propofol is the most widely used induction agent globally.[1] There is significant heterogeneity in the reported association between propofol use and relevant clinical outcomes during EAM in critically ill patients. A secondary analysis of INTUBE findings reported that propofol administration was the only independent risk factor for haemodynamic collapse (odds ratio 1.23; 95% confidence interval 1.02, 1.49).[4] However, in a recent study comparing propofol, ketamine, and etomidate for TI in critically ill patients, propofol use was associated with better outcomes.[5] Similarly, a retrospective study observed hypotension (defined as systolic blood pressure < 70 mmHg) in only 4% of critically ill adults who received propofol for TI.[6] Etomidate and ketamine are usually considered to afford higher haemodynamic stability when compared to propofol, but various reports concluded mixed results. A 2009 study found no significant difference in mortality or maximum Sequential Organ Failure Assessment (SOFA) score for patients receiving etomidate or ketamine for TI,[7] whereas a recent trial comparing these two drugs observed that patients who received etomidate had higher 7-day mortality but no difference in 28-day mortality.[8] Etomidate's ability to inhibit 11β-hydroxylase and cause adrenal suppression is a concern, but this has not been consistently demonstrated to impact clinical outcomes. However, given the risk of adrenal suppression, caution

remains for etomidate's use in septic shock patients. A sub-study of the CORTICUS trial found an increased rate of inadequate response to corticotropin as well as an increased 28-day mortality when etomidate was used.[9] The study had limited power and was not designed to test the outcomes prospectively. Thus, there remains ambiguity over the superiority of etomidate or ketamine during EAM in critically ill patients, and the choice to use one over the other may come down to provider preference and the physiologic profile of the patient.

Benzodiazepines are another common class of drugs that may be used by themselves or in combination with other drugs, such as ketamine. In a prospective observational study conducted across Spanish intensive care units (ICUs), benzodiazepines were used in 66% of critically ill patients undergoing TI,[10] while the INTUBE study reported their use in 36% of the patients.[1] While the use of benzodiazepines in critically ill patients has been associated with increased risk of delirium, ICU and hospital length of stays, and increased healthcare costs,[11] their use as an induction agent for EAM needs further testing and studies comparing outcomes between the use of benzodiazepines and other hypnotic drugs in this setting are required. Although the use of barbiturates such as sodium thiopentol as hypnotic-anaesthetic agents has significantly decreased, slow, titrated use of this drug in resource-limited circumstances may be considered.

Recently, ketofol has been proposed as an ideal induction drug for TI in patients with a physiologically difficult airway, with minimal impact on haemodynamics. The current literature on the use of ketofol, however, is limited. Only two small, single-centre randomised controlled trials have evaluated the use of ketofol for induction of anaesthesia in clinical settings.[12,13] Of these, one was conducted in healthy patients undergoing general anaesthesia,[12] and the other, comparing ketofol with etomidate in critically ill patients undergoing TI, was unable to show better haemodynamics with the use of ketofol.[13] Considering that the use of ketofol in TI requires the mixing of two drugs in a ratio that may not be standardised or pre-mixed, the concentration of these two drugs in this admixture may not be consistent. In addition, as ketofol involves the mixing of two individual drugs, the ratio of which is neither well-defined, standardised, or approved, a pre-mixed formulation may not be available from the pharmacy, and the bedside nurse may not be licenced to mix two different medications (including a controlled substance), especially in the absence of an accepted universal ratio. However, the use of ketofol may be justified in patients with or having a high likelihood of adrenal insufficiency and in situations where haemodynamic alterations may be detrimental to patient outcomes. Ketofol also has analgesic properties and may reduce the need for additional sedatives such as midazolam or fentanyl.[14]

The admixture of propofol and etomidate, propadate, has also been proposed as an alternative induction agent.[15] Theoretically, this combination might provide a better haemodynamic profile, and the transient adrenal suppression reported using etomidate could be less likely with this admixture. However, the data regarding the safety and efficacy of propadate is scarce. The drug combination has been explored for sedation for gastroscopy, and a recent meta-analysis reported that co-administration of propofol and etomidate can result in favourable haemodynamic stability.[16] The propofol and etomidate admixtures comparisons trial (PEAC), NCT05358535, is currently underway to evaluate different ratios of these two induction drugs in the admixture.[17]

In conclusion, at present, no specific anaesthesia induction drug can be considered the most appropriate for EAM in patients with a physiologically difficult airway. Well-designed randomised controlled trials accounting for patient phenotypes and their response to specific induction agents might be needed to help clinicians choose the ideal induction agent for a particular patient and situation to help improve outcomes during EAM in critically ill patients.

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