Rapid sequence intubation and the role of the emergency medicine pharmacist:
Literature update

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**Purpose:** The dosing, potential adverse effects, and clinical outcomes of the most commonly utilized pharmacologic agents for rapid sequence intubation (RSI) are reviewed for the practicing emergency medicine pharmacist (EMP).

**Summary:** RSI is the process of establishing a safe, functional respiratory system in patients unable to effectively breathe on their own. Various medications are chosen to sedate and even paralyze the patient to facilitate an efficient endotracheal intubation. The mechanism of action and pharmacokinetic/pharmacodynamic profiles of these agents were described in a 2011 review. Since then, the role of the EMP as well as the published evidence regarding RSI agents, including dosing, adverse effects, and clinical outcomes, has grown. It is necessary for the practicing EMP to update previous practice patterns in order to continue to provide optimal patient care.

**Conclusion:** While the agents used in RSI have changed little, knowledge regarding optimal dosing, appropriate patient selection, and possible adverse effects continues to be gained. The EMP is a key member of the bedside care team and uniquely positioned to communicate this evolving data.

**Keywords:** oxygenation, paralysis, pharmacist, rapid sequence intubation, sedation
Key Points

- The basic principles of rapid sequence intubation—effective induction and paralysis with resultant first pass success—have changed little over the past decade.

- Among other recent developments, evidence of adrenal suppression following etomidate induction is of low quality overall, data supporting coadministration of ketamine and propofol ("ketofol") for induction continues to grow, and some data suggest sugammadex may have a role in paralysis reversal in certain rare situations.

- Postintubation sedation is a vital component of management of the intubated patient, and the emergency medicine pharmacist is uniquely situated to facilitate this aspect of care.
Emergency medicine pharmacists (EMPs) continue to be recognized as key stakeholders in the optimization of patient care in the emergency department (ED). In the last decade, notable medical organizations have released policy statements supporting EMPs in the ED.\textsuperscript{1,2} These policy statements endorse EMPs as integral to the safety and care of all patients through their critical role in ensuring efficient, safe, and effective medication use in the ED.\textsuperscript{1,2} In addition, in February 2020 the Board of Pharmacy Specialties formally recognized emergency medicine (EM) pharmacy as a specialty practice area. The acknowledgment of EM pharmacy as a specialty solidified the role of EMPs as specialized clinicians in the delivery of direct patient care and further defined EMPs as critical members of the emergency care team who are able to anticipate pharmacotherapy needs in the fast-paced environment of the ED and have expertise in the management of time-dependent emergencies.\textsuperscript{3}

Awareness of the ED being a complex environment that presents unique challenges for medication selection, dosing, administration, and monitoring as well as caring for high-risk populations such as the critically ill, geriatric patients, pediatric patients, and those with multiple comorbidities that often require the use of high-risk medications and the need for time-sensitive medication decisions is imperative. It is important that EMPs are involved and knowledgeable in the bedside patient care process involving high-acuity patients such as with trauma or cardiac arrest and those requiring rapid sequence intubation (RSI).\textsuperscript{4} In addition, the ASHP Guidelines on Emergency Medicine Pharmacist Services state that EMPs should be involved in direct patient care activities to guide medication selection, dosing, and preparation and have a unique position in reducing medication errors.\textsuperscript{5}
The goal of this article is to provide updates regarding RSI within EM practice since the publication of an article on this topic by Hampton in 2011, but our intent is not to supersede that publication. The authors suggest referring to the 2011 article with regard to foundational knowledge of RSI, including mechanism of action and common dosing. For this publication, the focus will be on the valuation of recently published literature on pertaining to RSI indications, contraindications, and dosing strategies, as well as adverse effects of medications used throughout the procedure, in addition to postintubation management strategies.

Overview

RSI is the most common method for emergency control and securement of the airway. Many clinical studies have highlighted the beneficial role RSI plays in first pass intubation success (the subjective successful placement of an endotracheal tube during the initial intubation attempt) and in reducing the incidence of complications of difficult airways in the critically ill patient. Historically, the “seven P’s” of RSI have been taught to healthcare providers. The mnemonic was developed to outline the key steps that clinicians should employ for RSI planning and performance. Since the mnemonic’s inception, the employment of the seven P’s and their definition, as well as the tasks appropriate for the EMP to provide (Table 1), have evolved. The new seven P’s highlight that instead of these steps occurring in sequential order, several steps, especially the ones leading up to tube placement, need to happen simultaneously. Since the 2011 publication, the third “P” (originally denoting pretreatment) has been updated to denote preintubation optimization; this update was secondary to a lack of high-quality studies supporting use of pretreatment agents such as lidocaine and fentanyl and indicating there is no clear benefit to the patient. Historically, lidocaine has been
recommended for pretreatment in traumatic brain injury (TBI) to blunt an increase in intracranial pressure (ICP) that may occur during intubation. The evidence has been mixed and limited to data from small studies. Due to lack of evidence, weighed with the risk of hypotension secondary to lidocaine administration, use of pretreatment agents has fallen out of practice.\textsuperscript{12,13} As the body of evidence describing the activity and elimination of RSI medications grows, so too does the understanding that no two disease states are alike. In this article, a thorough update on RSI medications for the EMP is provided.

Induction

Etomidate. The agents utilized to initiate unconsciousness, also referred to as induction, have changed little over the past decade. Etomidate remains the preferred induction agent for RSI in the ED. A 2015 multinational registry study identified etomidate as the sedative utilized in 91\% of more than 17,000 emergent intubations over a 10-year period.\textsuperscript{14} Rapid onset of action, a consistent, predictable dose-response curve, neutral hemodynamic effects, and a short duration of action leave little to be desired in this medication in the context of RSI induction.

