Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department

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PREFACE

Emergency medicine training provides physicians with expertise in critical care, airway and pain management. Accordingly, expertise in procedural sedation and analgesia is a core competency in emergency medicine practice.[1,2] Emergency physicians routinely provide sedation, analgesia, respiratory, and hemodynamic management of critically ill patients.

Procedural sedation has received a great amount of attention in recent years. Several groups have produced documents covering its use, including the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which has made it an area of intense review. Unfortunately, most of these promulgated advisory materials are not truly evidence-based.

The following clinical policy, developed by the Clinical Policies Committee of the American College of Emergency Physicians (ACEP), updates the original clinical policy approved on January 13, 1998.[3] This clinical policy attempts to remove the bias from recommendations for procedural sedation by creating a document that is, to the degree possible, evidence-based. There remains a relative lack of high-quality data in some areas of procedural sedation. It must be carefully noted, however, that despite the statements made in this policy, individual institutions will still be accredited on the basis of the criteria of the respective accrediting organization, such as the JCAHO.

A MEDLINE search of original research on sedation and analgesia from the past decade revealed that emergency physicians are doing the majority of research in this area. A substantial body of evidence supports the routine safe use of procedural sedation and analgesia by emergency physicians.[4-21]

INTRODUCTION

The emergency department (ED) is a unique environment where a variety of patients with emergent and urgent conditions are managed. Many of these conditions result in significant pain and are associated with varying degrees of anxiety. Accordingly, the management of sedation and analgesia is an important component of comprehensive emergency medical care for patients of all ages and, therefore, a primary concern for the emergency physician. Pain control often is not adequately provided for a variety of reasons, including fear of oversedation, concern of altering physical findings, or underestimation of patient needs.[22,23] However, proactively addressing pain and anxiety may improve quality of care and patient satisfaction by facilitating interventional procedures and minimizing patient suffering. Many of the drugs used for sedation and analgesia have the potential to cause central nervous system, respiratory, or cardiac depression. According to the JCAHO 2004 *Comprehensive Accreditation Manual for Hospitals*, the standards for sedation and anesthesia care apply when patients in any setting receive, for any purpose and by any route, moderate or deep sedation, as well as general, spinal, or other major regional sedation and anesthesia.[24] To minimize complications, the appropriate drug(s) and dosages must be chosen, monitored, and administered in the proper setting, and a patient evaluation should be performed before, during, and after their use. Many drug and dosing regimens used in procedural sedation and analgesia have been discussed in-depth in other publications.[25-28]

It is good medical practice to discuss with patients all medications and interventions that will be provided. The discussion should include the risks, benefits, potential side effects, and alternatives. There is no literature to support that the use of an informed consent form separate from the general informed consent obtained at registration in the ED has an effect on patient satisfaction or on clinical outcome. In some cases, procedural sedation and analgesia is provided in situations when the patient is in severe pain or extremely anxious because of the circumstances surrounding the ED visit; such situations limit the patient's ability to comprehend issues presented in the informed consent process. In other circumstances, the informed consent process is limited by an altered mental status, which affects the patient's capacity to understand risk and benefit. Procedural sedation and analgesia under implied consent may be appropriate in these circumstances.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

DEFINITIONS

Procedural sedation refers to a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function.[3] Procedural sedation and analgesia is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently. Moderate sedation, previously referred to as "conscious sedation," is defined as a drug-induced depression of consciousness during which patients respond purposefully.[24] Specifically, the drugs, doses, and techniques used are not likely to produce a loss of protective airway reflexes. As part of the continuum of sedation, deep sedation is defined as a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. These patients may require assistance in maintaining airway patency and ventilatory effort.[24] General anesthesia is defined as a drug-induced loss of consciousness during which patients are not arousable and may have an impaired cardiorespiratory function requiring varying degrees of support.[24] The patient under general anesthesia is profoundly compromised and does not exhibit movement or autonomic nervous system responses to a standard surgical stimulus. On the basis of recognition that proper administration of sedative medications is a continuum and it is often difficult to predict how an individual will respond to a specific sedative agent, practitioners should possess the skills required to rescue a patient 1 level greater than the intended level of sedation. Therefore, should deep sedation be required to perform a procedure, the practitioner is expected to be competent in skills involving cardiovascular support and airway management as in general anesthesia.[26] Due to emphasis in the emergency medicine training curriculum, these qualities are now considered core skills for all board-certified emergency physicians.[1,2]

A separate category of sedation has been suggested in an effort to better classify and describe the dissociative sedative agents. Dissociative sedation is described as a "trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability." The terms moderate, deep, and general anesthesia sedation refer to forms of sedation that do not apply to dissociative sedation.[29]

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. A MEDLINE search of English-language articles published between January 1992 and January 2004 was performed using combinations of the key words "conscious sedation," "moderate sedation," "deep sedation," "analgesia," "sedation," "standards," "guidelines," "complications," and "emergency department." Terms were then exploded as appropriate. Abstracts and articles were reviewed by subcommittee members, and pertinent articles were selected. These articles were evaluated, and those addressing the questions considered in this document were chosen for grading. Subcommittee members also supplied references from bibliographies of initially selected articles or from their own files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[30] This policy is a product of the ACEP clinical policy development process and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, individual members of ACEP's Pediatric Emergency Medicine Committee and Section, and individual members of the American Society of Anesthesiologists. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All publications were graded by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence. Some articles were downgraded on the basis of a standardized formula that considers the size of study population, methodology, validity of conclusions, and potential sources of bias (Appendix A).

During the review process, all articles were given a baseline "strength of evidence" by the subcommittee members according to the following criteria:

Strength of evidence Class I—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

Strength of evidence Class II—Observational studies including retrospective cohort studies, case-controlled studies, aggregate studies including other meta-analyses.

Strength of evidence Class III—Descriptive cross-sectional studies, observational reports including case series and case reports, consensus studies including published panel consensus by acknowledged groups of experts.

Strength of evidence Class I and II articles were then rated on elements subcommittee members believed were most important in creating a quality work. Class I and II articles with significant flaws or design bias were downgraded on the basis of a set formula (Appendix B). Strength of evidence Class III articles were downgraded if they demonstrated significant flaws or bias. Articles downgraded below strength of evidence Class III were given an "X" rating and were not used in formulating recommendations in this policy. An Evidentiary Table was constructed and is included in this policy.

Recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This clinical policy is intended for: (1) ED patients of all ages who have emergent or urgent conditions that require pain and/or anxiety management to successfully accomplish an interventional or diagnostic procedure. A separate multidisciplinary clinical policy has been developed highlighting medications and particular considerations commonly encountered in the practice of sedation and analgesia in children.[31]

(2) High-risk patients (eg, those with underlying cardiopulmonary disorders, multiple trauma, head trauma, or who have ingested a central nervous system depressant such as alcohol) are included with the understanding that these patients are at increased risk of complications from procedural sedation and analgesia.[4,5,10,26]

Exclusion Criteria. Excluded from this guideline are: (1) patients receiving inhalational anesthetics, (2) patients who receive analgesia for pain control without sedatives, (3) patients

who receive sedation solely for the purpose of managing behavioral emergencies, and (4) patients who are intubated.

