Delayed Sequence Intubation: A Prospective Observational Study

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Study objective: We investigate a new technique for the emergency airway management of patients with altered mental status preventing adequate preoxygenation.

Methods: This was a prospective, observational, multicenter study of patients whose medical condition led them to impede optimal preintubation preparation because of delirium. A convenience sample of emergency department and ICU patients was enrolled. Patients received a dissociative dose of ketamine, allowing preoxygenation with high-flow nonrebreather mask or noninvasive positive pressure ventilation (NIPPV). After preoxygenation, patients were paralyzed and intubated. The primary outcome of this study was the difference in oxygen saturations after maximal attempts at preoxygenation before delayed sequence intubation compared with saturations just before intubation. Predetermined secondary outcomes and complications were also assessed.

Results: A total of 62 patients were enrolled: 19 patients required delayed sequence intubation to allow nonrebreather mask, 39 patients required it to allow NIPPV, and 4 patients required it for nasogastric tube placement. Saturations increased from a mean of 89.9% before delayed sequence intubation to 98.8% afterward, with an increase of 8.9% (95% confidence interval 6.4% to 10.9%). Thirty-two patients were in a predetermined group with high potential for critical desaturation (pre–delayed sequence intubation saturations $\leq$93%). All of these patients increased their saturations post–delayed sequence intubation; 29 (91%) of these patients increased their post–delayed sequence intubation saturations to greater than 93%. No complications were observed in the patients receiving delayed sequence intubation.

Conclusion: Delayed sequence intubation could offer an alternative to rapid sequence intubation in patients requiring emergency airway management who will not tolerate preoxygenation or peri-intubation procedures. It is essentially procedural sedation, with the procedure being preoxygenation. Delayed sequence intubation seems safe and effective for use in emergency airway management. [Ann Emerg Med. 2014;■:1-8.]

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INTRODUCTION

Background

Preoxygenation and denitrogenation allow a safe buffer of oxygen to avoid hypoxemia during the apneic period of rapid sequence intubation.[1] However, some patients struggle against traditional means of preoxygenation because of altered mental status. In these patients, we would be forced to proceed with rapid sequence intubation without the safety buffer of a large oxygen reservoir. Many of them will become hypoxemic during the apneic period and then require bag-valve-mask ventilation, with its attendant increased risks of gastric insufflation and aspiration.

In contrast to rapid sequence intubation, the technique of delayed sequence intubation temporally separates administration of the induction agent from the administration of the muscle relaxant to allow adequate preintubation preparation.[2] The induction agent chosen is one that allows the continuation of spontaneous breathing and the retention of airway reflexes. The prototypical agent for this purpose is ketamine, a dissociative NDMA receptor antagonist. In the space of this separation, the patient can be preoxygenated and denitrogenated, and any necessary peri-intubation procedures can be performed. Only after completion of these crucial actions would the patient be paralyzed and intubated.

Importance

Patients who are intubated without adequate preoxygenation will have less apneic tolerance and are at risk for precipitous desaturation during intubation.[1] If the patient's preintubation oxygen saturation is less than or equal to 93%, he or she will likely continue to desaturate during the apneic period.[3] Patients with inadequate preoxygenation and denitrogenation will have much shorter times until

Editor's Capsule Summary

What is already known on this topic

Adequate preoxygenation is difficult or even impossible in some patients with agitated delirium.

What question this study addressed

This small, observational study addresses whether a brief period of sedation with ketamine would improve ventilation and preoxygenation before intubation.

What this study adds to our knowledge

Postsedation oxygen saturations were successfully increased in the majority of patients.

How this is relevant to clinical practice

Delayed sequence intubation provides a feasible option for preoxygenation in the patient with altered mental status resistant to standard preoxygenation. Clinical outcomes were not assessed, and a randomized trial is warranted.

desaturation during intubation attempts.[1] A technique to allow adequate preparation of delirious or combative patients for intubation could decrease the risk of hypoxemia and reduce peri-intubation morbidity and mortality.[4]

Goals of This Investigation

Our aim was to investigate the technique of delayed sequence intubation in a cohort of emergency department (ED) and critical care patients requiring emergency airway management in regard to improvement in preoxygenation and safety.