While etomidate is favored by EM physicians in most clinical situations, the potential for and impact of adrenal suppression following its use remains unclear. The inhibition of several enzymes required in cortisol production by etomidate has been documented for decades.\textsuperscript{15,16} The exact mechanism of this inhibition is suggested to be due to an interaction between the imidazole ring of etomidate and an iron-containing heme group present in affected enzymes.\textsuperscript{17,18} Evidence of an association of increased mortality with etomidate use is currently confined to secondary outcomes in clinical studies. Much attention has been paid to results of the CORTICUS study, published in
The efficacy of bolus-dose hydrocortisone therapy against placebo was evaluated in patients septic shock. Ninety-six (19.2%) of a total of 499 patients received etomidate, with selection of induction agent left to provider discretion. Etomidate-treated patients responded less often to a corticotropin stimulation test than patients who did not receive etomidate (60.4% vs 43.4%, \( P = 0.004 \)). A substudy of this trial explored the effect of etomidate, with the researchers noting a 13% increase in 28-day mortality (odds ratio [OR], 1.7; 95% CI, 1.07-2.68). Multiple logistic regression analyses were conducted via 2 different models. The first model adjusted for baseline Simplified Acute Physiology Score (SAPS II score), hydrocortisone group, nonresponse to corticotropin stimulation test, and cortisol. No significant correlation was observed until a second model testing for all first model predictors in addition to baseline sequential organ failure assessment (SOFA) score showed a significant association between etomidate use and increased mortality risk (OR, 1.75; 95% CI, 1.06-2.9). Notably, an increase in mortality was not observed until 10 days after receipt of etomidate. The CORTICUS study was not powered nor designed to evaluate etomidate in this context, rendering it hypothesis generating in this regard.

Several systematic reviews and meta-analyses have investigated the influence of etomidate on mortality. Gu et al\(^{20}\) examined mortality data from 18 studies including a total of 5,552 patients who received a single dose of etomidate. Risk of death was not elevated in either of the included randomized controlled trial study populations (relative risk [RR], 1.2; 95% CI, 0.84-1.72) or in the remaining 16 observational studies (RR, 1.05; 95% CI, 0.79-1.39). A Cochrane review similarly found there is no strong evidence of a link with increased mortality and etomidate administration in critically ill patients (OR, 1.17; 95% CI, 0.86-1.60).\(^{21}\) A meta-analysis by Albert and Sitaula\(^{22}\) sought to determine if mortality increases with escalating severity of illness scores. Their
evaluation found etomidate use was tied to adrenal insufficiency (RR, 1.54; 95% CI, 1.42-1.67) as well as increased mortality in patients with critical illness severity scores greater than the median score in each study analyzed (RR, 1.2; 95% CI, 1.12-1.29). They observed no relationship in patients with scores below the median. The choice of sedative agent in critically ill patients needing RSI remains a topic of healthy debate among pharmacist and physician clinicians alike. The suggested courses of action in Hampton’s 2011 article regarding the use of etomidate in patients with concerns for adrenal insufficiency still apply today.

An additional adverse effect that bears revisiting is etomidate-induced myoclonus. While not under scrutiny with regard to increasing mortality or causing renal dysfunction, the phenomenon has been described extensively in the anesthesia literature. The exact mechanism remains unclear, but etomidate-induced myoclonus occurs in up to 70% to 90% of cases of both procedural sedation and induction for general anesthesia.23,24 These episodes can be transient and possibly underappreciated when etomidate is administered with paralytic medications. Regarding duration, they may last only a few seconds or can last longer, with some cases being recorded as lasting more than 500 seconds.24 Several agents, including opioids, midazolam, and dexmedetomidine, have been studied for prevention of etomidate-induced myoclonus in elective procedures25-27; for the rapidly deteriorating patient, the utility of these medications is unknown, but their use would likely lead to potentially costly delays. The impact of etomidate on the seizure threshold is also not well understood. When utilized for electroconvulsive therapy, induction with etomidate was not demonstrated to result in longer seizure duration compared to use of propofol or thiopental.28 As a member of the RSI team, the EMP should be cognizant and ready to counsel providers and nurses of this common adverse effect, especially in patients whose provider does not wish to
induce paralysis. An alternative agent should be considered in patients with concerns of seizure-like activity, as etomidate-induced myoclonus cannot be differentiated from epileptogenic seizure activity at the bedside.

**Propofol.** Propofol remains an effective choice for maintaining sedation in ventilated patients. Since the introduction of etomidate, propofol utilization has decreased significantly, with the agent being used in as few as 2% of intubations, as described in a multinational registry study. The effect of propofol on postintubation hypotension has been studied with conflicting results in the trauma population. Compared to use of agents other than propofol, propofol use increased the risk of postintubation hypotension (OR, 3.64; 95% CI, 1.16-13.24) in a retrospective review of 83 adult trauma patients. A larger, multicenter study of more than 2,000 adult trauma patients showed no statistically significant differences between etomidate, ketamine, and propofol in mean (SD) systolic blood pressure (SBP) change (0.2 [50] mm Hg vs 5.2 [32.3] mm Hg vs −1.8 [32] mm Hg, respectively; $P = 0.4$). The extent to which this data can be extrapolated to nontrauma patients remains to be seen; at this time, it is suggested to exercise caution when considering propofol for RSI induction, especially in patients with preexisting hypotension.

A long-held contraindication to propofol is a hypersensitivity to egg protein, soy, or peanut products. Asserhøj et al conducted a 2-pronged retrospective study in Denmark to investigate an association of these hypersensitivities and allergic reaction following propofol exposure. In the first arm of the study, 153 patients received propofol. Four patients (2.6%) developed hypersensitivity reactions but none had a documented history of egg protein, soy, or peanut allergy. In the second arm, reactions to propofol were assessed in 99 patients with documented hypersensitivities to egg, soy, or peanut products. No hypersensitivity reactions were documented following
propofol administration. Avoidance of propofol due to a documented egg, soy, or peanut allergy is no longer necessary.

**Ketamine.** Ketamine is a nonbarbiturate, phencyclidine derivative that rapidly produces a state of anesthesia characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, and cardiovascular and respiratory stimulation.\(^{32}\) Based on its mechanism of action and safety profile, ketamine may be considered the induction agent of choice in patients with reactive airway disease.\(^{33}\) It has been considered a good choice for patients who are hypotensive, volume depleted, or hemodynamically unstable secondary to sepsis, although new data may cast doubt on this notion.