CRITICAL QUESTIONS

I. What are the personnel requirements needed to provide procedural sedation and analgesia in the ED?

Personnel providing procedural sedation and analgesia must have an understanding of the drugs administered, the ability to monitor the patient's response to the medications given, and the skills necessary to intervene in managing all potential complications.

JCAHO anesthesia standards reinforce that sedation-to-anesthesia is a continuum, and it is not always possible to predict how individual patients receiving medications will respond. It is therefore important for individual institutions to ensure that all individuals performing moderate or deep sedation are trained to: (1) administer pharmacologic agents to predictably achieve desired levels of sedation, (2) monitor patients and maintain them at desired levels of sedation, and (3) manage complications observed during procedural sedation and analgesia.[24] Procedural sedation and analgesia at both moderate and deep levels has been demonstrated to be both safe and effective when properly administered by experienced emergency physicians.[4-6,8-10,12,15,18,19]

The literature does not provide clear evidence on the number of personnel necessary to safely provide procedural sedation and analgesia. The presence of a support person assumes increased importance when the physician is involved in a procedure that precludes the ability to continually assess the patient's clinical status. However, there are situations where exceptions are permissible, such as when low doses of pharmacologic agents are used and the physician is able to maintain visual or verbal communication with the patient. During procedural sedation and analgesia, there must be an individual available who is capable of recognizing and managing respiratory and hemodynamic emergencies. As a result, all physicians who are working or consulting in the ED should coordinate all procedures requiring procedural sedation and analgesia with the ED staff.

Personnel Recommendations: What are the personnel requirements needed to provide procedural sedation and analgesia in the ED?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. During moderate and deep sedation, a qualified support person should be present for continuous monitoring of the patient.

Procedural sedation and analgesia in the ED must be supervised by an emergency physician or other appropriately trained and credentialed specialist.

II. What are the key components of the patient assessment before initiating procedural sedation?

There is a lack of outcome-based studies to mandate more extensive evaluation beyond vital signs, mental status, and airway and cardiopulmonary assessment. An increased risk with procedural sedation and analgesia may exist in select subsets of patients such as those with difficult facial or neck anatomy, patients who are very old, or patients with underlying cardiopulmonary disease.

There is no literature to support the need for routine diagnostic testing before procedural sedation and analgesia; diagnostic testing is driven by the patient's status.

Patient Assessment Recommendations: What are the key components of the patient assessment before initiating procedural sedation?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Obtain a history and perform a physical examination to identify medical illnesses, medications, allergies, and anatomic features that may affect procedural sedation and analgesia and airway management.

No routine diagnostic testing is required before procedural sedation.

III. Is preprocedural fasting necessary before initiating procedural sedation?

The combination of vomiting and loss of airway protective reflexes is an extremely rare occurrence with procedural sedation and analgesia, making aspiration an unlikely event.[6,12,32-35] Recent studies and consensus statements have recommended varying fasting periods based on the specific substance ingested, but fasting patterns remain variable with no uniformly accepted practice standards.[26,32,35-41] Much of the aspiration data have been extrapolated from the general anesthesia literature where the potential of aspiration is increased with manipulation of the airway during intubation and extubation. Thorough reviews of this topic demonstrate a lack of evidence that gastric emptying has any impact on the incidence of complications or on outcome in procedural sedation and analgesia. A prospective observational study of 1,014 children identified no difference with airway complications, emesis, or other adverse events between patients classified by their preprocedural fasting status. Of the 509 (56%) patients who did not meet preprocedural fasting guidelines for elective procedures as suggested by the American Academy of Pediatrics and the American Society of Anesthesiologists, no episodes of aspiration were documented. The authors correctly acknowledge that the study is underpowered to detect significant differences in the rate of emesis with and without aspiration due to the extremely rare incidence of these combined events.[35] Despite the paucity of data and in recognition of the potential risk for aspiration, a number of publications encourage careful consideration of timing and depth of procedural sedation and analgesia in the absence of an adequate fasting period.[32,41,42] In addition, pharmacologic agents including antacids have not been shown to improve outcomes and are no longer recommended as standard practice.[32,41,43] No study has determined a necessary fasting period before initiation of procedural sedation and analgesia.

There is insufficient evidence to determine absolute recommendations. Although recent food intake is not a contraindication for administering procedural sedation and analgesia, the emergency physician must weigh the risk of pulmonary aspiration and the benefits of providing procedural sedation and analgesia in accordance with the needs of each individual patient.

Preprocedure Fasting Recommendations: Is preprocedural fasting necessary before initiating procedural sedation?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Recent food intake is not a contraindication for administering procedural sedation and analgesia, but should be considered in choosing the timing and target level of sedation.

IV. What equipment and supplies are required to provide procedural sedation and analgesia?

Although rare, procedural sedation and analgesia may result in an allergic reaction, respiratory arrest, or cardiopulmonary arrest. The incidence of complications is dependent on the drugs used, rate and dose of administration, and patient sensitivities. Consequently, the appropriate equipment to monitor the patient's condition, to manage airways, allergic reactions, and drug overdoses, and to treat respiratory and cardiopulmonary arrest should be readily available; use of specific monitoring equipment is discussed in the subsequent sections.

Supportive equipment for procedural sedation and analgesia includes oxygen, suction, medications, and advanced life support equipment (eg, a bag-mask ventilation device, and intubation equipment). The need for intravenous access is dependent on the medications, the dose, and the route used.[4,12,15,44,45] Ketamine, which has been shown to exhibit a wide safety margin with preservation of protective airway reflexes and no cardiovascular suppression, is often administered intramuscularly.[45] This is especially beneficial in the pediatric population where additional needle sticks may not be desirable. Procedural sedation and analgesia with opioids or benzodiazepines may result in respiratory suppression or transient hypotension despite route of administration; therefore, physicians may consider intravenous access necessary in select patients.[4-6] When opioids or benzodiazepines are used, the opioid antagonist naloxone and the benzodiazepine antagonist flumazenil should be available.[6,46,47]

Equipment and Supplies Recommendations: What equipment and supplies are required to provide procedural sedation and analgesia?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Oxygen, suction, reversal agents, and advanced life support medications and equipment should be available when procedural sedation and analgesia is used.

Intravenous access should be maintained when intravenous procedural sedation and analgesia is provided. Intravenous access may not be necessary when procedural sedation and analgesia is provided by other routes.

V. What assessment and monitoring are required to provide procedural sedation in the ED?

Monitoring the patient's condition involves visual observation and assessment of the level of consciousness and physiologic changes. The monitoring process should be documented. The components of monitoring may include but are not limited to the level of consciousness, respiratory rate, oxygen saturation, exhaled carbon dioxide, heart rate, blood pressure, and cardiac rhythm monitoring. The patient's ability to follow commands is a method of monitoring level of consciousness. There are times when patients receive procedural sedation and analgesia and then must be transported outside the ED. In such cases, every attempt must be made to provide the same level of monitoring during the transport that was used within the ED.

In general, documentation of the patient's preprocedure status and clinical status during and after the procedure is recommended. The available literature provides little guidance as to the minimum frequency at which vital signs should be recorded.

