

Dexmedetomidine as a Sedative for Awake Fiberoptic Intubation

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Learning Objectives: 1) To understand the challenges of intubation in patients with unstable cervical spine and define the ideal method of intubation in this population. 2) To identify alternative methods for sedation in patients who undergo awake intubation. 3) To recognize the characteristics of dexmedetomidine, its benefits, and unfavorable properties when used for sedation in awake intubations.

Abstract

Intubation might be a challenge in patients with an unstable cervical spine. In trauma patients who have not had cervical spine clearance with clinical and radiologic examination, there is always the worry that intubation can increase the neurologic injury. The most favorable method in this situation is awake intubation, in which the patient can communicate if there is any change in neurologic status and in whom a postintubation neurologic examination is possible. Different methods of sedation for awake intubation have been suggested. Dexmedetomidine is a useful alternative method for sedation because it has anxiolytic, analgesic, and sedative characteristics. It has minimal respiratory depressive effects and patients are easily aroused for a neurologic examination.

Tracheal intubation is usually considered to be the gold standard for airway management in patients with severe trauma as it can protect the airway from gastric material, allows for high concentrations of oxygen to be delivered, provides a means for positive pressure ventilation and administration of positive end-expiratory pressure in patients with acute lung injury, and allows for hyperventilation in patients with increased intracranial pressure. However, despite the importance of tracheal intubation in this situation, achieving this objective may be difficult sometimes in the trauma setting: adequate preoxygenation may not be possible, particularly in agitated patients or in patients with facial injuries; cervical spine immobilization may make laryngoscopy difficult; and the presence of oropharyngeal vomitus, blood, tissue debris, and edema may all contribute to poor visualization of the laryngeal structures. Figure 1 exemplifies these challenges.

Regrettably, in many cases the challenges of airway management are not well met. In the American Society of Anesthesiology Closed Claims Study by Caplan et al¹ adverse clinical outcomes related to



Figure 1. Clinical airway management can be particularly complicated in cases illustrated in this figure of a man who sustained trauma to head and neck following an assault. Note that when there is a La Forte III fracture, as in this case, placing a nasogastric tube or nasotracheal intubation may worsen the clinical situation, and should be avoided in suspicious cases. (Source: Charles Frosolone, MD, via the trauma image bank at www.trauma.org. Used with permission.)

respiratory events constituted the single largest class of injury, with death or brain damage occurring in 85% of cases. Unfortunately, most of these disasters could have been prevented.

Three mechanisms accounted for three fourths of the adverse respiratory events: inadequate ventilation (38%), esophageal intubation (18%), and difficult tracheal intubation (17%). These results suggest that improvements in patient monitoring, airway technology, and clinical training of anesthesiologists may result in important safety advantages to patients undergoing tracheal intubation.

Evaluation of the airway is the starting point in all cases of airway management, looking for, among other things, conditions that may make intubation difficult (Table 1), conditions that may lead to airway obstruction (Table 2), or conditions that may make mask ventilation difficult²: age over 55 years, body mass index exceeding 26 kg/m², presence of a beard, lack of teeth, and history of snoring. Of particular importance, the American Society of Anesthesiologists has developed a useful algorithm for managing the patient with a difficult airway, an updated edition of which was published in 2003,³ with a version also in development that is specifically related to the trauma patient.⁴

On completion of the evaluation, the clinician will have developed an impression as to the likelihood of difficulty with laryngoscopy and intubation, the potential need for awake intubation methods, the role of supraglottic devices like the laryngeal mask airway, and other related issues. Occasionally, patients will provide