Mohr et al\(^{34}\) published results of a multicenter observational cohort study of 531 patients with sepsis from the National Emergency Airway Registry (NEAR). The primary outcome was induction agent choice for sepsis intubations, and secondary outcomes focused on safety parameters, ie, first-pass intubation success, hypotension, complications, etc. Of the 531 patients included in the study, 68% (n = 363) received etomidate and 27% (n = 140) received ketamine. First-pass success was similar between groups (89% with ketamine vs 84% with etomidate), and there were no differences between ketamine and etomidate with regard to serious adverse drug events or cardiac arrest. There was a significantly higher incidence of postintubation hypotension among patients receiving ketamine vs etomidate (74% vs 50%; CI, 1.9%-4.5%), although the clinical significance of this finding has yet to be determined. It should also be noted that this study evaluated outcomes in the immediate postintubation period and therefore did not evaluate the incidence of worsening adrenal suppression and/or mortality. It bears noting that ketamine has both catecholamine reuptake inhibition and myocardial depressant effects. In patients who
are not catecholamine depleted, the reuptake effect predominates and typically leads to a transient increase in SBP. However, in patients who are catecholamine depleted, ie, patients in septic shock, the myocardial depressant effects predominate, thereby explaining the significant drop in SBP noted in this study. It would therefore seem reasonable to utilize an alternative induction agent in patients who present in septic shock, but what if the patient is not septic but, rather, is hemodynamically unstable?

Ishimaru et al\textsuperscript{35} conducted a 46-month study as part of the Japanese Emergency Airway Network (JEAN) to determine whether the use of ketamine for intubation is associated with a lower incidence of postintubation hypotension in hemodynamically unstable patients as compared to use of propofol and midazolam. This study included 977 patients with a preintubation Shock Index (SI) of >0.9. The SI is calculated by dividing heart rate (HR) by SBP; a normal SI is less than 0.7, and a preintubation SI of >0.9 is a predictor of hyperlactatemia and 28-day mortality. The primary outcome of this trial was the incidence of postintubation hypotension (defined as SBP of <90 mm Hg) occurring within 30-minutes following intubation, or a decrease of >20% in SBP between the preintubation and immediate postintubation periods. The authors found that ketamine use was associated with a significantly reduced risk of postintubation hypotension as compared to propofol and midazolam (15% with use of ketamine vs 29% with use of the other agents; \( P < 0.001 \)). Unfortunately, this study was somewhat limited in that etomidate was not utilized as a comparator agent.

Avoidance of ketamine in patients with elevated ICP historically had been advised after early case reports and case studies described increased cerebral oxygen consumption, increased cerebral blood flow, and increased ICP after the drug’s administration.\textsuperscript{36,37} However, recently published systematic and retrospective reviews have called these findings into question, raising doubt regarding their clinical
significance. Cornelius et al.\textsuperscript{38} performed a retrospective analysis of 89 patients with TBI arriving via air transport to the ED. Those authors aimed to evaluate the effect of sedative administration on length of stay (LOS), morbidity, and mortality. It was determined that patients who received ketamine experienced a significantly lower decrease in SBP than those who received either etomidate or midazolam for induction. Patients who received ketamine were also found to have a longer LOS than those who received etomidate or midazolam (29.5 days vs 15.8 and 14.1 days, respectively). This finding, however, is unsurprising when one considers that ketamine was associated with a significantly lower mortality rate (13.3\% vs 38.3\% with etomidate and 40.7\% with midazolam) and that a higher proportion of patients who received ketamine were discharged to a long-term care facility (LTCF) (60\% of those treated with ketamine, compared to 36.2\% treated with etomidate, and 33.3\% treated with midazolam). Taken as a whole, the data indicate that patients presenting with TBI who receive ketamine are more likely to survive to hospital discharge but are more likely to be discharged to an LTCF. One explanation provided by the researchers was that patients treated with ketamine experienced a more complicated course of care, which could explain the longer LOS relative to LOS in patients treated with etomidate or midazolam. Stated another way, agent selection appears to influence patient outcome in the setting of TBI. Compared to etomidate and midazolam, ketamine is associated with a reduced mortality rate, which may be attributed to ketamine’s ability to better regulate SBP. However, the reduction in mortality with ketamine use is exchanged for an increased likelihood of discharge to an LTCF.

Cohen et al.\textsuperscript{39} performed a systematic review of the literature on the effect of ketamine on ICP and cerebral perfusion pressure (CPP) relative to the effect of fentanyl, sufentanil, remifentanil, and etomidate. The primary outcome was changes in ICP and
CPP, and secondary outcomes were ICU LOS, mortality, and neurologic outcomes. The
investigators identified 5 randomized trials that yielded data on 854 patients and 5
prospective controlled trials that yielded data on 99 patients. Two of the included
studies showed small, clinically insignificant reductions in ICP and 2 studies showed
increases in ICP with use of ketamine versus the other agents. However, most studies
reported no difference in ICP after ketamine administration. There was no evidence of
sustained changes in ICP or CPP in any of the studies, and no significant differences
were found regarding secondary outcomes. The researchers stated that ketamine does
not adversely affect ICP, CPP, neurologic outcomes, or mortality when compared to
other agents used for sedation/induction, thereby invalidating the dogma of ketamine
avoidance in the setting of TBI.

Several studies have indicated that while ketamine increases cerebral blood flow
and cerebral metabolism in spontaneously breathing patients, it does not appear to
increase ICP in patients undergoing controlled ventilation and sedation.\textsuperscript{40-45} In fact,
mean arterial pressure (MAP) is maintained, vasopressor use is decreased, and CPP
remains stable when ketamine is used instead of benzodiazepine and opioid
combinations for analgesia and sedation in intubated, head-injured patients.\textsuperscript{42-44} This
stabilization of CPP may be of benefit in hypotensive patients with severe blunt head
trauma. Hypotension in the presence of blunt head trauma has been associated with
increased mortality, meaning every effort should be made to maintain an SBP above 90
mm Hg.\textsuperscript{30} Ketamine may be a reasonable induction choice in this setting.