MATERIALS AND METHODS

Study Design

This was a prospective, observational study of patients whose medical condition or mental status led them to impede optimal preoxygenation, denitrogenation, or preintubation procedures. A convenience sample of patients was enrolled during the study period. Clinicians made attempts to preoxygenate and denitrogenate the study participants. If these patients did not allow the necessary preintubation preparations because of delirium, ketamine was administered until they became dissociated. At this point, preoxygenation and any necessary procedures were performed. After adequate preparation, in most cases the patients then received muscle relaxants and were intubated.

The study design complied with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement.[5] This study was approved by our institutional review board, as well as the Danish data protection agency; consent beyond what was standardly obtained for intubation was deemed unnecessary because delayed sequence intubation was considered usual care in these institutions.

Setting

The study was conducted at 3 institutions: a US 540-bed Level I trauma center, a US 1,100-bed quaternary referral center, and a Danish 1,200-bed Level I trauma center. This was primarily a study of ED patients; patients intubated in the ICU immediately on admission from the ED were also included at one of the study sites.

Selection of Participants

Patients included in this trial were undergoing emergency airway management. Patients were aged 18 years or older, spontaneously breathing, and not predicted by clinicians to have an anatomically difficult airway requiring awake intubation. Delayed sequence intubation was performed on patients who remained uncooperative after maximal attempts of traditional means of preoxygenation. Lack of cooperation included any of the following: verbal statements of inability to tolerate a mask or procedure, tearing off the mask, or inability to remain in the stretcher or bed. Attempts to perform preoxygenation included calm reassurance, help holding the mask, and explanations of the importance of preoxygenation. In most cases, delayed sequence intubation was performed after 3 attempts to facilitate standard preoxygenation.

Interventions

Patients undergoing delayed sequence intubation received titrated ketamine in a dose sufficient to achieve a dissociated state with continued spontaneously breathing and maintenance of airway reflexes (Figure 1). The recommended initial dose of ketamine was 1 mg/kg; additional aliquots of 0.5 mg/kg were administered until the patient was in a dissociated state.

Once the dissociated state was achieved, the patients were placed in an at least 30-degree head-up (semi-Fowler) positioning. They then received preoxygenation and denitrogenation with high-flow oxygen, using nonrebreather masks. If the nonrebreather mask was insufficient to raise the pulse oximeter saturation to greater than or equal to 95%, the patients began receiving noninvasive positive pressure ventilation (NIPPV), with