Vital sign monitoring includes assessment of blood pressure, pulse rate, respiratory rate, and pulse oximetry. A prospectively collected database of 1,367 pediatric patients found the highest risk of serious adverse events occurred within 25 minutes of receiving the last dose of intravenous medications.[48] Adverse events occurred in 184 (13%) of the patients. Of those, 169 (92%) occurred during the procedure and 14 (8%) occurred in patients after the procedure. The median time for serious adverse events occurred approximately 2 minutes after administration of the final medication.[48] In 1 study using midazolam and fentanyl, all cases of apnea occurred within 5 minutes of drug administration.[49] In another study, using diazepam and fentanyl, all episodes of desaturation occurred within 20 minutes.[50] Despite a recommendation in a consensus statement,[26] there is no evidence that cardiac monitoring during procedural sedation and analgesia is of benefit, especially if the patient has no underlying cardiopulmonary disease.

General Recommendations: What assessment and monitoring are required to provide procedural sedation in the ED?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Obtain and document vital signs before, during, and after procedural sedation and analgesia. Monitor the patient's appearance and ability to respond to verbal stimuli during and after procedural sedation and analgesia.

VI. How should respiratory status be assessed?

Pulse Oximetry. Pulse oximetry provides continuous noninvasive estimates of arterial oxygen saturation and is a reliable tool in detecting early decreases in oxygen saturation and

changes in the patient's heart rate.[51] Under most circumstances, there is excellent correlation between the pulse oximeter saturation, measured by spectrophotometry, and arterial hemoglobin oxygen saturation measured by oximetry. However, when the hemoglobin saturation decreases below 80%, accuracy may be affected.[51,52] The limitations of oximetry include its inability to detect early decreases in the adequacy of ventilation and, thus, the detection of the onset of hypercarbia that may occur before the development of apnea. The administration of oxygen during procedural sedation and analgesia may delay the onset of hypoxemia and, thus, the detection of hypoventilation.

Many studies have demonstrated the utility of pulse oximetry in detecting decreases in oxygen saturation; most of these studies define hypoxemia as a saturation of less than 90%.[4,13,45,49]

It has been clearly demonstrated that many of the drugs used in procedural sedation and analgesia predispose the patient to the development of hypoxemia, and that drug combinations, especially benzodiazepines and opioids, have a potentiating effect in suppressing respirations.[49,53] Despite the evidence that desaturation may occur during procedural sedation and analgesia, there is little information regarding the clinical significance of transient desaturation. Studies have demonstrated that decreases in oxygen saturation occur without clinical consequence, and in fact, transient decreases in oxygen saturation have been reported during sleep in healthy volunteers. In 1 series, 43% of asymptomatic men had desaturation to below 90% during sleep, with 13% below 75%.[54] The results from at least 2 studies suggested that the only consistent predictor of desaturation during procedural sedation and analgesia was age greater than 55 years.[10,55]

It has been hypothesized that failure to properly monitor oxygenation has led to drug-related deaths in procedural sedation and analgesia.[49] There are no studies showing that detection of a decrease in oxygen saturation alone during procedural sedation and analgesia has an impact on patient outcome. When the patient's level of consciousness or respiratory efforts can be adequately assessed, procedural sedation and analgesia has an extremely low risk of morbidity and mortality.[6,9,13,18,19,45,48,50,56,57]

However, the rarity of adverse events results in low statistical power for detecting decreases in the adverse event rate. Without devaluing its utility as a monitoring adjunct, pulse oximetry should not substitute for clinical assessment during procedural sedation and analgesia, but rather be utilized as a reliable adjunct.

Capnometry. Procedural sedation and analgesia may cause hypoventilation[49,58] and an increase in end-tidal carbon dioxide ($ETCO_2$).[59] Capnometry is a technique used to monitor $ETCO_2$ and, therefore, may detect early cases of inadequate ventilation before oxygen desaturation takes place.[60,61] An increase in $ETCO_2$ might be the only clue to hypoventilation and potential respiratory compromise.[62] There is an excellent correlation between $PACO_2$ and $ETCO_2$ even when the $ETCO_2$ is measured through a nasal cannula while the patient is receiving oxygen.[61]

Theoretically, early detection of hypoventilation with capnometry may be beneficial. However, there is no evidence that this benefit has an impact on patient outcome when used in procedural sedation and analgesia. In 1 study of 27 ED patients receiving procedural sedation and analgesia with a benzodiazepine and/or opioids, the average $ETCO_2$ increased from 36 to 42 mm Hg while the oxygen saturation decreased from 98% to 94%, but this study had low statistical power to detect differences in outcome. These changes were without clinical consequence.[61] One patient in this study had a desaturation level of 83%, but responded to verbal and tactile stimuli. A more recent prospective study evaluated whether $ETCO_2$ could be used to detect respiratory depression and measure depth of sedation.[60] No correlation was found between the $ETCO_2$ and the level of sedation measured by the Observer's Assessment of Alertness and Sedation Scale. A post-hoc analysis of the 74 patients revealed that all patients with respiratory depression demonstrated an $ETCO_2$ greater than 50 mm Hg, an absent waveform, or an absolute change from baseline in $ETCO_2$ greater than 10 mm Hg. The authors conclude that in the presence of $ETCO_2$ monitoring, these identifiers may allow more rapid identification of hypoventilation than pulse oximetry alone. In the study, pulse oximetry would have identified only 11 of the 33 patients meeting the predetermined definitions for respiratory depression of an oxygen saturation less than 90%, $ETCO_2$ of greater than 50 mm Hg, or an absent waveform. This study does not address the question as to whether earlier recognition of hypoventilation has any significant impact on outcomes. Hypoventilation and subsequent transient hypercapnea without hypoxemia during procedural sedation and analgesia has no identified impact on outcome.

Bispectral Index. The Bispectral Index has been validated as an objective measure of sedation depth in the operating room, which has led some researchers to suggest its utility in procedural sedation. The Bispectral Index reflects the varying levels of a patient's sedation as expressed by mathematical evaluations involving relevant, descriptive electroencephalographic measures from the frontal cortex.[63-65] Although early evidence is supportive,[21,66] there is insufficient evidence to advocate its routine use in procedural sedation and analgesia.

Respiratory Status Recommendations: How should respiratory status be assessed?

Level A recommendations. None specified.

Level B recommendations. Pulse oximetry should be used in patients at increased risk of developing hypoxemia, such as when high doses of drugs or multiple drugs are used, or when treating patients with significant comorbidity.

Level C recommendations. When the patient's level of consciousness is minimally depressed and verbal communication can be continually monitored, pulse oximetry may not be necessary.

Consider capnometry to provide additional information regarding early identification of hypoventilation.

VII. Can ketamine, midazolam, fentanyl, propofol, and etomidate be safely administered for procedural sedation and analgesia in the ED?