The impact of ketamine on intraocular pressure remains unclear, particularly in
the setting of suspected or confirmed increased intraocular pressure such as can occur
with open-globe injuries. Available evidence suggests ketamine does not increase
intraocular pressure to a clinically significant degree; however, that evidence is limited
data from studies of pediatric patients undergoing procedural sedation.\textsuperscript{46,47} The National Association of Emergency Medical Technicians (NAEMT) guideline on tactical combat casualty care states that eye injuries do not preclude the use of ketamine.\textsuperscript{48} Nevertheless, cautious use of ketamine in cases of possible ocular injury, as well as consideration of alternative agents, is advised.

The usual induction dose of ketamine in RSI is 1.5 mg/kg intravenously.\textsuperscript{35} In catecholamine-depleted patients, it is not recommended to exceed a dose of 1.5 mg/kg. If being used for prolonged postintubation sedation and analgesia, ketamine should be initiated at 10% of the induction dose, with dosing repeated as needed and titrated to effect. Alternatively, an infusion of 0.1 to 0.5 mg/min may be initiated to maintain postintubation sedation.\textsuperscript{30}

**Ketamine-propofol combination therapy.** A relatively recent addition to the provider’s arsenal of induction agents is the combination of ketamine and propofol, colloquially known as “ketofol.” This combination produces opposing physiologic effects, reducing unwanted adverse effects while yielding synergistic, dose-sparing sedation. Propofol produces dose-dependent respiratory depression and negative inotropy and may therefore precipitate hypotension in susceptible patients, particularly in elderly and/or volume-depleted patients.\textsuperscript{49}

Ketamine, as opposed to propofol, both bronchodilates and maintains airway reflexes. It is a catecholamine reuptake inhibitor, a class typically associated with an increase in blood pressure (BP) following administration. It facilitates a state of dissociative sedation and simultaneously exhibits analgesic activity mediated by mu-receptor agonism. Ketamine is also known to be emetogenic. In addition to the synergistic and dose-sparing sedation that occurs when ketamine and propofol are
combined, the physiologic effects counter each other, leading to a balanced effect on BP while maintaining airway reflexes, providing analgesia, amnesia, and antiemetic effects.

There is no standardized mixture of ketofol, although it is conventionally administered in a 1:1 ratio by mixing equal parts ketamine (10 mg/mL) and propofol (10 mg/mL) into the same syringe. Providers must be diligent and communicate clearly with the team when calculating the appropriate dose of ketofol. For example, if a dose of “1 mg/kg of ketofol” is requested, it is imperative that the pharmacist clarify whether this means 1 mg/kg of ketamine and 1 mg/kg of propofol or, rather, 0.5 mg/kg of each component. In the chaotic environment of the ED, further confusion may arise from the changing concentration that occurs when combining the agents in the same syringe. When mixing equal parts of 10-mg/mL ketamine solution and 10-mg/mL propofol solution, the final concentration of each component decreases by half (to 5 mg/mL) since the total amount of drug remains the same but the volume doubles. Some of this confusion may be alleviated by preparing the dose on a volume per kilogram basis rather than in milligrams per kilogram. If the goal is to administer 0.5 mg/kg of each component, it is sometimes easier to dose the 1:1 ketofol mix as 0.1 mL/kg. For example, to administer a 0.1-mL/kg dose to a 70-kg patient, the EMP would prepare 7 mL of the 1:1 ketofol solution, which would contain 3.5 mL (35 mg) of ketamine and 3.5 mL (35 mg) of propofol, yielding a dose of 0.5 mg/kg of each component. Alternatively, the Institute for Safe Medication Practices recommends preparing and administering the ketamine and propofol in separate syringes in order to avoid any confusion.

Although the first known report of ketofol use was published in 1991 describing its use for providing total anesthesia, ketofol use did not become widespread until after 2007, when descriptions of its role in the provision of procedural sedation and analgesia (PSA) began to be published. Since that time, the body of knowledge
regarding use of ketofol for PSA has expanded dramatically. However, there remains a paucity of evidence regarding the role of ketofol for induction in RSI.

In a randomized, parallel-group superiority trial, Smischney and colleagues\textsuperscript{52} compared the combination of ketamine and propofol to etomidate for intubation in a critically ill population consisting of adult patients admitted to a medical, surgical, or oncologic/transplant ICU and requiring emergent intubation. The primary endpoint was the change in MAP from baseline (defined as 1 minute prior to drug administration) to 5 minutes post drug administration. Secondary endpoints included any change in MAP at 10 minutes and 15 minutes from baseline; change from baseline in the average MAP area under the curve in the first 15 minutes; new-onset vasopressor use; narcotic use; intubation difficulty score; new-onset delirium; transfusion requirements; and ventilator-free days, starting at the time a patient was transitioned from mechanical ventilation to noninvasive ventilation. Subjects (N = 160) were randomly assigned to receive either ketofol (n = 84; 0.5 mg/kg of ketamine plus 0.5 mg/kg of propofol) or a reduced dose of etomidate (n = 76; 0.15 mg/kg). Both groups could receive one repeat bolus if necessary. The researchers noted that “50 mcg fentanyl was administered to blunt the hemodynamic response.” This dose, however, would be insufficient to affect catecholamine release, as this effect is typically noted with fentanyl doses ranging from 2 to 4 µg/kg. There was no statistically significant difference with regard to the primary endpoint of MAP changes in the first 5 minutes. However, analysis of the secondary endpoints yielded statistically significant findings, including the finding that more patients in the etomidate group required non–red blood cell transfusions (platelets, cryoprecipitate, or plasma) (16 patients [22%] treated with etomidate vs 8 patients [10%] treated with ketofol; $P = 0.046$) and the finding that among those who had adrenal testing performed, more patients in the etomidate group developed immediate
adrenal insufficiency (13 [81%] vs 5 [38%]; \(P = 0.027\)). The investigators summarized their findings by noting that ketofol was not superior to a reduced dose of etomidate in terms of hemodynamic impairment. They also noted that because adrenal suppression is known to occur with even a reduced dose of etomidate but not with ketofol, and since both agents appear to confer similar hemodynamic stability, the use of ketofol for induction in RSI may be advantageous in preserving adrenal function in critically ill patients.