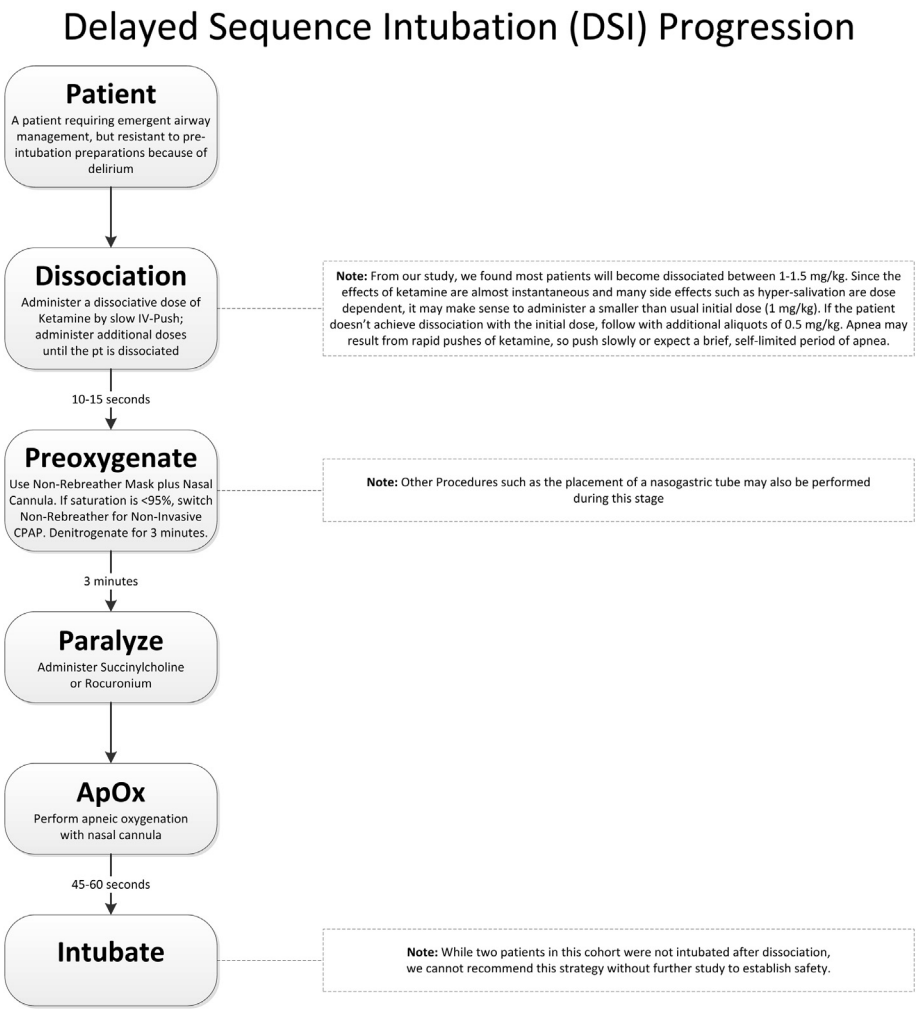

Figure 1. Elaboration of the procedure of delayed sequence intubation.

continuous positive airway pressure settings of 5 to 15 cm H_2O, with no mandatory rate (spontaneous breath trigger). At this point, any procedures clinicians deemed necessary were performed, such as nasogastric tube placement.

After 3 minutes of denitrogenation, patients then received a muscle relaxant (succinylcholine or rocuronium) and began receiving nasal cannula apneic oxygenation, and intubation attempts were made 45 to 60 seconds afterward. In some cases, if the clinicians deemed the patient's improvement after preoxygenation was so profound that intubation was no longer necessary, the procedure was delayed and the patient was allowed to emerge from dissociation. This was predicated on clinical judgment and not part of our delayed sequence intubation protocol. In these patients, the post–delayed sequence intubation oxygen saturation for the primary outcome was at 3 minutes after the administration of ketamine (the time muscle relaxants would have been administered).

Outcome Measures

The primary outcome of this study was the difference in oxygen saturations after maximal attempts at preoxygenation before delayed sequence intubation compared with saturations just before intubation. Maximal attempts at preoxygenation included attempting to verbally persuade the patient to keep on the oxygen mask or NIPPV mask or to allow the procedure and, if that failed, gently holding the mask on the patient's face, without straps. The 2 points for the oxygen saturations were defined as the saturation just before the decision to proceed with ketamine administration (pre–delayed sequence intubation) compared with the oxygen saturation just before muscle relaxant administration (post–delayed sequence intubation). Predetermined secondary outcomes included the number of patients with pre–delayed sequence intubation saturations likely to progress to critical desaturation ($\leq$93%) and their post–delayed sequence intubation saturations,[3] the number of successful