Agents such as ketamine result in a dissociative state in which a patient may not speak or respond purposefully to verbal commands. Use of ketamine in the doses recommended for procedural sedation and analgesia does not result in a loss of protective reflexes. The medical literature documents the safety of its use for procedural sedation and analgesia in pediatric populations.[44,45,67] In a well-designed randomized controlled trial in 260 children aged 5 to 15 years, Kennedy et al[67] found that a ketamine and midazolam combination was safer and more efficacious than a fentanyl and midazolam combination for sedation in orthopedic procedures. Hypoxia occurred in 6% of patients receiving ketamine and midazolam versus 20% of patients in the fentanyl and midazolam group. Efficacy as determined by objective measures of physician and parental satisfaction were thought to be superior in the ketamine and midazolam study arm.[67] In a consecutive case series of 1,022 children, Green et al[45] report that ketamine at doses of 4 to 5 mg/kg intramuscularly produced adequate sedation in 98% of children. They reported airway complications in 1.4% of patients that included laryngospasm, apnea, and respiratory depression, all of which were quickly identified and treated without intubation or sequelae. Emesis occurred in 6.7% without evidence of aspiration.

In regard to nondissociative sedation agents such as midazolam and fentanyl, a key to minimizing complications in procedural sedation and analgesia is the titration of drugs to the desired effect. Rapid administration of drugs may be associated with hypotension or respiratory depression. In addition, the combination of drugs may accentuate the potential side effects associated with each drug individually. In 1 study, use of benzodiazepines alone resulted in no significant respiratory depression, whereas use of an opioid alone caused hypoxemia in 50% of volunteers and caused a decrease in ventilatory response to carbon dioxide, but did not cause apnea. When the benzodiazepine and opioid were used together, hypoxemia occurred in 92% of subjects, and apnea occurred in 50%.[49] Although there was no clinical correlation of these findings to patient outcome, this study does suggest that the combined use of benzodiazepines and opioids increases the risk of respiratory compromise. Pohlgeers et al[50] also reported no association of benzodiazepine dose with desaturation. High doses of opioids without careful and slow titration also increased the risk of respiratory compromise. In a case report, Yaster et al[47] presented a child who had a respiratory arrest after 10 μg/kg of fentanyl was given over approximately 4 minutes.

It has been suggested that when both a benzodiazepine and an opioid are used, the opioid, which poses the greater risk of respiratory depression, should be given first and the benzodiazepine dose titrated.[68]

There is a growing body of evidence supporting the safe use of propofol for procedural sedation by emergency physicians. In a prospective observational study performed in the ED, propofol-induced procedural sedation was reported to have the lowest rate of respiratory depression when compared with methohexital, fentanyl/midazolam, and etomidate.[21] There were no significant complications. A prospective randomized trial with 103 patients receiving propofol or methohexital within the ED compared the depth of sedation with Bispectral Index scores and rates of respiratory depression assessed by $ETCO_2$. Of note, approximately one half of the patients in both groups met predefined criteria for respiratory depression. The study did not detect a difference in either the level of sedation by Bispectral Index or the level of subclinical respiratory depression between the 2 agents. The authors found no significant adverse events with either sedative.[20] In another prospective study of 43 children comparing midazolam and propofol, the authors reported successful sedation but also significant hypoxemia and oversedation; however, no significant complications were reported.[15] In another pediatric study involving 40 patients, Skokan et al[16] reported a significant incidence of oxygen desaturation; however, again, there were no clinical sequelae.

The literature regarding safety and efficacy of etomidate in the ED is also mounting. A prospective, double-blinded, randomized trial of 46 adult patients undergoing anterior shoulder dislocation reduction in the ED compared midazolam with etomidate.[17] Burton et al[17] found approximately a 90% procedural success rate for both groups. Patients experienced no episodes of hypotension or arrhythmia. Adverse respiratory events in the 19 etomidate patients included 4 episodes of desaturation with one 75-year-old patient requiring bag-mask ventilation for a brief period of apnea. There was no significant difference between the groups with episodes of hypoxia. Patient and physician visual analog pain assessment scores were similar between groups. Dickinson et al,[11] in a retrospective review of 53 children, with the majority of these children older than 10 years, described the drug's use in the reduction of pediatric orthopedic procedures. The authors found an 83% success rate after the first attempt. Documented side effects included 1 patient with nausea and 1 patient requiring a fluid bolus for transient hypotension. There were no reported incidences of patients who required assisted ventilation of any kind.[11] Ruth et al[12] performed a prospective study on 51 consecutive patients. Ninety-eight percent of the patients achieved adequate sedation: 5 patients desaturated below 90% and 1 patient vomited; however, no patient required assistance with ventilation or had a clinically significant complication. Vinson and Bradbury[10] retrospectively reviewed 134 patients treated with etomidate for procedural sedation. Ninety-five percent of the patients were "extremely" satisfied with their care. They reported a 5% rate of adverse events including 5 cases of desaturation below 94%, all of whom recovered uneventfully. Another smaller retrospective chart review of 46 adults and 2 children identified 4/48 (8%) patients with procedural failure.[13] These authors found 10/48 (21%) patients with adverse reactions. Respiratory complications included 1 patient who developed transient apnea requiring bag-mask ventilation, while another patient required a nonrebreather for a desaturation below 90%. Other commonly reported side

effects of etomidate include pain with injection and myoclonus.[12,17,69-71] Myoclonus reports ranging from 0% to 21% of patients receiving etomidate usually last less than 1 minute, but can be dramatic and may resemble seizure activity.[10,12,17,70] These tremors are generally benign and not epileptigenic activity, but they can result in brief desaturation.[69,72]

In conclusion, there is a growing body of literature supporting the safe use of a large variety of agents for procedural sedation and analgesia in the ED. Ketamine, midazolam, fentanyl, propofol, and etomidate are just a few of these agents in common usage. Respiratory depression is the most concerning of side effects related to the use of these agents; however, careful preparation and administration have been shown to prevent harmful sequelae.

Drug Administration Recommendations: Can ketamine, midazolam, fentanyl, propofol, and etomidate be safely administered for procedural sedation and analgesia in the ED?

Level A recommendations. Ketamine can be safely administered to children for procedural sedation and analgesia in the ED.

Level B recommendations. Propofol can be safely administered for procedural sedation and analgesia in the ED.

Nondissociative sedation agents should be titrated to clinical effect to maximize safety during procedural sedation in the ED.

The combination of fentanyl and midazolam is effective for procedural sedation and analgesia in the ED.

Level C recommendations. Etomidate can be safely administered for procedural sedation and analgesia in the ED.

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Evidentiary Table.