Smischney and colleagues\(^5\) conducted a follow-up trial to a 2012 randomized, double-blind, placebo-controlled trial evaluating the use of ketofol as an induction agent among patients undergoing surgery requiring general anesthesia. In this trial, 84 patients were randomly assigned to receive either 2 mg/kg of propofol, with the option to receive a 1-mg/kg rescue dose if necessary (n = 43), or ketofol (ketamine 0.75 mg/kg plus propofol 1.5 mg/kg), with the option to receive a rescue dose of ketamine 0.25 mg/kg plus propofol 0.5 mg/kg if necessary (n = 41). All subjects received midazolam 2 mg preoperatively, and 1 to 2 \(\mu\)g/kg of fentanyl at the time of induction. Subjects also received volatile anesthetics for maintenance of intraoperative anesthesia. The primary endpoint was the incidence of a 20% or greater decline in SBP measured 5, 10, and 30 minutes post induction. Secondary endpoints included the effect on cardiovascular performance factors (BP, HR, cardiac output/cardiac index [CO/CI], stroke volume/stroke index [SV/SI], total peripheral resistance/total peripheral resistance index [TPR/TPRI]), postoperative pain, time to discharge from the postanesthesia care unit (PACU), and incidence of nausea, vomiting, and psychomimetic effects. The researchers found that compared with use of ketamine, propofol use was more commonly associated with a decrease of greater than 20% in SBP from baseline at 5 minutes (48.8% vs 12%; OR, 6.87 [CI, 2.07-26.15]; \(P < 0.001\)) and at 10 minutes (67.4%
vs 39%; OR, 3.24 [CI, 1.21-8.75]; \( P < 0.001 \). There was not a significant difference in SBP at 30 minutes post administration, nor was there a difference in the use of intraoperative vasoactive agents. With regard to secondary endpoints, ketofol was associated with a lesser reduction in both SV/SVI (7.8 vs 12.2; CI, 0.5-8.4; \( P = 0.029 \)) and TPR/TPRI (161.8 vs 261.2; CI, 28.1-199.1; \( P < 0.01 \)). At 10 minutes post administration, the between-group difference in SV/SVI approached significance (\( P = 0.051 \)) and no difference in TPR/TPRI was noted. At 30 minutes, there were no differences in any parameters, nor were there differences in the incidence of postoperative pain, nausea, vomiting, or psychomimetic effects. The investigators summarized their findings by noting that compared with propofol, ketofol was associated with lesser reductions in SBP, DBP, and MAP, and its use did not lead to significant increases in these parameters in any instances. Ketamine is known to be associated with psychomimetic and sympathomimetic effects when administered as a single agent, and propofol is associated with peripheral vasodilation, negative inotropy, and a reduction in BP. This study supports the notion that combining ketamine with propofol yields a favorable hemodynamic profile, with each agent balancing the undesirable effects of the other.

In a 2015 case series, Gallo de Moraes\(^55\) evaluated the use of ketofol for induction when intubating 6 critically ill patients. Patients ranged in age from 25 to 77 years, and concurrent illnesses included septic shock, hypotension, cirrhosis, atrial fibrillation, hematemesis, and pneumonia. Each patient had received a standardized dose of 0.5 mg/kg of propofol and 0.5 mg/kg of ketamine to facilitate induction. Data collection points included total doses of all medications administered; fluid administration requirements; complications; Confusion Assessment method for the ICU (CAM-ICU) scores; and vital signs during the initial 15 minutes post administration. The researchers noted that these 6 patients had different primary diagnoses and
circumstances, but all received the same induction agent and dosing. Four of 6 patients were successfully intubated on the first attempt, and 4 of 6 maintained a MAP of >65 mm Hg for up to 15 minutes post intubation without the need for vasopressors. Of note, one patient received 200 µg of phenylephrine to bolster BP even though the MAP was greater than 65 mm Hg, and the other patient receiving vasopressors was already on a norepinephrine infusion prior to intubation and no dosage changes were required post intubation. There was no difference in fluid resuscitation requirements in the 24 hours before and after intubation, and no evidence of recovery agitation was noted. The researchers noted that although this was a small case series that did not have a comparator group, ketofol use appeared to be associated with adequate sedation and hemodynamic stability for up to 15 minutes post intubation and may be considered a viable option for induction among critically ill patients.

In summary, although evidence regarding its use for induction in RSI is limited, ketofol appears to be a viable option for this purpose. Published studies indicate that it leads to good intubating conditions, confers hemodynamic stability, is not associated with significant adverse effects. It is most commonly administered as a 1:1 mixture of ketamine and propofol, and induction doses range from 0.5 mg/kg to 1mg/kg of each constituent.

Paralysis

**Succinylcholine vs rocuronium.** The practice of paralysis with induction remains a common practice today, as demonstrated in a multicenter, multinational study wherein 84% of ED patients intubated received paralysis with sedation. Several nondepolarizing neuromuscular blocking agents, such as vecuronium, pancuronium, and cisatracurium, exist; these medications may have a role in the care of intubated
patients. However, for this update we will review recent evidence regarding the most commonly utilized paralytic agents in RSI: succinylcholine and rocuronium.\textsuperscript{14}

General weight-based dosing recommendations for nondepolarizing and depolarizing neuromuscular blockers have remained consistent since Hampton's 2011 review.\textsuperscript{6} Dosing of nondepolarizing agents in obesity deserves exploration due to the risks of under- and overdosing. Patanwala and Sakles\textsuperscript{56} described only 76% first-pass success in patients weighing more than 120 kg while also observing decreasing doses of succinylcholine in increasingly heavier patients. Unlike succinylcholine, which should be dosed by actual body weight as a result of degradation by plasma butyrylcholinesterases, dosing of nondepolarizing agents in obese patients is less straightforward. Rocuronium, in contrast, is eliminated primarily via hepatic mechanisms. Ideal body weight should be utilized for rocuronium dosing when treating morbidly obese patients, given data describing prolonged paralysis in obese patients compared to nonobese patients.\textsuperscript{57,58} When ideal body weight cannot be reliably calculated or estimated, actual body weight may be used, as prolonged paralysis is generally desired over an insufficient period of paralysis.