Table 1. Clinical Factors in Airway Evaluation

Clinical history	Patient provides a “difficult intubation” letter. Previous difficulty with intubation or use of awake intubation noted in review of old anesthetic records. Patient reports broken teeth at previous intubation.
Mouth opening	Should be adequate to easily allow laryngoscope plus the endotracheal tube. Patients with trismus or temporomandibular joint disease may not be able to open widely.
Mallampati view of oropharynx	Rated from class I to IV.
Thyromental distance	The thyromental distance is the distance of the lower mandible from the mentum to the thyroid. The neck should be fully extended during the measurement. If the thyromental distance is less than 6 cm (about three fingerbreadths), there is less space for the tongue to be displaced during laryngoscopy.
Teeth	Edentulous patients are always easier to intubate. Patients with poor teeth or prominent teeth may be more difficult to intubate.
Tongue	Tongue should not be large, immobile, or edematous.
Head mobility	Limited neck extension is associated with poor laryngeal view and difficult intubation. Almost all of the extension of the neck takes place at the atlanto-ocipital joint. Patients with immobile heads (e.g., ankylosing spondylitis) may not be able to be positioned into the “sniffing position.”
Trauma-related	The nature of the injuries sustained may have an impact on the airway management techniques that can be used. Examples include use of a Philadelphia collar, presence of a fractured larynx, or the presence of a head injury with increased intracranial pressure.

Table 2. Factors That May Predispose to Upper Airway Obstruction during Anesthesia

<ul style="list-style-type: none"> • Obesity with resulting redundant oropharyngeal tissue • Diagnosis of obstructive sleep apnea • Tonsillar hypertrophy (especially lingual tonsils) • Glottic/supraglottic/laryngeal edema • Vocal cord pathology (e.g., vocal cord polyps) • Maxillary or mandibular hypoplasia • Bulbar muscle weakness (e.g., myasthenia gravis) • Upper airway tumors or foreign bodies • Nasal obstruction (e.g., nasal polyps, deviated septum) • Trauma-related problems <ul style="list-style-type: none"> • Hematomas compressing the airway • Fractured larynx • Fractured maxilla • Fractured mandible

detailed documentation about previous difficulties with intubation, perhaps in the form of a MedicAlert bracelet or a “Difficult Intubation Letter.”

In many cases, awake intubation using a fiberoptic bronchoscope will be the safest technique to secure the airway. In such cases, the choice of drug for sedation can be problematic because of respiratory depression effects. In particular, conventional sedatives like the benzodiazepines, propofol, or opiates have respiratory-depressant properties that may be detrimental in tenuous airway situations. Fortunately, dexmedetomidine is a drug whose clinical profile makes it especially well suited for this task. It is a highly specific α_2 -agonist that can produce sedation, anxiolysis, analgesia, and profound levels of sedation in the absence of respiratory depression. The latter property is of special interest in difficult airway cases because during dexmedetomidine administration a stable respiratory pattern is usually seen, with little or no deterioration in respiratory pattern or change in oxygenation. In this article we briefly review the use of dexmedetomidine in awake intubation, with special emphasis on the trauma setting.

Awake Intubation

A difficult airway is one in which ventilation and/or intubation is difficult as a result of anatomic or pathologic problems or as a result of a situation in which optimal positioning of the patient may be unsafe. According to the American Society of Anesthesiologists’ guidelines for management of the difficult airway,³ there are three important issues that must be addressed in order to establish a plan prior to attempting intubation: (1) nonsurgical versus surgical airway, (2) awake intubation versus intubation under general anesthesia, and (3) spontaneously ventilating a patient versus administration of paralytics.

One may be more likely to encounter a difficult intubation situation in the trauma patient, especially if there is involvement of the head and neck.⁵ Careful attention to head and neck positioning and cervical immobilization are especially important components of patient care in patients with possible cervical trauma.⁶ The acute management of a patient with spinal cord injury begins at the scene of the accident.⁷ In most cases, the patient's cervical spine has been immobilized in the field by paramedics, and clinical and radiological evaluation for the possibility of cervical spine injury may not have yet been completed. In situations in which there is mental status change, neck pain or tenderness, or symptoms referable to cervical cord injury, the cervical spine is usually immobilized in the field.⁸⁻¹⁰ Clinical criteria for cervical spine clearance in the out-of-hospital setting have not been well validated¹¹ and in most cases, patients arrive at the emergency department with cervical spine immobilization. In many instances, the time required to "clear" the cervical spine may be limited because there may be a need for emergently establishing an airway. In such cases, one may face a dilemma in choosing the method for intubation, but in any event, the ultimate goal in a patient whose cervical spine is not "cleared" is to intubate the trachea with minimal cervical spine motion.