Study	Design	Findings	Limitations	Conclusions	Grade
Terndrup et al[4]	Descriptive retrospective chart review; 487 pediatric patients identified who received demerol, phenergan, and thorazine for procedural sedation and analgesia in the ED	3 (0.6%) patients found to have significant respiratory depression requiring naloxone	Design	Demerol, phenergan, and thorazine combination appears to be safe in pediatric ED patients	III
Chudnofsky et al[5]	Retrospective chart review	841 patients receiving fentanyl; average dose 180 μg (range 25–1,400 μg); 6 (0.7%) respiratory compromise; 3 (0.4%) hypotension; no sequelae associated with comorbid factors (ie, alcohol, head trauma)	Design	Fentanyl is safe when used in the ED; the safety window can be maximized by careful dosing and titration of fentanyl during administration; the authors suggest that naloxone be available during procedural sedation and analgesia	III
Chudnofsky et al[6]	Prospective, observational trial	ED study of 70 patients aged >18 y all of whom received 0.07 mg/kg of IV midazolam followed by 2 mg/kg of IV ketamine; indications for procedural sedation and analgesia included incision and drainage (26%), fracture/joint reduction (26%), and other (8%); there were no episodes of hallucinations, delirium, or other emergency reactions; 18 (25%) patients recalled dreaming during sedation, 2 (3%) were unpleasant, and 3 (4%) were both pleasant and unpleasant	No control group and lack of interrater reliability in recognition of emergence reactions	Midazolam and ketamine in combination provide effective and safe procedural analgesia in adult ED patients	II
Wathen et al[7]	Double-blind, randomized, controlled study	ED study of 266 patients aged 4.5 mo to 16 y to evaluate frequency and severity of adverse effects in patient receiving ketamine with or without midazolam for sedation; 129 patients received ketamine and 137 received ketamine and midazolam; the incidence of emergence reaction was not affected by the addition of midazolam	No major limitations	Ketamine and combined ketamine and midazolam provide equally effective sedation	I
Dachs and Innes[8]	Observational study	30 children aged 18 mo to 8 y were enrolled; a bolus of 1.5 mg/kg produced adequate sedation in 17/18 (94%) patients	Design	Ketamine is an effective method of producing sedation and analgesia in children	III
Barsan et al[9]	Prospective, multicenter clinical trial	72 patients receiving 1.5–3 mg/kg of IV meperidine; complications included 3 patients with nausea, 6 with vomiting, and 1 with hypotension; no reversal with naloxone was needed	Limited number of patients to demonstrate complications that occur with low frequency	High-dose narcotic analgesia is safe when used in selected patients before painful procedures	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Vinson and Bradbury[10]	Retrospective observational study in 3 affiliated suburban EDs; 134 patients enrolled, aged 6–93 y; chart review performed with prospective questionnaire sent to patients with 120 (90%) completed	Moderate sedation achieved in 48 (32%) patients and deep sedation induced in 102 (68%) patients as measured by the Aldrete Postanesthetic Recovery Score; 5 (4.7%) of 7 adverse reactions were the result of O_2 desaturation requiring face mask O_2; 4 of 5 also received bag-assisted ventilation; these patients were >55 y and had received relatively higher doses of etomidate (0.23 mg/kg vs 0.19 mg/kg in the nonrespiratory compromised patients); no intubations; 2 patients experienced emesis; 114 (94%) responders stated they would be "extremely" willing to have this medication again	Design; no standardized dosing; adjunctive medications given in 23% of procedures; only patients meeting ASA status I or II were candidates for procedural sedation; some patients were entered into the study more than once	The authors concluded that etomidate appears to be a brief, safe, and effective drug for emergency procedural sedation; however, as the authors point out, the power of the study is not enough to evaluate incidence of all complications	III
Dickinson et al[11]	Retrospective descriptive study; 53 charts of children aged <18 y who received IV etomidate were studied	There were no major adverse effects; 1 patient reported nausea and another was given a fluid bolus for transient hypotension; no patient required ventilatory assistance	Retrospective design; selection bias; documentation concerns as demonstrated by no reported cases of myoclonus	Results suggest that etomidate may be used safely in children but the authors warn that further larger prospective studies are indicated	III
Ruth et al[12]	2-phase feasibility study; retrospective pilot followed by a prospective descriptive study	Procedural success was achieved in 56/60 (93%) patients, with adequate sedation as documented by the physician in 59/60 (98%) patients; 12 complications were reported, including O_2 desaturation <90% (5), myoclonus (4), vomiting (1), pain with injection (1), and a "brief" bradycardic episode; none of the patients required ventilatory assistance	13 patients had missing nursing records and another 4 patients lacked depth of sedation information	Etomidate administered IV for procedural sedation in the ED was both effective and safe in this group of patients	III
Keim et al[13]	Retrospective chart review; the charts of 46 adults and 2 children were reviewed	10/48 (21%) patients had adverse reactions; 1 (2%) patient had transient apnea requiring bag-mask ventilation (this patient had multiple doses of analgesics as well); 1 (2%) patient required a nonrebreather for a desaturation <90%; emesis in 2 (4%) patients; anxiety in 2 (4%) patients; and 4 (8%) patients had failed procedures	Design; not an etomidate-only study so some adverse side effects may be related to other sedatives and analgesics; documentation concerns as demonstrated by no reported cases of myoclonus	The authors conclude that although further study is indicated, etomidate holds promise as a procedural agent in the ED; the authors further stress the need for adequate monitoring in the ED when using agents that may induce deep sedation	III
Swanson et al[14]	Convenience sample; 20 patients received 2 μg/kg of fentanyl and propofol (0.21 mg/kg/min)	3 patients had pain on injection; 1 patient experienced hypotension <1 min and 1 patient had apnea <30 s, responded to stimulation; 1 patient had apnea with desaturation to 86% requiring "brief" bag-mask ventilation	Design, limited study power	Further study required	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Havel et al[15]	Prospective, randomized, blinded, comparison trial; 89 patients, aged 2–18 y received morphine for pain, and then midazolam or propofol for sedation in the ED	Sedation scores and rates of O_2 desaturation similar between groups; recovery time for the propofol group was 14.9±11.1 min, compared with 76.4±47.5 min for the midazolam group (P<.001)	Sample size small for comparison of complication rates	Propofol induced sedation as effectively as midazolam but with a shorter recovery time; complication rates for propofol and midazolam were comparable	I
Skokan et al[16]	Prospective, observational study of pediatric patients receiving propofol for procedural sedation and analgesia in the ED	Mean dose 3.3 mg/kg; 30% experienced O_2 desaturation, but only 1 required assistance with ventilation; mean recovery time 18 min	Not controlled and not randomized	Propofol provides safe and effective sedation for procedural sedation and analgesia	III
Burton et al[17]	Prospective, double-blinded, randomized trial of etomidate and midazolam for procedural sedation in anterior shoulder dislocation reductions; opiates for analgesia given at physician discretion; all patients aged >18 y	19/41 patients included for analysis in the etomidate group; the median time for procedural sedation was 10 min for etomidate and 23 min for midazolam (P<.001); no significant difference for the medial lowest PAR score was observed between agents; 1 patient in each group required brief bag-mask ventilation; myoclonus was noted in the etomidate group in 4/19 (21%) patients; successful reduction occurred in all but 2 patients in each group	No predefined target depth of sedation; limited power to identify potential complications	Etomidate provides effective sedation for performance of shoulder dislocation reduction; duration of procedural sedation with etomidate is shorter than sedation performed with midazolam	II
Guenther et al[18]	Prospective, observational trial evaluating propofol for procedural sedation in 87 patients with 291 separate sedations; all sedations performed in ED sedation unit; propofol dosing was an initial dose of 1 mg/kg followed by 0.5 mg/kg supplements as needed; fentanyl used as a single bolus dose for analgesia in 97% of cases; median age 6 y	100% success rate for all procedures; success defined as completion of procedure with no adverse events; 93% of children maintained saturations >90%, 4% developed partial airway obstruction corrected with jaw thrust, 3/291 (1%) experienced apnea mandating brief bag-mask ventilation; transient decrease in systolic blood pressure noted in all but 4 patients; no evidence of poor profusion noted; 1 episode of emesis; no report of aspiration	Patients were preselected and scheduled for elective procedures; no objective monitoring for depth of sedation; no $ETCO_2$ monitoring	Propofol is safe and effective when administered by pediatric emergency physicians in ED-associated sedation units	II
Bassett et al[19]	Prospective observational study of 392 consecutive patients aged 1–18 y (median age 8 y) with 393 procedures; all participants received propofol with a narcotic for analgesia; initial dosing of propofol of 1 mg/kg with subsequent dosing of 0.5 mg/kg at physician discretion	O_2 saturation was maintained >90% in 95% of patients; median duration of hypoxia ranged from 1–3 min with no patients requiring intubation; partial airway obstruction was noted in 11/393 (3%) patients; an additional 3/393 (0.08%) patients required bag-mask ventilation for 5 s to 1 min; 23/393 (6%) patients experienced clinically insignificant transient bradycardia; 331/393 (84%) patients experienced clinically insignificant decreases in systolic blood pressure with no episodes of poor profusion documented; all procedures were completed successfully	Design; depth of sedation was not objectively scored; no standardization for timing of repeat dosing of sedative agent; no $ETCO_2$ monitoring for detection of hypoventilation	Propofol is safe and effective when administered in the ED	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Miner et al[20]	Prospective, randomized comparison of methohexital and propofol for procedural sedation and analgesia in the ED; morphine used on all patients for pain control	Respiratory depression rate of 48% for methohexital and 49% for propofol (P=.88); BIS 66.2 for methohexital and 66 for propofol (P=.50); 11/34 patients receiving single dose of medication experienced respiratory depression; 39/69 patients receiving multiple doses experienced respiratory depression (P=.021)	Not blinded	Both agents equally efficacious for procedural sedation and analgesia for fracture reduction in the ED	II
Miner et al[21]	Prospective, observational study using a convenience sample that included patients receiving propofol, methohexital, etomidate, and fentanyl/midazolam to determine if a correlation existed between the BIS and the rate of respiratory depression, patients' pain perception, recall of the procedure, and satisfaction	108 patients were divided into 4 groups on the basis of the lowest BIS recorded during the procedure; no serious adverse effects were noted; the rate of respiratory depression in the 2 groups with scores >70 was significantly lower than the 2 groups with scores $\leq$69 (P=.019); the group with the lowest BIS (>85) had significantly higher rates of pain (P=.003) and recall (P=.001) compared with the combined group of patients (<85)	Design; patients' state of health before study was not described	The optimally sedated patients were represented by those with the lowest BIS between 70 and 85 as illustrated by the same VAS outcome as more deeply sedated patients and the same rate of respiratory depression as patients who were less sedated	III
Wilson and Pendleton[22]	Chart review	198 charts reviewed of patients admitted through the ED with a wide range of acutely painful medical and surgical conditions	Design	Both emergency physicians and consultants were providing a significant degree of oligoanalgesia	III
Brown et al[23]	Retrospective cohort	Analysis of the ED component of the NCHS NHAMCS; total of 2,828 isolated closed extremity and clavicle fractures; 73% of patients aged 0–$\geq$70 y received analgesia, and 54% received narcotic analgesia among patients with documented moderate and severe pain	Design	Patients with documented fractures frequently do not receive analgesia; compared with adults, pediatric patients are less likely to receive analgesics including narcotics	III
JCAHO[24]	Standards document		Design		III
Krauss and Green[25]	Review		Design		III
American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists[26]	Clinical guideline		Design	ASA clinical guideline	III
EMSC Grant Panel on Pharmacologic Agents Used in Pediatric Sedation and Analgesia in the ED[31]	Evidence-based review of the safety and efficacy of etomidate, fentanyl/midazolam, ketamine, methohexital, pentobarbital, and propofol in children		Design	The policy provides an evidence-based approach to drugs used in pediatric sedation and analgesia in the ED	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Green and Krauss[32]	Review	Review of pulmonary aspiration risk during ED procedural sedation and analgesia with extensive list of references	Design	The risk of aspiration during ED procedural sedation and analgesia appears to be extremely low; also there is no compelling evidence that mandates specific time frames for presedation fasting for either solids or liquids	III
Pacifico et al[33]	Case series of 162 patients undergoing ICD implantation under procedural sedation with combination of midazolam, morphine, promethazine, and etomidate	No episodes of apnea, hypoxia, or hypotension	Not randomized, not blinded; small sample size	ICD implantation is safe under moderate and deep sedation protocols using combinations of intravenous anesthetic agents including etomidate, midazolam, morphine, and promethazine	III
Pena and Krauss[34]	Prospective observational study; 1,180 patients <21 y undergoing procedural sedation in ED for painful procedures and diagnostic imaging	2.3% experienced adverse events including hypoxia, paradoxical reactions, laryngospasm, bradycardia, stridor, or emesis	Not randomized, not blinded	2.3% adverse reaction rate with no serious complications	III
Agrawal et al[35]	Prospective, observational study	1,014 patients studied; inadequate fasting documentation in 11%; no significant difference in adverse outcomes between fasting and nonfasting patients	Inadequate power to determine differences in aspiration after emesis; nonblinded sedation recorders (ED nurses caring for patients); no follow-up of patients after ED discharge	56% of patients not fasted; no difference in adverse events between fasted and unfasted groups	III
Ferrari et al[36]	Survey of preoperative fasting guidelines at pediatric anesthesia fellowship programs	44/55 institutions responded; no clear consensus on guidelines; in 50% of institutions: clear liquids were allowed up to 2 h before anesthesia and solids were restricted after midnight in all children >3 y	Design; evaluates practices in preparation for general anesthesia and not procedural sedation	There is a large degree of variation in preoperative fasting practices for children undergoing elective surgery	III
Maekawa et al[37]	Prospective randomized trial of 105 pediatric patients aged 1–14 y; the study evaluates the effects of preoperative fasting at 2-h, 4-h, and 12-h intervals	Gastric aspirates taken from patients immediately after intubation revealed no significant difference between groups with gastric volumes or gastric fluid pH	Insufficient gastric aspirates volumes prohibited pH evaluation in 28 samples; however, there was no difference between groups	There was no significant difference in the gastric pH and gastric volumes of patients who were fasted for 2 h, 4 h, and 12 h preoperatively	I

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Splinter et al[38]	Prospective randomized single-blinded trial of 121 patients aged 2–12 y; the study evaluates the effects of unlimited clear fluids up to 3 h before general anesthesia induction compared with prolonged fast	Prolonged fast with mean duration of 14 h demonstrated no significant difference in gastric volumes and gastric pH compared with 3-h fast	No major limitations	Drinking clear fluids up to 3 h before surgery has no significant effect on gastric volume or gastric pH	I
Soreide et al[39]	Prospective observational study of healthy female volunteers in which ultrasonography was used to determine the amount of food particles remaining after a light meal	Subjects were found to have solid food particles after 2 h, and all volunteers demonstrated empty stomachs after 4 h	Unable to evaluate pH changes	In healthy subjects, complete stomach emptying after a light meal may not occur until 240 min after ingestion	II
Ingebo et al[40]	Prospective observational study of 285 pediatric patients aged 1–18.6 y; gastric contents were collected immediately after IV sedation via endoscopic suction; duration of fasting after clear fluid ingestion ranged from 0.5–24 h (mean 6.7 $\pm$ 5.3 h)	The results demonstrated no significant difference between gastric volumes and gastric pH when comparing groups with fasting times >30 min	Compared data to historical standards; does not specifically look at time from ingestion of milk and solids before sedation	Fasting >2 h after ingestion of clear liquids does not significantly change gastric pH or gastric volumes during procedures	II
American Society of Anesthesiologists Task Force on Preoperative Fasting[41]	Clinical guideline		Design	ASA guideline for preoperative fasting	III
Engelhardt and Webster[43]	Review	Review of risk factors of gastric aspiration during general anesthesia	Design	The incidence of pulmonary aspiration in general surgical patients is only slightly greater in the pediatric and obstetric patients	III
Green et al[44]	Prospective uncontrolled trial; 108 children aged 14 mo to 13 y, mean age 54 mo, using IM ketamine 4 mg/kg	6 emesis during recovery; 1 case of emesis and laryngospasm with transient cyanosis with no adverse sequelae	Design; no validated outcome measure	Ketamine can be used effectively in the ED, but providers should have expertise in airway management	II
Green et al[45]	Retrospective observational study; an IM ketamine protocol was followed in a collection of 1,022 pediatric cases aged <15 y; 431 prospectively collected data sheets were then reviewed for complications, adjunctive medications, etc	Transient airway complications occurred in 1.4% of patients, with laryngospasm occurring in 4/431 patients and apnea in 2/431 patients	Design; only 431 of the treated patients had data sheets completed	Ketamine has a wide safety margin and may be administered safely in the ED with appropriate monitoring and defined protocols; IV access may not be required with ketamine sedation	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Chudnofsky[46]	Multicenter, randomized, double-blind controlled trial; patients received 2 μg/kg fentanyl followed by midazolam titrated to sedation; patients then received placebo or flumazenil	Flumazenil dosing did not decrease time to discharge	No major limitations	Flumazenil is safe and effective in reversing midazolam-induced sedation in ED patients	I
Yaster et al[47]	Case report	Large incremental doses of both midazolam and fentanyl over a 4-min period; no supplemental O_2 available; respiratory arrest, "instantaneous resolution" with naloxone	Design	Reversal agents should be available during procedural sedation and analgesia	III
Newman et al[48]	Prospective cohort in which a database review was performed evaluating timing of 184 adverse events documented in 1,341 sedation events in a pediatric ED; median age with adverse events was 64.4 mo	160/184 records for timing of events were complete; 92% of adverse events occurred during the procedure with 8% occurring after the procedure; serious adverse events occurred a median of 2 min after the final medication dosing; no primary serious adverse effects occurred >25 min after final medication	Incomplete database; no standardized discharge criteria	In children without serious adverse effects during procedural sedation, discharge from the ED may be safe approximately 30 min after final medication administration	II
Bailey et al[49]	Randomized, double-blind crossover study	The authors investigated the respiratory effects of midazolam (0.05 mg/kg) and fentanyl (2 μg/kg) in 12 volunteers; apnea was defined as no respirations for 15 s and was observed in 50% of volunteers receiving both drugs; no complications noted; midazolam alone caused no hypoxemia; fentanyl alone caused hypoxemia in 50% without clinical correlate; midazolam plus fentanyl caused hypoxemia in 92% without clinical correlate and apnea in 50%	Small sample size; selected volunteers	Patients receiving both midazolam and an opiate are at risk for hypoxia and apnea; adequate precautions including monitoring of patient oxygenation with pulse oximetry, the administration of supplemental O_2, and the availability of persons skilled in airway management are recommended	II
Pohlgeers et al[50]	Retrospective chart review of a standardized protocol in 133 consecutive patients	11% desaturation to <90%, 0.7% vomited, 0.7% pruritus	Design	The combination of diazepam and fentanyl for moderate sedation is safe in the pediatric patient requiring emergent orthopedic procedures	III
American Medical Association Council on Scientific Affairs[51]	Literature review		Design		III
Aughey et al[52]	Prospective, cross-sectional study	Paired measurements of pulse oximetry vs hemoglobin saturation	Design	Strong correlation was found between study groups	II
Rubin et al[53]	Randomized controlled trial; 46 ASA I and II study subjects received 0.7 μg/kg of fentanyl and titrated midazolam	1 group received nitrous oxide and the other group received 100% O_2 with $ETCO_2$ and O_2 saturation measured	Low power to show difference	No significant difference in $ETCO_2$ and O_2 between study groups	III
Block et al[54]	Prospective observational trial	Desaturation in 43% of asymptomatic males documented during sleep	No major limitations	Significant desaturation occurs during sleep in normal study patients	I

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Bilotta et al[55]	103 consecutive patients aged 22–96 y undergoing colonoscopy; diazepam plus meperidine	41% desaturation rate; age correlated to desaturation ($P<.05$), but pulse oximetry and other historical measures did not	No clinical correlation; not blinded	No adverse outcomes; oximetry monitoring may not be clinically useful	III
Arrowsmith et al[56]	Aggregate study using computer-based data collection system: 19,363 procedures using midazolam, diazepam with or without narcotics	0.3 deaths/1,000 procedures; 5.4 serious cardiopulmonary events/1,000 procedures (not defined)	Study limited by retrospective design and lack of information on indications for procedures and on patient clinical status; 17 sites, 1 site reported 54% of the midazolam-associated cardiorespiratory events	Serious cardiorespiratory events and death are uncommon during procedural sedation; concomitant use of narcotics and urgent and emergent procedures, however, did increase the risk of serious cardiorespiratory events	III
Ceravolo et al[57]	10,000 periodontal cases over a period of 11 y using IV meperidine, diazepam, and methohexital in 7,443 patients; diazepam plus methohexital in 2,557 patients (ages 9–78 y)	4.1% phlebitis; 0.37% with nausea; 0 cases of vomiting	Retrospective; lack of generalizability	No major complications recorded in 10,000 cases of procedural sedation and analgesia	III
Tobias[58]	Prospective case cohort; 50 children undergoing procedural sedation and analgesia with midazolam and ketamine had sidestream $ETCO_2$ measured	3 episodes O_2 desaturation; 2 episodes of hypercapnia ($ETCO_2$ >50 mm Hg); 1 episode apnea detected only by $ETCO_2$ monitor	Not randomized, not blinded, not controlled	The addition of capnometry provides an additional monitor to detect respiratory depression	III
McQuillen and Steele[59]	Prospective, observational series of 106 children aged 1–16 y undergoing procedural sedation and analgesia; main outcome measure was change in $ETCO_2$	$ETCO_2$ increased a mean of 6.7 mm Hg (range 0.16–22.3; $P<.00001$)	Not randomized	$ETCO_2$ is useful in assessing ventilatory effort during procedural sedation and analgesia	II
Miner et al[60]	Prospective observational study; 74 adults treated with various agents, monitored with capnometry, oximetry, OAA/S	Respiratory depression in 45% of patients; oximetry detected one third of the patients with respiratory depression; no correlation between OAA/S and capnometry; capnometry changes ($ETCO_2$ >50 mm Hg, absent $ETCO_2$ waveform, or change in $ETCO_2$ >10 mm Hg) able to detect all clinical cases of respiratory depression	Post-hoc analysis of $ETCO_2$ performance	Capnometry may add to safety of procedural sedation and analgesia by early detection of hypoventilation	II
Wright[61]	Prospective, nonblinded, nonrandomized, noncontrolled observational trial; 27 treated with benzodiazepine and/or narcotic	Average $ETCO_2$ increased from 36 to 42 mm Hg; O_2 saturation decreased from 98% to 94%; 1 episode of apnea lasting 30 s responded to verbal stimuli	No clinical correlation	Pulse oximetry recommended for detection of unrecognized hypoxemia during conscious sedation	II

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Hart et al[62]	42 patients randomly assigned to fentanyl, fentanyl-midazolam, or MPC; $ETCO_2$ prospectively measured during procedural sedation and analgesia	Respiratory depression occurred in 20% of fentanyl, 23% of fentanyl-midazolam, and 11% of MPC patients, respectively (P=NS); capnometry detected subclinical respiratory depression better than oximetry	Small number of study subjects	Capnometry provides earlier detection of subclinical respiratory depression than does pulse oximetry or respiratory rate alone	II
Rosow and Manberg[63]	Summary article		Design		III
Bower et al[64]	Prospective, observational study of 50 adults undergoing procedural sedation and analgesia for endoscopy; BIS analysis compared to the OAA/S	Temporal correlations between BIS analysis and OAA/S (r=0.59; P<.0001)	Not blinded	BIS monitoring temporally correlates with the OAA/S scale, providing an objective measure of sedation	II
Gill et al[65]	Prospective observational study measuring BIS and the modified Ramsay Sedation Scale score in ED patients undergoing procedural sedation and analgesia; convenience sample of 37 patients; 270 paired readings obtained	Statistically significant (P<.0005) but clinically moderate correlation (Spearman ρ=0.690) that showed "wide variability"; ROC curves demonstrate moderate discriminatory power at all Ramsay Sedation Scale score thresholds	Convenience sample design; small sample size; Ramsay Sedation Scale score assigned by multiple investigators	BIS monitoring reliably predicts patients undergoing procedural sedation and analgesia who are sedated to the level of general anesthesia, but didn't discriminate between mild-moderate sedation or moderate-deep sedation	III
Agrawal et al[66]	Prospective observational trial; evaluated ability of BIS to monitor depth of sedation in nondissociative procedural sedation; convenience sample of 20 children undergoing procedural sedation in the ED; 217 paired readings obtained	Significant correlation between BIS and Ramsay Sedation Scale scores (P<.001); BIS showed increased variability at moderate-to-deep levels of sedation as measured by the Ramsay Sedation Scale score; ROC curves demonstrate moderate-to-high discriminatory power at moderate Ramsay Sedation Scale score thresholds	Convenience sample design; small sample size	BIS monitoring correlated with traditional clinical sedation scores; BIS values between 60 and 90 predicted with moderate accuracy and reliability clinical levels of sedation	II
Kennedy et al[67]	Prospective, single-blinded, randomized controlled trial of ketamine and midazolam vs fentanyl and midazolam; 260 patients aged 5–15 y undergoing orthopedic procedures; all patients were ASA I-II; videotaped blinded assessments of adequacy of sedation, documented efficacy assessments, and objective monitoring were used	Ketamine and midazolam resulted in hypoxic events in 6% of patients compared with 25% in the fentanyl and midazolam group (P=.001); there was documented greater physician satisfaction with ketamine and midazolam measured by VAS 8.71 ± 2.21 vs 9.61 ± 0.78 (P=.001) with fentanyl and midazolam and a lower OSBD-R scored by blinded observers and blinded treating physicians 1.08 ± 1.12 vs 2.70 ± 2.16 (P<.0001)	Only evaluated children aged 5–15 y; unclear if these results apply outside of this age range especially in the very young and elderly	Both drug regimens are safe and effective in the study groups; however, ketamine and midazolam appears more efficacious and demonstrated a higher safety profile with fewer episodes of documented hypoxia and/or airway interventions	I
Bell et al[68]	British Society of Gastroenterology, endoscopy guidelines		Design	Policy guideline	III

Evidentiary Table (continued).

Study	Design	Findings	Limitations	Conclusions	Grade
Helmers et al[69]	Prospective double-blind controlled trial to determine if IV injection of droperidol or fentanyl before etomidate could attenuate side effects of pain and myoclonus; 83 patients aged 14–78 y; a severity score was assigned to pain and involuntary movements	The incidence of pain on delivery in patients was: etomidate+normal saline 17% (5/29), etomidate+droperidol 16.7% (4/24), etomidate+fentanyl 18.5% (5/27); incidence of myoclonus was: etomidate+normal saline 37.9% (11/29), etomidate+droperidol 12.5% (3/24), etomidate+fentanyl 11% (3/27); $P<.5$ for the groups using etomidate+another drug vs etomidate alone	Not a sedation study; side effects measured after initial induction only; potential bias in scoring of pain and myoclonus	Both fentanyl and droperidol showed a significant difference in attenuating myoclonus after etomidate administration	II
Van Keulen and Burton[70]	Case report of myoclonus during procedural sedation after etomidate administration	3 cases of myoclonus described ranging from brief, mild tremors to severe myoclonic tightening with at least 1 patient experiencing transient desaturation to 85%	Design	Physicians must be prepared to provide brief periods of support including respiratory assistance when etomidate-associated myoclonus is encountered	III
McDowall et al[71]	Retrospective review of 971 pediatric oncology patients at a university hospital; 101 received IV etomidate (0.3 mg/kg) combined with either fentanyl or alfentanil for brief diagnostic or therapeutic procedures	Etomidate was associated with more episodes of vomiting (9.9%) and agitation (4%) compared with propofol (0.5% and 1.2%, respectively); no procedural failures reported with etomidate	Retrospective design; efficacy was not objectively measured	Etomidate is an effective agent but had more vomiting and agitation compared with propofol; however, propofol had a greater incidence of hypoxia (15.7%) than etomidate (2%)	III
Modica and Tempelhoff [72]	Prospective observational study; included 8 patients with space-occupying lesions and undergoing surgery; aged 18–71 y; anesthesia was induced with 0.2-mg/kg of etomidate followed by a 20-mg/min infusion	Patients were monitored during induction with IV etomidate for EEG burst suppression and changes in intracranial pressure; the etomidate bolus required to reach burst suppression was 1.28 ± 0.11 mg/kg	Small sample size	Etomidate resulted in significant reduction in intracranial pressure during intubation	II

ASA, American Society of Anesthesiologists; *BIS,* Bispectral Index Score; *EEG,* electroencephalogram; *ICD,* implantable cardioverter defibrillator; *IM,* intramuscular; *IV,* intravenous; *MPC,* meperidine-promethazine-chlorpromazine; *NCHS,* National Center for Health Statistics; *NHAMCS,* National Hospital Ambulatory Medical Care Survey; *NS,* not significant; *OAA/S,* Observer's Assessment of Alertness and Sedation; *PAR,* postanesthetic recovery; *ROC,* receiver operating characteristic; *VAS,* visual analog scale.

Appendix A. Literature classification schema.*

Design/ Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing ≥2 interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X