While succinylcholine and rocuronium remain the primary paralytic agents for RSI in the ED, there remains healthy, if not spirited, debate regarding which is the superior agent. Studies in the preoperative anesthesia setting were among the first to compare the effectiveness of succinylcholine and rocuronium. In this setting, musculoskeletal outcomes such as train-of-four twitch ablation, specific muscle group relaxation, and time to hemoglobin desaturation have been evaluated.\textsuperscript{58-61} In an emergency care setting, such outcomes are neither realistic nor relevant.

A Cochrane review published in 2014 concluded that succinylcholine was superior to rocuronium for achieving the primary outcome of excellent intubating
conditions (risk ratio, 0.86; 95% CI, 0.81-0.92) in an analysis of 50 studies including 4,151 patients. Five studies (n = 1,073) were identified as including patients intubated under emergency situations; this subgroup had a risk ratio for excellent intubating conditions favoring succinylcholine over rocuronium (0.84 [95% CI, 0.73-0.98]). There were no significant differences in secondary outcomes including acceptable intubating conditions in emergency situations as well as serious adverse effects. When evaluating high-dose rocuronium (ie, 1.2 mg/kg), no significant between-group difference in the primary outcome was observed. The investigators concluded rocuronium should be reserved for situations in which succinylcholine is contraindicated. Despite this strongly worded conclusion, the debate did not subside, as newer studies demonstrated conflicting results. In an analysis of 5,071 ED intubation encounters in the NEAR database, April and colleagues described similar first pass success rates with succinylcholine and rocuronium (87% vs. 87.5%; risk difference, 0.5% [95% CI, –1.6% to 2.6%]). While this was not a prospective study, the mean (median) doses of succinylcholine and rocuronium were consistent with RSI dosing (1.8 mg/kg [1.5 mg/kg] and 1.2 mg/kg [1.1 mg/kg], respectively), thus maintaining external validity.

One suggested advantage of rocuronium over succinylcholine is a longer safe apneic period. One study found that the median time to attain oxygen saturations of 100% and 95% after the blinded administration of succinylcholine or rocuronium to young healthy adults were 358 and 378 seconds, respectively. Another study in obese adults found that the mean time of desaturation from 100% to 92% was 283 seconds in the succinylcholine group versus 329 seconds in the rocuronium group. The mechanism proposed by the researchers suggests more oxygen is consumed from muscular fasciculations induced by succinylcholine. In the studies, intubations were conducted by anesthesiologists in a controlled operating room setting. The difference between
these agents has not been thoroughly studied in the critically ill population, so it is unknown if these differences remain clinically important in ED settings.

**Sugammadex.** Sugammadex is a novel modified γ-cyclodextrin that exerts its pharmacological effect by forming a complex with rocuronium or vecuronium circulating in the plasma, thereby reversing neuromuscular blockade. The sugammadex/neuromuscular blocker complex is renally eliminated and is not known to undergo any hepatic metabolism. The half-life of the sugammadex complex is approximately 2 hours and is prolonged in renal impairment. Due to its ability to reverse rocuronium induced paralysis, sugammadex has various potential applications in RSI.

The use of sugammadex in the ED remains limited, as the bulk of data regarding its use is focused on the surgical population. Sugammadex could potentially be useful in RSI performed in the ED in a “cannot intubate, cannot ventilate” situation. However, significant barriers to its use exist. Teams not regularly using rescue doses of sugammadex can experience clinically significant delays to administration as well as dosing errors. Some literature has suggested the routine use of sugammadex for reversal of rocuronium-induced neuromuscular blockade as an alternative to the quick offset of succinylcholine. This strategy, however, may not add any benefit over an extended paralysis period and could result in unnecessary costs.

It is also imperative to consider the underlying condition of the patient when neuromuscular blockade is reversed. In the ED, often the indication for intubation is urgent, and the failure to quickly secure the airway may be detrimental. The ED setting differs from the often more controlled setting of the operating suite. Additionally, many of the standard induction agents may cause significant respiratory depression at doses used for RSI. These factors need to be taken into consideration when considering
whether to reverse neuromuscular blockade or to use that critical time preparing to place a different type of airway.

A role for sugammadex in the reversal of neuromuscular blockade to facilitate neurological examination has been described in the setting of subarachnoid hemorrhage. Sugammadex reversal may be considered in other disease states in which time-sensitive neurological or neuromuscular evaluation is needed, such as acute ischemic stroke and status epilepticus.

Product labeling suggests that for the immediate reversal of a 1.2-mg/kg dose of rocuronium, 16 mg/kg of sugammadex should be given. Near complete reversal of the neuromuscular blockade can be expected 2 to 3 minutes after administration. Doses as low as 2 to 4 mg/kg have been used to reverse neuromuscular blockade. These doses have been primarily described as being used in surgical patients, with depth of blockade (measured by train-of-four assessment) to guide dosing. While train-of-four testing may not be feasible in many EDs, sugammadex doses lower than 16 mg/kg may be reasonable if the airway is secure. Actual body weight is has been typically used to determine the dose. Some data suggests using an adjusted body weight in obese patients; however, the need to completely reverse the neuromuscular blockade should be weighed against the slim adverse effect profile of sugammadex when choosing a dosing weight. Package labeling states that use of sugammadex is not recommended in patients with renal failure who have a creatinine clearance of <30 mL/min. There is a theoretical risk of recurrence of neuromuscular blockade in patients who have delayed clearance of sugammadex. To date, case studies and retrospective and observational trials of sugammadex given to patients in renal failure have shown sugammadex to be effective, and no occurrences of neuromuscular blockade were reported; however, larger safety-driven prospective studies are needed to confirm those findings.
that clearance of sugammadex may be delayed in the critically ill population, if reinduction of neuromuscular blockade is desired for the patient in the next 24 hours, an alternative class of neuromuscular blocker, such as succinylcholine or cisatracurium, should be considered.

Warnings for sugammadex include the risk of impaired hemostasis. Studies have found that sugammadex use was associated with increases in prothrombin time and activated partial thromboplastin time of 3% to 5%, with a return to baseline values after approximately 1 hour, and no significant increase in bleeding risk in postoperative patients. However, the clinical significance of these effects in patients with active bleeding disease states is unknown.