Many studies have examined cervical spine movement during intubation, using different intubating techniques.¹²⁻¹⁸ Lennarson et al¹⁷ studied the movement of the cervical spine during direct laryngoscopy on cadavers using fluoroscopy, in which a complete C4-C5 ligamentous injury had been created. They compared the cervical spine movement in situations in which there was no stabilization, as well as with manual stabilization and with Gardner-Wells traction. Although cervical immobilization eliminated distraction and decreased angulation, it increased subluxation; on the other hand, traction increased distraction; however, orotracheal intubation without stabilization increased angulation.

Brimacombe et al¹⁹ published a study using cinefluoroscopy on cadavers with posterior destabilized C3 vertebra. They recorded the degree of displacement of the injured segment using the following methods: in-line stabilization using face mask ventilation, intubating and standard laryngeal mask airways, laryngoscopy-guided oral intubation, use of the Combitube, and fiberoptic-guided nasal intubation. They reported that in this kind of injury, the safest technique was fiberoptic-guided nasotracheal intubation.

In situations in which the patient is unconscious, the inability to perform a complete physical examination prevents the clinician from checking for baseline neurologic deficits. In these situations, a fiberoptic intubation can often be performed without sedation. In one study, 65 of 94 patients found to have cervical spine or spinal cord injury were alert.²⁰ In a conscious patient, the postintubation neurologic examination can help indicate if intubation led to any neurologic impairment. In patients who already have a neurologic deficit before attempting the intubation, any change in clinical findings during the intubation process can alert the clinician to discontinue airway manipulation.

The decision to intubate a patient with a possible cervical spine injury has always made anesthesiologists concerned about possible injury exacerbation. There is no clear-cut rule about the best intubation method in such a setting, even though numerous methods have been suggested. However, if there is concern about cervical spine injury, the general agreement is to avoid cervical movement as much as possible. Awake intubation is a safe method in patients with cervical spine injuries.²¹

Awake fiberoptic intubation may be particularly helpful in conscious patients with trauma when at least one of the following is present: (1) The cervical spine has not been cleared by clinical or radiologic methods. (2) There is a new neurologic impairment that could be related to cervical trauma. (3) There is a need for a neurologic examination after intubation and positioning of the patient.

The Art of Sedation

Even though patients should be alert enough to communicate during the intubation procedure, as well as for the postintubation neurologic examination, it does not mean that they cannot benefit from judicious sedation. In addition to awake fiberoptic intubations, other forms of awake intubation may also benefit from pharmacologic sedation.²² The level of anxiety will vary between patients. In patients who are brought to the emergency department after severe trauma, there may be a higher level of anxiety as compared with a patient who is in the operating room for an elective surgical procedure. In an alert and oriented patient, the key to success is in obtaining cooperation by creating a good rapport with the patient.

The goal of sedation is to create a comfortable and tolerable situation for the patient during the procedure. Numerous agents have been suggested for this purpose. Some clinicians prefer using sedatives and avoiding any opiates. Although opioids can decrease the pain and discomfort from manipulation of the upper airway, as well as provide sedation, depress the laryngeal reflexes, and are antitussives, the respiratory depression caused by these agents can result in hypoventilation and hypercarbia. This may result in a vicious circle of hypoventilation, hypercarbia, and oversedation, a consequence of which is hypoxia. As a result, intubation becomes a dire emergency and the plan of having an awake intubation can fail. However, there are reports of using different opioids in controlled small doses for awake fiberoptic intubation. Morphine, fentanyl, alfentanil,²³ sufentanil,²² and remifentanil²⁴⁻²⁹ are the most commonly used opiates. Although opiates can be effective analgesics, they have a limited effect as anxiolytics. Many clinicians use benzodiazepines alone or along with other sedatives for this purpose. When benzodiazepines are used, flumazenil should be available to treat any inadvertent overdose.