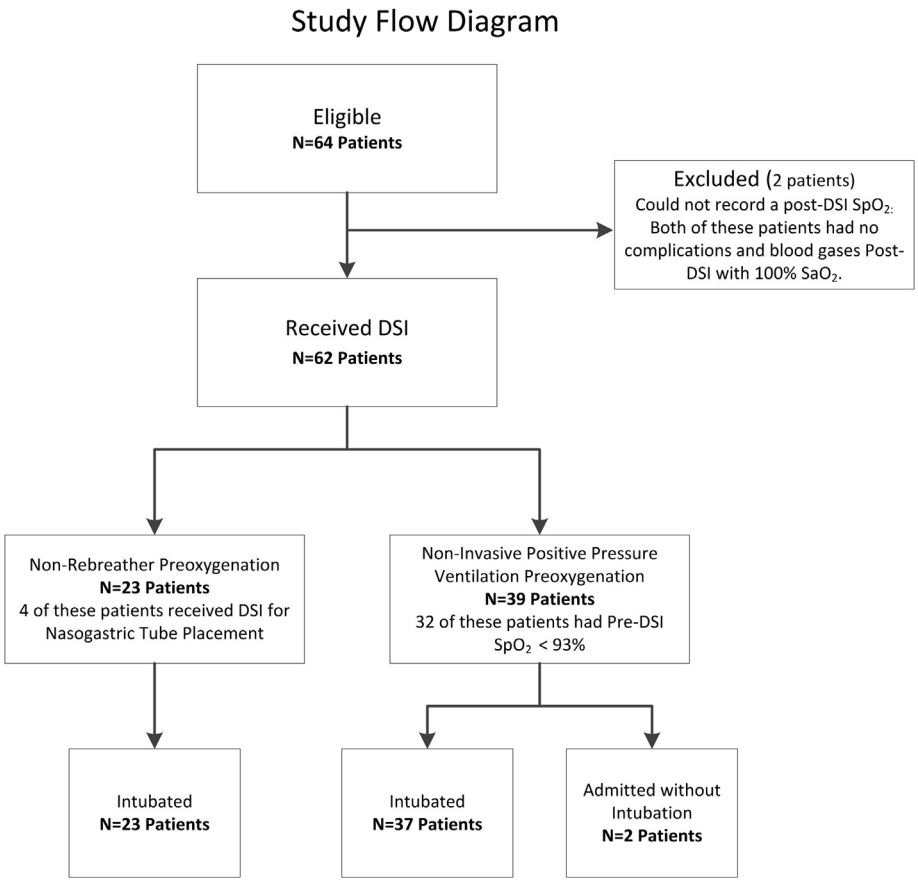

Figure 2. Enrollment and flow through the study.

nasogastric tube placements in patients who would not tolerate attempts at this procedure during their preintubation preparations, and the number of successful denitrogenations (defined as ≥3 minutes of tidal volume breathing while continuously exposed to a high-FiO_2 source without any room-air breaths[6]). Complications associated with delayed sequence intubation were tracked as well; the predetermined complications included pre–muscle relaxant apnea (defined as any apnea from 10 seconds after the administration of ketamine until the administration of muscle relaxant), peri-intubation emesis, and peri-intubation cardiac arrest or mortality (within 3 hours of intubation).

Primary Data Analysis

Descriptive statistics were assessed with means (SD). Mean differences between the saturations pre– and post–delayed sequence intubation were assessed with a paired *t* test because the data were normally distributed. Data were also analyzed with nonparametric methods (Wilcoxon signed rank test), with no difference in results. Computer analysis was performed with SPSS (version 22; IBM Corporation, Armonk, NY).

RESULTS

Sixty-four patients with delayed sequence intubation were included from May 2011 to December 2013 (Figure 2). Two patients were excluded because the pulse oximeter would not register a post–delayed sequence intubation oxygen saturation. Both of these patients had arterial blood gases sent from their arterial lines at this point; the SaO_2 values of these blood gases were both 100% and neither of these patients had any complications.

The Table summarizes the characteristics of the remaining 62 study patients. The mean patient age was 54 years; 33% were women. The Table also shows the patients' underlying condition, the primary reason for intubation, and the reason delayed sequence intubation was needed. Fifty-five patients were intubated in an ED setting; 7, in an ICU. The mean total dose of ketamine administered to facilitate delayed sequence intubation was 112 mg. For the 42 patients with available weight data, the mean total dose was 1.4 mg/kg.

Saturations increased from a mean of 89.9% before delayed sequence intubation to 98.8% afterward, with an increase of 8.9% (95% confidence interval 6.4% to 10.9%). Figure 3 shows the saturation changes of the individual

Table. Characteristics of study patients.

Characteristics	All Patients (N=62)
Age, mean, y	54
Range, y	18–79
Female, %	33
Location of intubation, Pts	
ED	55
Critical care unit	7
Condition leading to need for intubation, Pts	
Pneumonia	20
Asthma	7
Acute pulmonary edema	3
Chronic obstructive pulmonary disease	1
Acute lung injury	8
Anaphylaxis	2
Smoke inhalation	2
Sepsis encephalopathy	2
Hepatic encephalopathy	8
UGIB	6
Cardiogenic shock	1
Trauma	2
Primary reason for intubation, Pts (%)	
Oxygenation (type I) failure	42 (68)
Ventilatory (type II) failure	2 (3)
Airway protection	18 (29)
Reason for DSI, Pts (%)	
Intolerance of nonrebreather mask	19 (31)
Intolerance of NIPPV	39 (63)
Intolerance of nasogastric tube placement for UGIB	4 (6)

Pts, Patients; *UGIB*, upper gastrointestinal bleeding; *DSI*, delayed sequence intubation.

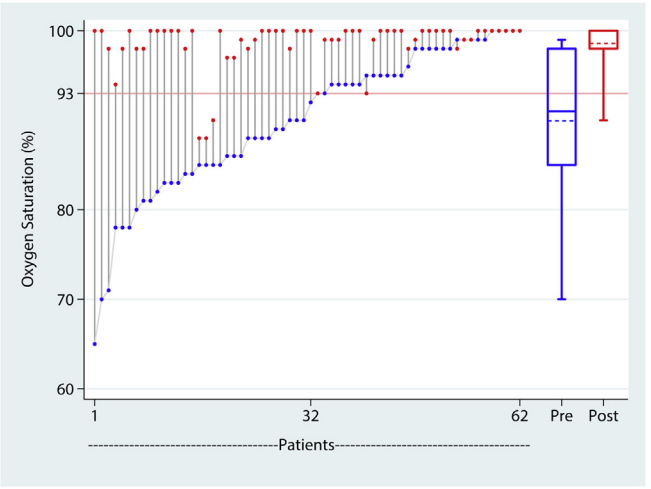

Figure 3. Oxygen saturations (SpO_2) pre– and post–delayed sequence intubation for the 62 enrolled patients. Blue dots indicate pre-DSI saturation and red dots indicate post-DSI saturation. When there was no change during the dissociative period, a red dot indicates both saturations. The oxygen saturations of the 32 patients whose pre-DSI saturation was less than 93% (red line) can be seen on the left side of the plot.

patients. Thirty-two patients were in the predetermined group with high potential for critical desaturation (pre–delayed sequence intubation saturations ≤93%). All of these patients increased their saturations post–delayed sequence intubation; 29 (91%) of them increased their post–delayed sequence intubation saturations to greater than 93%. All but 1 of these patients received NIPPV for preoxygenation during delayed sequence intubation.

Four patients with upper gastrointestinal bleeding received delayed sequence intubation to allow the placement of a nasogastric tube to drain their gastric blood before intubation; all 4 of these patients had successfully placed tubes confirmed by postintubation radiography. Of the 19 patients who received delayed sequence intubation to allow nonrebreather mask preoxygenation or denitrogenation, all were successfully denitrogenated for the 3-minute period.

Two patients were not intubated post–delayed sequence intubation. Both of them were asthmatic, with altered mental status. After administration of ketamine, both of these patients tolerated NIPPV. They received nebulized asthma medications and steroids. The clinicians deemed that the patients' respiratory status improved sufficiently post–delayed sequence intubation that intubation could be avoided. Both of these patients emerged with continued improved respiratory status and were able to be admitted to the hospital, receiving NIPPV. They were subsequently discharged without the need for intubation.

No patients had pre–muscle relaxant apnea, peri-intubation emesis, cardiac arrest, or death. Two patients' oxygen saturations decreased from the pre– to the post–delayed sequence intubation periods. The first patient's saturation decreased from 99% to 98%; the second patient's, from 95% to 93%. Both of these patients were receiving preoxygenation by nonrebreather masks without nasal cannula oxygen during their dissociation.

LIMITATIONS

This was not a randomized trial and therefore it is unknown what the patient outcomes would have been in these cases if delayed sequence intubation had not been used. We collected patients as a convenience sample when the clinician deemed that delayed sequence intubation would have been beneficial; hence, there may be inherent selection bias. It is possible that a delayed sequence intubation was performed at one of these centers but the patient was not enrolled in the study. This is unlikely because all intubations were reviewed by a research associate specifically to screen for missed delayed sequence intubation.

All delayed sequence intubations were supervised by clinicians with extensive experience with ketamine sedation in adults; clinicians lacking familiarity with the medication

may not have the same results. Furthermore, the study authors performed many of these intubations and may have given a higher level of care and attention because of a vested interest in good outcomes.

The study was small; there may be rare complications that will emerge only on the performance of larger trials, though a reassurance of safety can be extrapolated from the complication rate of ketamine for procedural sedation in adults.[7] The safety of NIPPV in this cohort cannot be applied to all patients with altered mental status, such as obtunded or brain-injured patients. Although no patients in this cohort had tachycardia or hypertension necessitating treatment, these adverse events are potentially those of ketamine. Only adult patients were included; the safety and efficacy of delayed sequence intubation in the pediatric population is unknown, though there have been case reports of its use.[8,9]

DISCUSSION

In this prospective trial, we found that delayed sequence intubation allowed the provision of preoxygenation and denitrogenation to a patient population who would otherwise have been resistant to these important procedures. Traditionally, these patients would have proceeded directly to rapid sequence intubation, exposing them to the risks of peri-intubation bag-valve-mask ventilation such as gastric insufflation and aspiration. In patients with physiologic shunting, inadequate recruitment and preoxygenation can lead to severe hypoxemia and peri-intubation cardiac arrest. In this study, delayed sequence intubation was demonstrated to be effective and without observed complications in these patient groups during emergency airway management.

Delayed sequence intubation is often conflated with NIPPV preoxygenation. Although the 2 complement each other, delayed sequence intubation can be performed with standard preoxygenation as well. In this trial, 39 patients received preoxygenation with NIPPV; the remaining 23 patients achieved adequate preoxygenation and denitrogenation with nonrebreather mask alone.

There is a belief that NIPPV is contraindicated in patients with altered mental status. Although some ICUs have begun to challenge this prohibition in many classes of patients,[10-12] the traditional reasons for the contraindication are not applicable to delayed sequence intubation. Ketamine-induced dissociation leads to the retention of airway reflexes and spontaneous breathing, in contrast to other causes of altered mental status.[13] We believe this is a safe practice during the few minutes of preoxygenation as long as patients are carefully monitored by advanced airway practitioners throughout the delayed sequence intubation-preoxygenation.

In this study, a dose of 1 to 1.5 mg/kg was usually sufficient to dissociate patients requiring emergency airway management. Many of the complications of ketamine, such as hypersalivation, are dose dependent.[13] Because ketamine will show its full clinical effects within seconds, it is logical to administer a smaller initial dose, such as 1 mg/kg, and then administer continued aliquots of 0.5 mg/kg until dissociation is achieved. In patients in whom immediate control is needed, a larger dose can be administered initially because even in 10-fold overdose spontaneous breathing and airway reflexes are retained.[13]

In 2 of the delayed sequence intubations, the patients were judged by the clinicians to not require intubation after ketamine administration. Both of these were asthmatic patients who had significant improvement after beginning to receive NIPPV. Although this is not a recommended aspect of delayed sequence intubation, it bears future study. Other trials have examined the use of sedation to facilitate the provision of NIPPV.[14] Ketamine may serve a similar role, but this trial is only suggestive of this possibility. If a clinician opts to attempt this technique, we recommend administering an antiemetic such as ondansetron[15] because, although peridissociation emesis from ketamine has not been reported in adults, postdissociation emesis is common.[7] If such patients are allowed to emerge from sedation and are still in respiratory distress, they can be intubated with standard rapid sequence intubation technique because there will have already been an extensive period of preoxygenation.

The oxygen saturations of 2 of the patients minimally decreased while they were receiving denitrogenation. If during delayed sequence intubation there is a precipitous decrease in oxygen saturation, proceeding to standard rapid sequence intubation is likely the best course. These patients will likely be desaturating as a result of the continued effects of physiologic shunting, so a device incorporating positive and expiratory pressure should be used when reoxygenation of the patient is attempted (bag-valve-mask with positive and expiratory pressure valve, ventilator, etc).[1]

The trial researchers have explored the use of other agents to facilitate delayed sequence intubation, such as dexmedetomidine, droperidol, and remifentanil. However, they require further study before they can be recommended for this purpose. In contrast to ketamine, these agents require provision of an additional induction agent at administration of the muscle relaxant to ensure amnesia and adequate sedation. Some have suggested that standard induction agents such as etomidate or propofol or sedation agents such as midazolam could also be used for delayed sequence intubation. We strongly recommend against this because the nonapnea-inducing dosages of these agents may be very different in a patient requiring

resuscitation than one receiving elective procedural sedation.[16]

Delayed sequence intubation will not be commonly needed because most patients are able to tolerate peri-intubation preparation without additional sedation. Therefore, because it will not be performed often, if delayed sequence intubation is needed it is imperative to perform the procedure in a regimented fashion. All equipment for preoxygenation, intubation, and the possibility of difficult intubation should be at the bedside before ketamine administration. Medications for rapid sequence intubation should be drawn up and present at the bedside, including additional ketamine. A clinician should carefully observe the patient from the moment ketamine is administered until the endotracheal tube is placed and confirmed. Suction and ventilation devices should be prepared before the administration of ketamine.

Ketamine may cause a few seconds of transient apnea after initial rapid administration. Though ketamine-induced prolonged apnea has not been reported in the adult literature,[7] we cannot exclude the possibility of this rare complication. In the event this occurs, we recommend the immediate administration of a muscle relaxant (succinylcholine or rocuronium), which will place the patient in the same situation as if standard rapid sequence intubation had been performed. A similar circumstance is ketamine-induced laryngospasm. Although relatively common in pediatrics, it has been reported only once in the adult cohort.[17] Most situations of upper airway obstruction in adult ketamine dissociations are actually due to poor airway positioning, not laryngeal spasm. If actual laryngospasm occurs during delayed sequence intubation, the muscle relaxant should be administered, allowing standard rapid sequence intubation.

Additional information and media about delayed sequence intubation can be found at http://emcrit.org/dsi/.

Delayed sequence intubation could offer an alternative to rapid sequence intubation in patients requiring emergency airway management who will not tolerate preoxygenation or peri-intubation procedures. It is essentially procedural sedation, with the procedure being preoxygenation. Using this technique, a resuscitationist retains a higher degree of control when intubating a delirious patient. The traditional alternative is to progress to rapid sequence intubation without adequate preparation, which may result in morbidity. Randomized controlled trials of this technique would be welcome, but would be difficult, given this patient population. Delayed sequence intubation seems safe and effective for use in emergency airway management.

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Author contributions: SDW was responsible for the overall study and statistical review, was the principal investigator, collated comments from other authors, prepared the final article, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. ST, JS, and NS were responsible for data collection. SDW and SSR were responsible for analysis and interpretation of the data and for study design. All authors critically reviewed the article. SDW takes responsibility for the paper as a whole.

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