Few drug-drug interactions with sugammadex have been reported. One notable exception is the interaction with oral contraceptives. In vitro data suggests there may be significant binding of sugammadex with the progesterone and progesterone-like components of oral contraceptives, leading to decreased efficacy of the contraceptives. Though this is unlikely to affect practice in the ED, it may be a consideration for the transition of care.

Postintubation management

Role of the EMP. While pharmacist involvement during RSI is important, postintubation medication management by the EMP is just as vital, if not more crucial, to reduce complications. Both sedation and analgesia should be addressed immediately following intubation. Sedative infusions should be prepared while RSI medications are being procured to ensure that delays in initiating post-RSI management do not occur. This is of particular importance in situations where a long-acting neuromuscular blocking agent, such as rocuronium, has been used, thereby placing the patient at higher
risk for being awake and paralyzed. Patient awareness paralysis is a phenomenon that has been described in the clinical literature as a patient recalling sensory perceptions while under the effects of a neuromuscular blocking agent, and the incidence of patients experiencing it in ED and ICU settings is higher than has been reported in operating room settings.\textsuperscript{78,79} Patient awareness paralysis has been associated with long-term psychological ramifications such as posttraumatic stress disorder, complex phobia disorders, and clinical depression.\textsuperscript{80,81} Pappal and colleagues\textsuperscript{79} conducted a clinical trial to assess for the prevalence of awareness with paralysis in ED patients requiring mechanical ventilation. In this single-center, prospective, observational study of 383 patients, they assessed if patients recalled any sensory perceptions while paralyzed by utilizing the Brice questionnaire. Of the 383 patients questioned, 2.6\% (10/383) had awareness of paralysis. Exposure to rocuronium during the ED visit significantly increased the likelihood of awareness of paralysis (unadjusted OR, 5.1; 95\% CI, 1.30-20.1). In addition, patients experiencing awareness with paralysis had higher mean values on the threat perception scale included in the Brice questionnaire than patients who did not report awareness of paralysis (13.4 [SD, 7.7] vs 8.5 [SD, 6.2]; mean difference, 4.9; 95\% CI, 0.94-9.9).

In addition to ensuring adequate pain control and sedation during the postintubation period, it is also imperative to provide the appropriate depth of sedation. Early deep sedation in the first 48 hours of hospitalization has been shown to increase mortality in critically ill patients.\textsuperscript{82,83} A single-center cohort study showed that early deep sedation was common in mechanically ventilated patients in the ED (occurring in 64\% of 254 patients), and a deeper sedation score was associated with mortality, which led to larger trials being conducted to evaluate sedation practices.\textsuperscript{84} In a study by Fuller and colleagues,\textsuperscript{85} they evaluated the incidence of deep sedation (defined as a Richmond
Agitation-Sedation Scale [RASS] score of −3 to −5) in the ED setting. In this multicenter, prospective cohort study, 52.8% of patients (n = 171) received deep sedation while in the ED. The most commonly used agents were fentanyl (64.5%), propofol (65.7%), and midazolam (23.8%), and deep sedation was associated with longer hospital stays (P = 0.03) and a higher incidence of acute brain dysfunction (P = 0.02). However, there was no difference in mortality between the deep-sedation and the light-sedation groups (P = 0.35). Based on these results, a multicenter, prospective trial was conducted to determine the feasibility of targeting the ED to improve sedation practices and reduce the frequency of deep sedation. The goal of the study was to improve sedation depth documentation and reduce the proportion of patients deeply sedated. Adult patients were included if they were mechanically ventilated in the ED and did not present with an acute neurologic injury or meet other exclusion criteria (death, chronic/home health mechanical ventilation, requirement of continuous neuromuscular blockade, transfer from another hospital, transfer from the ED to the OR, or transition to comfort/hospice care within the first 24 hours of hospitalization). In this pilot study, the incidence of deep sedation (defined as a RASS score of −3 to −5) was reduced from 60.2% (n = 118) to 38.8% (n = 85) (P < 0.01). Moreover, inadvertent extubation occurred in 3 patients (1.4%), with none of these patients requiring reintubation, and only 8 patients (3.6%) reported awareness with paralysis. The study results are promising because they add to emerging evidence that variability in ED sedation depth documentation can be reduced and that the rate of deep sedation in the ED can be decreased without adverse outcomes.

The studies summarized above highlight the important role EMPs can play in managing sedation practices in the ED whilst improving patient-centered clinical outcomes. It is important to note that the choice of analgesic and sedative agents, as
well as the use of intermittent versus continuous infusions of said agents, involves a balance that involves the EMP weighing risks and benefits against the patient’s current clinical status. A thorough understanding of the pharmacokinetic, pharmacodynamic, and adverse effect profiles of these agents is necessary to ensure appropriate agent selection for the patient (Table 2).

**Conclusion**

EMPs can play a vital role in the RSI process. They can assist in proper drug selection, dosing, preparation, and administration and in designing and implementing postintubation strategies. RSI provides pharmacists with a unique beside role in which they can directly impact patient care while being a valuable resource to the ED team.
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Table 1. The Seven P’s of RSI and Potential Action Steps for the Bedside EMP

**Actions for the EMP**

| Preparation          | - Verbalize plan for induction, paralysis, and postintubation sedation with provider prior to medication administration  
|                      | - Draw up and properly label necessary pharmacologic agents  
|                      | - Procure any other supplies needed at the bedside (ie, syringes, needles, or resuscitative agents)  
| Preoxygenation        | - Knowledge of current oxygenation status prior to intubation  
| Preintubation optimization | - Identification and mitigation of any possible cardiopulmonary vulnerability that may complicate resuscitative efforts  
|                      | - Stabilization of hemodynamic parameters  
|                      | - Consider contingency plans for unintended/unexpected outcomes (eg, inadequate sedation or paralysis, loss of IV access)  
| Paralysis with induction | - Perform induction prior to paralysis  
|                      | - Communicate to team expected duration of paralysis and when motor recovery may become evident  
| Positioning           | - Knowledge of pharmacokinetics, mechanism of action, and adverse effects of medications used in RSI (eg, succinylcholine-induced fasciculations) to determine and communicate when patient is at optimal intubation condition  