Combinations of benzodiazepines and opiates can further decrease the respiratory drive.^{30,31} Neuroleptanalgesia using droperidol with fentanyl has also been suggested for sedation in awake intubations^{32,33}; but even though the patients seem to be calm and pain-free, there are many reports of feeling mental restlessness and agitation, or the "locked-in" syndrome.³⁴ In a nonparalyzed patient who is not sufficiently anesthetized and adequate local anesthesia has not been given to diminish the airway reflexes, manipulation of the airway can cause obstruction and laryngospasm.³⁵

Dexmedetomidine: A Novel α_2 -Receptor Agonist

Clinicians have used α_2 -receptor agonists since the 1970s to treat hypertension and withdrawal from long-term drug or alcohol abuse.³⁶ The prototype α_2 -agonist, clonidine, has since been recognized as a useful adjunct to anesthesia and analgesia. The newer α_2 -agonist, dexmedetomidine, is a more selective α_2 -agonist, with 8 times greater affinity for the α_2 -receptor than clonidine and is 1,620 times more potent as an α_2 -agonist than an α_1 -agonist.^{36,37}

The effects of α_2 -agonists are mediated through transmembrane receptors, which belong to the G protein-coupled receptor superfamily.³⁶ The effector mechanisms of these G proteins are diverse and include adenylate cyclase, N-type voltage-gated calcium channels, potassium channels, Na⁺/H⁺ exchange, and polyphosphoinositide hydrolysis. Such diversity may account for the different physiologic and clinical effects elicited by these receptors.³⁸

α_2 -Adrenergic receptors are located in the nervous, cardiovascular, and respiratory systems. Within the nervous system, these receptors are present in the central and peripheral nervous system at the autonomic ganglia and presynaptic and postsynaptic

sites. In the central nervous system, activation of presynaptic and postsynaptic α_2 -receptors results in inhibition of noradrenalin release and neuronal firing.³⁹ A decrement in sympathetic activity, especially at the locus ceruleus, leads to sedation and hypnosis.⁴⁰ At the level of the medulla, α_2 -agonist activity at the dorsal motor nucleus of the vagus nerve may lead to bradycardia and hypotension.⁴¹ In the spinal cord, α_2 -adrenoreceptors are found to be concentrated in the intermediolateral cell column and substantia gelatinosa.⁴¹ The analgesic activity of α_2 -agonists seems to be mediated by binding to receptors in the spinal cord, although supraspinal and peripheral sites of analgesic action have also been reported.^{42,43}

The actions of the α_2 -agonist on the cardiovascular system are centrally and peripherally mediated. As mentioned previously, the centrally mediated decrease in sympathetic and increase in parasympathetic activities leads to bradycardia and hypotension. Because of the peripheral receptors in the arterial and venous smooth muscles, α_2 -agonists also lead to transient vasoconstriction and an increase in blood pressure with subsequent decrease in heart rate and cardiac output.⁴⁴

Within the respiratory system, activation of α_2 -receptors leads to bronchodilation and attenuation of response to CO_2 increase.³⁸

In 1999, the recently released α_2 -agonist, dexmedetomidine, was approved by the Food and Drug Administration for short-term (<24 hours) sedation of the critically ill patient.⁴⁵ Dexmedetomidine can facilitate achieving the major goals of sedation in the intensive care unit: anxiolysis, analgesia, hemodynamic stability, avoidance of respiratory depression, and lightly sedated and cooperative patients.

The anxiolytic property of dexmedetomidine has been shown to be effective in surgical patients and has been reported to be comparable with the anxiolysis obtained from benzodiazepine.⁴⁶⁻⁴⁸

When administered perioperatively, dexmedetomidine has been demonstrated to reduce the opioid analgesic requirement. When used for sedation in the intensive care unit setting, it has also been described to have analgesia-sparing components.^{49,50}

Unlike clonidine, dexmedetomidine has a shorter half-life, making titration as an intravenous infusion possible.^{36,43} After intravenous (IV) infusion, dexmedetomidine exhibits the following pharmacokinetic variables: a rapid distribution phase with a distribution half-life of approximately 5 minutes, and a terminal elimination half-life of 120 minutes.⁵¹⁻⁵³ Context-sensitive half-life after infusions of different durations is not known. Talke et al⁵² reported dexmedetomidine plasma concentration was halved within 20 minutes after 60 minutes of continuous infusion at a rate of 1.15 mcg/hr. Cardiovascular response to dexmedetomidine bolus has been described to be a transient increase in blood pressure and decrease in heart rate followed by a decrease in blood pressure.^{44,52} Such consistent hemodynamic changes have not been found to increase morbidity and can be managed by increased IV fluids.⁵⁴ A slow-loading bolus of 1 mcg/kg is administered during 10 to 20 minutes. Maintenance doses ranging from 0.2 to 0.6 mcg/kg/hr are recommended for less hemodynamic alterations.^{44,50}

Dexmedetomidine appears to have a clinically insignificant effect on respiratory function and gas exchange.⁵⁵ Arterial oxygen saturation does not decrease less than 90% and PaCO_2 does not increase differently than that seen during normal sleep.^{44,56} Although obstructive apnea has been associated with dexmedetomidine,⁵⁷ Hall et al⁵⁵ suggest that this is more related to rapid loading doses (during 2 minutes). Because α_2 -agonists should have little effect on respiration, based on receptor binding studies, Hall et al indicate that the apnea seen with dexmedetomidine is caused by deep sedation and oral/pharyngeal anatomic events.

One of the more interesting characteristics of dexmedetomidine is its ability to achieve sedation while preserving the patient's arousability. A small-dose infusion of this drug provided sedation that could easily be reversed by verbal stimuli.^{50,55}

Dexmedetomidine for Awake Intubation

Dexmedetomidine was originally approved for sedation in intubated and ventilated patients; extending this use to cover awake intubation is a natural clinical application of the drug.

Dexmedetomidine is an α_2 -adrenoreceptor agonist with several unique properties that make it ideally suited for the management of patients with difficult airways. First, a dexmedetomidine infusion provides a unique form of sedation in which patients appear to be sleepy, but if stimulated they are easily roused, cooperative, and communicative. Second, dexmedetomidine has moderate analgesic and antisialagogue effects. Third, dexmedetomidine causes minimal respiratory impairment, even when given in large doses,^{57,8} and arterial PCO_2 levels resemble those found in normal sleep. The fact that patients are sedated but maintain spontaneous respirations on dexmedetomidine while attempts are made to secure their airway while awake makes it an ideal agent for use in critical airways. The ability to arouse patients after intubation and perform a neurologic examination is another advantage of using dexmedetomidine for awake intubations. Patients are comfortable enough to tolerate the endotracheal tube while being cooperative during interactive neurologic examination, allowing the examiner to evaluate the effect of intubation on any change in the neurologic status.⁵⁹

Novel uses of dexmedetomidine are not restricted to clinical airway management. Hofer et al⁶⁰ described the anesthetic management of a 433-kg morbidly obese patient undergoing bariatric surgery (Roux-en-Y gastric bypass) whose intraoperative opiate management was entirely substituted with a dexmedetomidine infusion (0.7 mcg/kg/hr) because of concerns that opiates might cause postoperative respiratory depression. The authors noted that the anesthesia course was without incident, and that dexmedetomidine was associated with lowered anesthetic requirements. The authors concluded that "dexmedetomidine may be a useful anesthetic adjunct for patients who are susceptible to narcotic-induced respiratory depression." We have used dexmedetomidine as the sole anesthetic agent for awake tracheostomy for adult epiglottitis.

Dexmedetomidine has also seen application in children. Although oral premedication is often administered to children to help provide anxiolysis and lessen the psychological impact of hospitalization and/or medical procedures, IV dexmedetomidine may also be useful. Zub et al⁶¹ conducted a retrospective review of 13 patients aged 4 to 14 years who received oral dexmedetomidine in anticipation of procedural sedation or anesthetic induction. The mean oral dose of dexmedetomidine was 2.6 ± 0.83 mcg/kg with a range of 1.0 to 4.2 mcg/kg, with effective sedation being achieved in 11 of the 13 patients. When used for procedural sedation, "placement of an IV cannula was accomplished without difficulty in seven of eight patients with neurobehavioral disorders and with only mild resistance in the others." The authors also indicated that "no complications were noted and parental satisfaction ... was high."

Some might think the loading dose period suggested by the manufacturer might be long for a patient with traumatic injury and would need a more rapid induction of sedation for airway control.

Finally, as with all drugs, clinicians should be aware of possible unfavorable effects. In particular, because severe bradycardia is a possible adverse effect of dexmedetomidine, bradycardia leading to asystole is at least a theoretical concern. Ingersoll-Weng et al⁶² described a case of cardiac arrest in a patient receiving a dexmedetomidine infusion as a supplement to general anesthesia for resection of a thymoma. On sternal retraction, the patient's heart rate dropped into the 30s and asystole soon followed, despite receiving atropine treatment. She was treated with open cardiac massage and 300 mcg of IV epinephrine. The asystole episode lasted less than 2

minutes and no adverse sequelae occurred. The authors indicated that a number of factors may have contributed to the development of the asystole: a centrally mediated decrease in sympathetic outflow, an increase in parasympathetic outflow resulting from the dexmedetomidine, and the patient's autonomic response to abrupt surgical stimulation.

Summary

Dexmedetomidine appears to be a particularly useful pharmacologic agent for sedation during awake intubation. It has anxiolytic, analgesic, sedative, and easy arousability and respiratory-sparing properties. Such properties may be ideal for awake fiberoptic intubations indicated in cases of difficult airway and cervical spine instability. The sedative, anxiolytic, and analgesic properties of dexmedetomidine can add to the comfort of patients, enabling tolerance of the procedure. The preservation of arousability and respiratory-sparing properties would allow for safer conduct of awake fiberoptic intubations in difficult airway cases, and it would also allow for a patient's cooperation during neurologic assessment in cases of cervical spine instability.

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Dexmedetomidine Prevents and Treats Agitation, Delirium, and Withdrawal

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Learning Objectives: 1) To recognize the signs, symptoms and detrimental effects of agitation, delirium, and withdrawal. 2) To describe how dexmedetomidine prevents and treats agitation, delirium, and withdrawal.

Abstract

Agitation, delirium, and withdrawal present challenges to the health care provider. Agitated, delirious, or withdrawing patients may injure themselves and/or be ineffectual in assisting in their own care, providing a hindrance to their healing. Trauma patients are at particular risk for wound disruption and further injury in this setting. Dexmedetomidine prevents and treats agitation, delirium, and withdrawal and is poised to become a strong part of the clinician's armamentaria in caring for these patients.

Agitation is a frequent and challenging problem in the perioperative and intensive care unit (ICU) patient care. Contributing factors include underlying illness, pain, anxiety, and delirium. Agitation can result in dangerous consequences ranging from poorly tolerated invasive therapy to self-destructive behavior. Sedatives are often administered to facilitate care of agitated patients. Nevertheless, multiple pharmacologic agents are typically administered during perioperative and ICU care, and may result in significant and often unpredictable outcomes, even leading to or worsening agitation and confusion. Contributing agents include benzodiazepines, opioids, volatile anesthetics, anticholinergics, antibiotics, and muscle relaxants. These medications may interact unpredictably, leading to difficult patient care situation, particularly in the elderly patient. Frequently, the effects of these drugs are not related to the medication itself, but rather to multiple metabolites with varying rates of degradation and excretion.

One of the authors has an affiliation with a company named in this article.