The Dose of Emergency Medicine
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Out of Sequence: Alternatives to Rapid Sequence Intubation

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*This **Dose of Emergency Medicine** offers an overview of alternatives to rapid sequence intubation (RSI). The article will examine delayed sequence intubation (DSI), awake intubation, and ketamine-only breathing intubation (KOBI), outlining appropriate clinical scenarios, procedural techniques, and medications used to facilitate these approaches.*

- Define the key concepts of RSI, DSI, awake intubation, and KOBI in the emergency department setting
- Identify appropriate patient selection criteria and contraindications for DSI, awake intubation, and KOBI
- Summarize primary literature evaluating the efficacy and safety of key medications used to facilitate DSI, awake intubation, and KOBI in difficult airway management
- Implement appropriate procedural steps and monitoring strategies when performing DSI, awake intubation, and KOBI in the emergency department

Introduction

Airway management is a fundamental competency in emergency medicine. Intubation, the placement of an endotracheal or nasotracheal tube into the trachea to secure an artificial airway, remains a cornerstone procedure for ensuring adequate oxygenation, ventilation, and airway protection. Common indications for emergent intubation include mechanical obstruction or compromise of the upper airway (e.g., head or neck trauma, thermal injury, anaphylaxis), heightened risk of aspiration (e.g., massive gastrointestinal hemorrhage), and depressed level of consciousness with loss of airway protective reflexes (e.g., markedly reduced Glasgow Coma Scale).[1]

Each year, more than 400,000 patients in the United States undergo emergency intubation, with first-attempt success achieved in only about 87% of cases.[2] Failure on the initial attempt increases the risk of hypoxemia, aspiration, dysrhythmia, hemodynamic collapse, and cardiac arrest.[3] These complications highlight the importance of proper preparation, technique, and careful selection of pharmacologic strategies.

Rapid sequence intubation (RSI) remains the standard approach to emergency airway management. Near-simultaneous administration of an induction agent and a neuromuscular blocking agent rapidly produces sedation and paralysis, creating optimal laryngoscopic conditions and reducing aspiration risk. RSI has become the default method of intubation because it provides a balance of speed, safety, and effectiveness when performed under appropriate conditions.[4]

Preoxygenation is an essential component of RSI. By displacing alveolar nitrogen with oxygen, it creates an intrapulmonary reservoir that prolongs the safe apnea period – the interval before oxygen saturation declines below 90%. In most patients, effective denitrogenation is achieved with three minutes of tidal volume breathing at a high fraction of inspired oxygen (FiO_2). When time is limited, eight vital-capacity breaths within 60 seconds provide a comparable effect. In critically ill patients, advanced approaches such as noninvasive positive-pressure ventilation (NIPPV) or high-flow nasal cannula (HFNC) are superior to standard facemask oxygen, significantly reducing peri-intubation hypoxemia.[5] Intubation without adequate preoxygenation markedly increases morbidity and mortality, underscoring its role as a cornerstone of RSI preparation.[6,7]

Despite its advantages, RSI is not universally suitable. Profound agitation, anticipated difficult airways, and severe physiological instability may render RSI unsafe or infeasible. In such high-risk scenarios, techniques that preserve spontaneous ventilation and sustain oxygenation are considered. Delayed sequence intubation (DSI) harnesses ketamine's dissociative properties to facilitate preoxygenation in otherwise uncooperative patients, improving oxygen saturation before paralysis.[8] Awake intubation preserves airway reflexes and spontaneous breathing, granting increased safety when difficulty is anticipated. Ketamine-only breathing intubation (KOBI) maintains spontaneous respiration while permitting controlled sedation in critically hypoxemic or unstable patients.[9]

This *Dose of Emergency Medicine* will provide an overview of DSI, awake intubation, and KOBI as practical alternatives to RSI emphasizing their indications, pharmacologic foundations, and procedural considerations in the emergency department.

Delayed Sequence Intubation

Preoxygenation prior to intubation is essential to reduce the risk of hypoxemia and peri-intubation complications, but achieving adequate preoxygenation is often challenging in agitated, delirious, or uncooperative patients. These patients may not tolerate high-flow oxygen delivery devices or NIPPV, placing them at high risk for rapid desaturation if intubation proceeds without sufficient preoxygenation.[10]

Medication-assisted preoxygenation, also known as DSI, is characterized by the Society of Critical Care Medicine as a procedural modification involving the administration of a sedative-hypnotic to achieve adequate preoxygenation.[11] Preoxygenation should be performed with a non-rebreather mask plus nasal cannula for three minutes. If oxygen saturation remains below 95%, a bag-valve-mask is preferred over a non-rebreather mask. Once adequate oxygenation is achieved, a standard neuromuscular blocking agent is administered to facilitate intubation. This approach separates sedation from paralysis, preserves spontaneous ventilation during preoxygenation, and reduces the risk of critical hypoxemia. The procedural steps for performing intubation via DSI are detailed in **Appendix A**. Safe implementation of DSI requires careful operational planning. Continuous monitoring with pulse oximetry and capnography, ready access to suction, and coordinated roles for airway and oxygenation management are essential. Clinicians must also prepare for rapid progression to RSI if dissociation fails to provide adequate preoxygenation.[8]

Etomidate is a widely used induction agent for RSI. It enhances gamma-aminobutyric acid type A ($GABA_A$) receptor activity in the central nervous system, augmenting inhibitory neurotransmission and producing rapid sedation.[12] Although profound respiratory depression is more characteristic of agents like propofol, etomidate can still cause transient apnea, elevations in arterial carbon dioxide ($PaCO_2$), and reductions in tidal volume. Because of these respiratory effects, it is generally not favored for DSI.

Direct comparisons of sedative agents in DSI are lacking, but procedural sedation data support ketamine as the preferred agent. In a systematic review and meta-analysis, Zaki and colleagues compared ketamine with benzodiazepine-opioid combinations such as midazolam and fentanyl in emergency department procedural sedation. They found that while both regimens provided effective sedation, the benzodiazepine-opioid group carried a higher risk of respiratory compromise, whereas ketamine more reliably preserved airway reflexes and spontaneous ventilation.[13] Extrapolated to the DSI setting, these findings reinforce ketamine's role as the sedative of choice, given the critical need to maintain respiratory drive during preoxygenation.

Ketamine acts as a rapidly acting dissociative anesthetic by antagonizing N-methyl-D-aspartate (NMDA) receptors in the central nervous system.[14] Beyond its favorable respiratory profile, it induces a dissociative state that facilitates preoxygenation, while its sympathomimetic properties support blood pressure and heart rate, promoting hemodynamic stability before intubation.[9] Slow intravenous (IV) administration of ketamine at 1-2 mg/kg produces sedation within about one minute, with anesthetic effects lasting 5-10 minutes. When IV access is difficult, such as in a severely agitated patient, intramuscular (IM) ketamine at 4-6 mg/kg produces sedation within 3-5 minutes and lasts 15-20 minutes.[14]

Evidence supporting DSI remains limited. One of the first studies to assess in-hospital DSI was conducted by Weingart and colleagues. This prospective, multicenter, observational study assessed the change in oxygen saturation between maximal preoxygenation before DSI and the saturation immediately prior to intubation. Patients received 1 mg/kg of ketamine, with additional 0.5 mg/kg doses titrated until dissociation was achieved (mean total dose 1.4 mg/kg). In this cohort of 62 patients with altered mental status, DSI improved mean oxygen saturation from 89.9% to 98.8% (95% CI, 6.4-10.9). Among patients at highest risk for critical desaturation, oxygenation improved universally, with more than 90% achieving saturations above 93%, and no complications were reported.[8] These findings reinforce the role of DSI as a safe and effective alternative to RSI in patients who otherwise cannot tolerate preoxygenation.

Jarvis and colleagues conducted a retrospective pre-post study that compared standard RSI with ketamine and a paralytic (pre-intervention group) to a bundled approach incorporating patient positioning (elevated head, sniffing position), apneic oxygenation, DSI with ketamine and a paralytic, and goal-directed preoxygenation (post-intervention group) in patients managed by emergency medical services (EMS). Patients in cardiac arrest were excluded. They found that rates of peri-intubation hypoxia were lower in the post-implementation group compared to the pre-implementation group (3.5% vs 44.2% [95% CI -49.5% to -32.1%]).[15] These findings highlight the potential of DSI, particularly with ketamine, to enhance preoxygenation and reduce hypoxemic complications in high-risk patients.

DSI provides important benefits for select patients but requires careful consideration in high-risk scenarios. Patients who tolerate standard preoxygenation methods gain little from undergoing DSI, as rapid intubation minimizes the time the airway is unprotected.[8] Additionally, the role of ketamine in patients with severe intracranial hypertension remains controversial. Early concerns centered on its potential to impair cerebral circulation and worsen intracranial pressure; however, more recent evidence suggests that with controlled ventilation, ketamine may stabilize or even lower intracranial pressure.[16]

Current evidence suggests that DSI is a valuable modification of standard RSI for patients who cannot tolerate traditional preoxygenation strategies. By using ketamine to achieve dissociation while preserving spontaneous respirations, DSI provides time to optimize oxygenation and reduces the risk of peri-intubation hypoxemia. Although data is limited, both observational and pre-post studies demonstrate consistent improvements in oxygen saturation and fewer hypoxic complications, supporting DSI as a safe and effective option in carefully selected patients.

Awake Intubation

Awake intubation is a technique in which the airway is secured while the patient remains conscious and maintains spontaneous ventilation. This approach is primarily indicated for patients with an anticipated difficult airway, such as those with head and neck tumors, airway edema (e.g., angioedema), morbid obesity, or anatomical distortion (e.g., trauma), where loss of airway control after induction could result in fatal hypoxia or failed oxygenation.[17]

The American Society of Anesthesiologists states that awake intubation is the gold standard for management of the anticipated difficult airway, citing high success rates and safety in this population. Observational studies report successful awake intubation in 88-100% of anticipated difficult airway patients.[18] While this procedure is rarely performed, first attempt intubation success rates are high, ranging from 85% to 99% in elective and emergency settings, with low complication and failure rates.[19,20] However, data specifically describing awake intubation performed in emergency department populations remain limited.

Awake intubation requires careful preparation. The process begins with administration of glycopyrrolate to reduce airway secretions, followed by topical anesthesia of the airway to blunt reflexes and improve patient comfort. This is commonly achieved using local anesthetics, with lidocaine as the agent of choice. The goal is to achieve sufficient mucosal anesthesia to allow for patient comfort and optimal intubating conditions while maintaining spontaneous ventilation and airway patency. A bougie may also be used to assess pharyngeal reflexes before advancing the endotracheal tube, providing an additional measure of readiness for intubation.[21]

During the procedure, supplemental oxygen should be provided, typically via nasal cannula or HFNC, to minimize the risk of desaturation, especially in patients with limited respiratory reserve. Standard physiologic monitoring (pulse oximetry, noninvasive blood pressure, etc.) should be supplemented by continuous assessment of sedation depth, airway reflex suppression, and patient cooperation.

Capnography is advised when sedatives are used to detect early hypoventilation. Ongoing communication with the patient helps ensure tolerance of topical anesthesia and readiness for intubation.[21] The procedural steps for performing intubation via awake intubation are detailed in **Appendix A**.

Lidocaine is preferred due to its rapid onset and favorable safety profile. Typical concentrations range from 2% to 4%, with a general maximum single dose of 300 mg.[22] Topical anesthetic is most effective on dry mucosa and can be applied as cream, gel, or atomized spray to the tongue, pharynx, and larynx, with nasal anesthesia typically achieved using gel or insufflated cream. For endoscopic approaches, aqueous lidocaine may be administered in small aliquots via a "spray-as-you-go" technique. Nebulized lidocaine can supplement topical local anesthesia, helping distribute the anesthetic throughout the airway.[23] However, evidence supporting the use of nebulized lidocaine as monotherapy for awake intubation is limited. While glossopharyngeal, superior laryngeal, and recurrent laryngeal nerve blocks can provide dense regional anesthesia, they require specialized training and are not routinely used. These strategies together optimize patient comfort, preserve spontaneous ventilation, and improve intubation success.[21,24] At Lee Health, lidocaine is available as 4% cream, 2% jelly, and as 2% or 4% injectable solutions suitable for atomization or nebulization. If lidocaine is unavailable, benzocaine 20% can be used as a gel or as a mouth spray (Hurricaine) for atomization.

Low-dose sedatives, such as midazolam, ketamine, and dexmedetomidine, are used in adjunct or for premedication to relieve anxiety and reduce airway reflexes. **Table 1** summarizes recommended dosing for low-dose sedatives in awake intubation, based on current evidence. The choice and titration of sedative agents should be individualized based on patient comorbidities, airway risk, and procedural requirements.[21]

Table 1. Supplemental low-dose sedative dosing for awake intubation[25,26]

Agent	Dosing
Midazolam	0.02-0.05 mg/kg IV bolus over 1-2 minutes; additional 0.5-1 mg IV boluses every 2 minutes to achieve desired level of sedation
Ketamine	0.25-0.5 mg/kg IV bolus or 25-50 mg every 5-10 minutes titrated to patient comfort
Dexmedetomidine	0.5-1 mcg/kg IV bolus over 10 minutes, followed by 0.2-0.7 mcg/kg/hour infusion

Awake intubation should be avoided in patients who are unable to cooperate or follow instructions, such as those with severe agitation, delirium, or altered mental status, as patient responsiveness is essential for procedural safety and success. In time critical scenarios, such as active hemoptysis, hematemesis, or oral hemorrhage, awake intubation is often not feasible, as immediate airway control and ongoing resuscitation take priority. Additionally, awake intubation is relatively contraindicated in patients with high risk of aspiration who cannot protect their airway, as well as those with anatomical or physiological barriers that prevent effective topical anesthesia or intubation (e.g., severe facial trauma, massive oral bleeding, or inability to open the mouth).[17]

Awake intubation represents a critical tool for safely managing patients with anticipated difficult airways. By maintaining spontaneous ventilation and airway reflexes, this technique minimizes the risk of hypoxia and failed intubation in high-risk populations. Successful execution relies on careful patient selection, thorough topical anesthesia, and judicious use of low-dose sedatives tailored to the individual's physiological status and procedural needs.

Ketamine-Only Breathing Intubation

Compared with RSI, KOBI is performed using dissociative-dose ketamine without neuromuscular blockade, allowing patients to maintain spontaneous respirations throughout airway management. KOBI has also been described as ketamine-facilitated intubation, ketamine-supported intubation, or dissociated awake intubation. KOBI parallels DSI in both procedural approach and rationale for sedative choice, but the key distinction is the absence of a paralytic. This technique is particularly indicated for patients with critical hypoxemia, distorted airway anatomy, or those at high risk for failed first-attempt intubation with RSI.[9] Ketamine is administered for KOBI in a manner similar to its use in RSI or DSI, typically at a dose of 1-2 mg/kg intravenously.[14] The procedural steps for performing intubation via KOBI are detailed in **Appendix A**.

Patients appropriate for KOBI largely overlap with those selected for awake intubation. In a study by Driver and colleagues, KOBI demonstrated a lower first-pass success rate than awake intubation, with a 24% absolute difference favoring the awake approach (95% CI -37% to -12%). These results suggest that while KOBI effectively preserves ventilation and oxygenation without paralysis, awake intubation may achieve higher procedural success and safety in patients able to cooperate with topical anesthesia.[27] However, for patients who are uncooperative or require immediate airway control, KOBI remains a preferred approach over a lengthier awake technique.

Because KOBI depends on the patient maintaining spontaneous respiration, it is not suitable for individuals with compromised airway control. Patients at high risk of aspiration or those unable to protect their airway are generally not candidates. Beyond these considerations, a unique scenario where KOBI may be particularly valuable is severe salicylate toxicity. In this setting, RSI and DSI carry significant risk; even brief hypoventilation can abruptly lower pH in a patient maintaining a compensatory respiratory alkalosis, potentially leading to rapid decompensation and death. By eliminating the apneic window, KOBI provides a safer intubation strategy in these cases.[28]

Continuous physiologic monitoring, along with supplemental oxygen delivered via HFNC or non-rebreather mask, should be maintained throughout the procedure to minimize the risk of desaturation. Readiness to escalate to RSI, along with coordinated team roles and access to suction, is critical. Although existing observational data supports KOBI as a safe and effective approach for selected patients, high-quality evidence in emergency department populations is limited. Careful patient selection, vigilant monitoring, and preparedness for rapid airway intervention are essential to optimizing outcomes.[9]

Summary

- RSI remains the cornerstone of emergency airway management, using rapid induction and paralysis to secure the airway efficiently; however, alternatives such as DSI, awake intubation, and KOBI are valuable when standard approaches are unsafe or ineffective
- DSI employs ketamine to achieve dissociation while preserving spontaneous respirations, allowing effective preoxygenation in agitated or uncooperative patients; once adequate preoxygenation is achieved, a paralytic is administered to facilitate safe intubation
- Awake intubation relies on topical anesthetics, often with low-dose sedatives, to blunt airway reflexes while maintaining spontaneous ventilation, providing a safer option for patients with anticipated difficult airways
- KOBI uses dissociative-dose ketamine to sedate patients while preserving spontaneous breathing, allowing airway management without the need for paralysis

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CME and ACPE Information

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Appendix A. Overview of medication-assisted airway management techniques for intubation[8,9,11,17]

<table>
<tr><th></th><th>RSI</th><th>DSI</th><th>Awake intubation</th><th>KOBI</th></tr>
<tr><td>Patient population</td><td>- Patients requiring rapid airway control
- Risk of aspiration
- Acute respiratory failure/persistent hypoxemia</td><td>Intolerance to preoxygenation (e.g., agitation, delirium, lack of cooperation)</td><td>Anticipated difficult airways:
- Head and neck tumors
- Airway edema
- Morbid obesity
- Anatomical distortion</td><td>- Anticipated difficult airways
- Uncooperative patients (i.e. unable to undergo awake intubation)</td></tr>
<tr><td>Contraindications</td><td>- Patients in cardiac arrest
- Anticipated difficult airway
- Patients unable to tolerate apnea (e.g., severe hypoxemia despite preoxygenation)</td><td>- Patients in cardiac arrest
- Patients with adequate preoxygenation without agitation/delirium (i.e. DSI unnecessary)
- Severe intracranial HTN (controversial – ketamine may transiently raise ICP)</td><td>- Patients in cardiac arrest
- Uncooperative or severely agitation patients (cannot tolerate topical anesthesia)
- Facial/airway trauma
- Massive upper airway bleeding or secretions (obscures view, prevents scope passage)</td><td>- Patients in cardiac arrest
- Patients at high risk of aspiration (i.e. inadequate airway reflexes)
- Anticipated difficult airway requiring absolute immobility
- Severe intracranial HTN (controversial – ketamine may transiently raise ICP)</td></tr>
<tr><td>Preferred intraprocedural medications</td><td><u>Induction</u>
- Etomidate
- Ketamine
- Propofol
- Midazolam
<u>Paralysis</u>
- Succinylcholine
- Rocuronium
- Vecuronium</td><td><u>Induction</u>
- Ketamine
<u>Paralysis</u>
- Rocuronium
- Succinylcholine
- Vecuronium</td><td><u>Topical anesthesia</u>
- Lidocaine 2-4% (cream, gel, atomized, nebulized, nerve block)
- Alternative: benzocaine 20% (mouth spray, gel)
<u>Low-dose sedation</u>
- Midazolam
- Ketamine
- Dexmedetomidine</td><td><u>Induction</u>
- Ketamine monotherapy</td></tr>
<tr><td>Procedural steps</td><td>1. Patient preparation (standard airway setup, patient positioning)
2. Preoxygenation with HFNC, NRB mask, and/or NIPPV
3. Administration of induction agent
4. Administration of paralytic
5. Apneic oxygenation with nasal cannula for up to 60 seconds (if oxygen saturation remains <90%)
6. Tube placement and confirmation
7. Post-intubation sedation</td><td>1. Patient preparation (standard airway setup, patient positioning)
2. Dissociation with ketamine
3. Preoxygenation with NRB mask (or NIPPV) plus nasal cannula for three minutes
4. Administration of paralytic
5. Apneic oxygenation with nasal cannula for up to 60 seconds
6. Tube placement and confirmation
7. Post-intubation sedation</td><td>1. Patient preparation (standard airway setup, patient positioning)
2. Administration of glycopyrrolate
3. Topical anesthesia +/- airway nerve block with lidocaine
4. Low-dose sedation
5. Tube placement and confirmation
6. Post-intubation sedation
Supplemental oxygen throughout procedure (HFNC or NRB mask)</td><td>1. Patient preparation (standard airway setup, patient positioning)
2. Dissociation with ketamine
3. Tube placement and confirmation
4. Post-intubation sedation
Supplemental oxygen throughout procedure (HFNC or NRB mask)</td></tr>
</table>

RSI = rapid sequence intubation; DSI = delayed sequence intubation; KOBI = ketamine-only breathing intubation; HTN = hypertension; ICP = intracranial pressure; NRB = non=rebreather; NIPPV = noninvasive positive-pressure ventilation; HFNC = high-flow nasal cannula