Placement with proof

- Acknowledge proper endotracheal tube placement modalities (eg, carbon dioxide detector, lung field auscultation, postintubation chest radiograph)

Postintubation management

- Provide assistance to nursing staff in setting up and programming automated infusion pumps
- Workflow permitting, debrief with team regarding what went well in addition to any areas for improvement

Abbreviations: EMP, emergency medicine pharmacist; IV, intravenous; RSI, rapid sequence intubation.
| Medications Used for Induction, Paralysis, and Postintubation Sedation in RSI | Mechanism of action | Dosing | Pharmacokinetics | Monitoring considerations |
|---|---|---|---|---|
| **Induction** | | | | |
| Etomidate | GABA receptor agonist | 0.3 mg/kg IV push | Onset: 10-15 seconds Duration: 4-10 minutes | • Hemodynamically neutral  
• Transient, myoclonic (nonepileptogenic) jerking movement may occur |
| Ketamine | NMDA receptor antagonist (decreases glutamate activity) | 1-2 mg/kg IV push over 30-60 seconds | Onset: 30-60 seconds Duration: 5-15 minutes | • Laryngospasm may occur with rapid IV push administration  
• Consider if patient hypotensive, volume depleted, or hemodynamically unstable secondary to sepsis |
| Ketamine-propofol combination ("ketofol") | NMDA receptor antagonist (decreases glutamate activity) and GABA receptor agonist | 0.5-1 mg/kg IV push for each agent over 30-60 seconds | Onset: 10-60 seconds Duration: 5-15 minutes | • No standard mixture that can lead to medication errors  
• Institute for Safe Medication Practices recommends preparing and administering ketamine and propofol in separate syringes in order to avoid confusion |
| Midazolam | GABA receptor agonist | 0.1-0.3 mg/kg IV push | Onset: 10-60 seconds Duration: <2 hours | • Consider in patients presenting with seizures or agitation  
• Use 0.1-mg/kg dose in hemodynamically unstable patients (hypotension)  
• Clearance prolonged in renal failure, obesity |
| Propofol | GABA receptor agonist | 1-2.5 mg/kg IV push | Onset: 10-60 seconds Duration: 5-10 | • Hypotension common; consider lower doses for |
| Paralysis | Nondepolarizing neuromuscular blocking agent | Rocuronium | 1 mg/kg IV push | Onset: 60 seconds Duration: 40-60 minutes |
|-----------|--------------------------------------------|------------|----------------|-----------------------------------------|
|           |                                             |            |                |                                         |
|           |                                             |            |                | • Utilize ideal body weight for dosing calculations |
|           |                                             |            |                | • High-dose strategies (1.2-1.5 mg/kg) result in intubating conditions similar to those with succinylcholine use but also result in longer paralysis period |
| Succinylcholine | Depolarizing neuromuscular blocking agent | Succinylcholine | 1-1.5 mg/kg IV push | Onset: 45 seconds Duration: 10 minutes |
|           |                                             |            |                |                                         |
|           |                                             |            |                | • Contraindicated in known or suspected hyperkalemia and patients with personal or family history of malignant hyperthermia |
|           |                                             |            |                | • Utilize actual body weight for dosing calculations |
| Postintubation sedation | | | | |
| Analgesic Agents | | | | |
| Fentanyl | Mu-opioid receptor agonist | Fentanyl | 25-100 µg IVP loading dose | Onset: immediate Duration: 30-60 minutes |
|           |                                             |            |                |                                         |
|           |                                             |            |                | • Avoid in suspected serotonin toxicity |
|           |                                             |            |                | • Consider bowel regimen to minimize constipation adverse effects |
| Hydromorphone | Usual maintenance rate: 0.25-4 mg/h | Hydromorphone | 0.2-1 mg IVP | Onset: 5 minutes Duration: 3-4 hours |
|           |                                             |            |                |                                         |
|           |                                             |            |                | • No active metabolites; however, parent drug can accumulate in patients with renal failure |
|           |                                             |            |                | • Consider bowel regimen to minimize constipation adverse effects |
| Morphine | 2-10 mg IVP × 1 dose, then 2-4 mg | Morphine | 5-10 minutes | Duration: 3-5 |
|           |                                             |            |                |                                         |
|           |                                             |            |                | • Should be used intermittently |
|           |                                             |            |                | • Active metabolites |
every 1-2 hours as needed hours can accumulate in patients with renal failure

- Hypotension common
- Consider bowel regimen to minimize constipation adverse effects

| Sedative agents | | | |
|-----------------|------------------|-----------------|------------------|
| **Dexmedetomidine** | α₂-adrenergic receptor agonist | Typical starting rate: 0.2 µg/kg/h | Onset: 5-10 minutes Duration: 1-4 hours |
| | | Usual maintenance rate: 0.2-1.5 µg/kg/h | |
| **Ketamine** | NMDA receptor antagonist resulting in decreased glutamate activity | Typical starting rate: 0.1-0.5 mg/kg bolus | Onset: 30-60 seconds Duration: 5-15 minutes |
| | | Usual maintenance rate: 0.04-2.5 mg/kg/h | |
| **Midazolam** | GABA receptor agonist | 2-5 mg or 0.01-0.05 mg/kg IVP over 2 minutes | Onset: 10-60 seconds Duration: <2 hours |
| **Propofol** | GABA receptor agonist | Typical starting rate: 10-20 µg/kg/min | Onset: 10-60 seconds Duration: 5-10 minutes |
| | | | |
| | | Hypotension, bradycardia |
| | | Should be administered with GABA receptor agonist in alcohol withdrawal |
| | | Consider if patient hypotensive, volume depleted, or hemodynamically unstable secondary to sepsis |
| | | Consider in in patients with traumatic brain injury with hypotension or agitation |
| | | Avoid in patients with severe cardiac disease |
| | | Should be used intermittently; continuous infusions associated with delirium |
| | | Clearance prolonged in renal failure, obesity |
| | | Hypotension common |
| | | Considered first-line agent for neurological conditions (ie, traumatic brain injury) |
rate: 5-50 µg/kg/min

injury, epilepsy)

Abbreviations: GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate;