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## Dexmedetomidine and Hextend: Their Role in Trauma Care

- **Dexmedetomidine in Trauma Anesthesiology and Critical Care**  
*Joseph D. Tobias, MD*
- **Dexmedetomidine as a Sedative for Awake Fiberoptic Intubation**  
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INTERNATIONALE GESELLSCHAFT FÜR ANÄSTHESIE UND INTENSIVMEDIZIN IM TRAUMA

الجمعية العالمية لتخدير الإصابات والرعاية الحرجة

SOCIEDAD INTERNACIONAL DE ANESTHESIA Y REANIMACION EN TRAUMATOLOGIA

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## PRESIDENT'S MESSAGE

### Dexmedetomidine and Hextend: Their Role in Trauma Care

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Anesthesia now seems so safe that sometimes one may wonder how to further improve our patients' perioperative care. Perhaps we fine-tune existing strategies, such as adding the volatile agent sevoflurane, which improved acceptance of inhalation induction, decreased hemodynamic perturbations, and markedly impacted care of pediatric patients. Nonetheless, this may be just a reinvention of the same old wheel. When I first began practicing anesthesiology, I often imagined characteristics of an ideal perioperative drug. Ideally it would offer an easily arousable sedation, provide pain relief while not depressing respiratory drive, and have relatively mild hemodynamic effects. At a meeting in the spring of 2000 I found out that just such a drug, dexmedetomidine, a specific  $\alpha_2$ -adrenergic agonist that induces a sleep-like state, was soon to be introduced to the United States market. I quickly envisioned the utility of dexmedetomidine and, as chief of anesthesiology at my hospital, requested that dexmedetomidine be added to the formulary as soon as possible. Initially, I was interested in its potential for bariatric surgery patients, patients at significant risk for airway obstruction, atelectasis, and hypoxemia, but quickly realized its vast potential to augmenting perioperative pain control while maintaining respiratory drive with a predictable hemodynamic effect.

Over the intervening years, I have expanded my use of dexmedetomidine to include nearly all patient categories, ranging from same-day surgery to congenital cardiac surgery patients, and of course critically ill and injured trauma patients. Unfortunately, when the Food and Drug Administration approved the use of dexmedetomidine (Precedex, Hospira Inc., Lake Forest, Illinois) in 1999, it was for the limited indication of sedation for initially intubated and mechanically ventilated adult patients in intensive care units and limited to a 24-hour infusion. This relatively narrow indication limited use of dexmedetomidine in some medical centers, while in many other facilities, its off-label utilization grew as experience and comfort with dexmedetomidine expanded and clinicians realized the utility of this new class of medications.

This issue of *TraumaCare* contains three articles by clinicians with substantial experience with and interest in the use of dexmedetomidine in a variety of clinical settings. Their reports cover not only the approved uses of this powerful and selective sedative but also the extensions of its use into scenarios in which short-term blunting of physical responses is beneficial, as is the ability to arouse the patient by verbal stimuli. The issue concludes with a

review of another innovation in trauma anesthesia practice—the use of Hextend during trauma surgery.

Opening the issue is an extensive systems-based literature review, compiled by Joseph D. Tobias, MD, from the University of Missouri. Dr. Tobias discusses the preoperative, perioperative, and postoperative scenarios in which dexmedetomidine is, could be, and is not effective. Following a brief overview of the drug's pharmacokinetics, the article continues with a comprehensive discourse on the end-organ effects and clinical applications of dexmedetomidine. Cardiovascular and hemodynamic effects are described, as are effects on the sympathetic and central nervous systems. The passage on respiratory effects includes summaries of studies of drug combinations, emphasizing the need for careful monitoring of the respiratory function of patients receiving dexmedetomidine. It should be kept in mind that the amount of narcotics typically required to achieve comfort in the setting of dexmedetomidine is generally cut in half. Thus, if this is not accounted for, one may effectively give a patient a narcotic overdose, thereby blunting the respiratory drive.

Tobias introduces interesting thoughts regarding the anticonvulsant/proconvulsant effects of dexmedetomidine in brain-injured patients and the mechanism of action for the drug's neuroprotective effect. It is clear that dexmedetomidine offers distinct advantages for the control of shivering and opioid-induced muscle rigidity, again of particular importance in the trauma patient, particularly in head-injured patients in whom some degree of hypothermia may be desired for cerebral protection.

Other issues of importance in the intensive care unit include gastrointestinal motility, adrenocortical function, and inflammatory response. Tobias provides an illuminating review of dexmedetomidine's influence on these aspects of postoperative care and how, in contrast to other commonly used sedation medications, dexmedetomidine either supports or at least does not depress anabolic activities in the critically ill.

In clinical applications, Tobias notes that dexmedetomidine has been used as a premedication, as an intraoperative infusion, by intraoperative bolus dosing, and for postoperative sedation in intubated and nonintubated patients. The drug has been used in patients undergoing gynecologic procedures, hand surgery, and craniotomy. In balanced anesthetic technique, dexmedetomidine can decrease anesthetic requirements and improve intraoperative stability. It also may find a role as part of monitored anesthesia care with a regional anesthetic technique. Its postoperative analgesic effects are well established, and it may serve as a useful adjunct to epidural analgesia or patient-controlled analgesia (PCA). In my practice with bariatric surgery patients receiving postoperative dexmedetomidine infusions, I noted, as have others, a nearly halved utilization of PCA narcotic doses over the first 24 postoperative hours.

Several studies have documented the successful use of dexmedetomidine to prevent emergence agitation and delirium following general anesthesia with sevoflurane or desflurane. In addition, dexmedetomidine seems to decrease the incidence of coughing on emergence from anesthesia.

Although dexmedetomidine is effective for sedation during nonpainful procedures such as computed tomography and radiation

therapy (especially useful for calming children undergoing such procedures), it is not sufficient, when used alone, for painful invasive procedures such as gastroduodenoscopy unless extremely high doses (between 10 and 20 times the standard sedating doses) such as those used by Ramsey to provide a general anesthesia are given to the patient, as noted in Tobias's article. Unfortunately, such large doses result in excessive and prolonged sedation, making dexmedetomidine difficult to consider using as a full general anesthetic agent in the outpatient setting.

Tobias concludes the article with sections on the best known uses of dexmedetomidine: during mechanical ventilation and for the management of withdrawal symptoms. In numerous studies, dexmedetomidine has decreased the need for narcotics (i.e., morphine); however, other investigators have found no advantage offered by dexmedetomidine over those associated with propofol. For the management of withdrawal from opioids, benzodiazepines, and alcohol, dexmedetomidine has the advantages of a relatively short half-life and titratability. Reports on the administration of dexmedetomidine to mechanically ventilated children are beginning to emerge, cautiously documenting promising results. In my clinical experience, a majority of the pediatric congenital heart surgery patients I care for receive dexmedetomidine for postoperative sedation in our cardiac intensive care unit with a safe and satisfactory sedation.

In the second article, Rafi Avitsian, MD, Mariel Manlazaz, MD, and John Doyle, MD, PhD, from the Cleveland Clinic, describe the benefits conveyed to patients and practitioners in trauma scenarios requiring awake intubation. These authors compare dexmedetomidine with other  $\alpha_2$ -receptors that have been used in clinical practice for decades. The unique features of dexmedetomidine include its shorter half-life, which allows titration as an intravenous infusion; its insignificant effect on respiratory function and gas exchange; and its ability to effect sedation yet preserve the ability to arouse the patient. This latter characteristic is particularly useful during awake intubation of patients with potential cervical instability. Patients brought to a resuscitation unit following traumatic injury, particularly injuries of the head and neck, are understandably anxious, and thus can be uncooperative with airway-management procedures. Administration of dexmedetomidine allows the physician to achieve a desired level of sedation for awake intubation and to retain the ability to arouse the patient through verbal stimulation so that neurologic status can be monitored. In my own clinical practice, I have been using dexmedetomidine for awake fiberoptic intubations since shortly after I first gained access to the medication. I find that a convenient way to facilitate these fiberoptic intubations is to initiate an infusion of 1 mcg/kg/hr of dexmedetomidine and at the same time administer a nebulized lidocaine and Pontocaine treatment to augment topicalization of the airway. In the roughly ten minutes it takes for the nebulizer treatment, the patient will typically be comfortably sedated with the dexmedetomidine and ready for their awake intubation. In the rare circumstances when the patient still appears to need a bit more sedation, I may consider small doses (0.5-1 mcg/kg) of fentanyl and/or midazolam (0.1-0.2 mg/kg), dosed in increments until an acceptable degree of sedation is obtained.

The third article on dexmedetomidine, written by Mohanad Shukry, MD, from the Oklahoma University College of Medicine, and myself, focuses on the use of this drug to mitigate the agitation and confusion that accompany withdrawal from alcohol, benzodiazepines, and narcotics. Animal studies have shown that

dexmedetomidine is as effective as diazepam in easing withdrawal from alcohol. Extrapolation to alcohol-dependent humans awaits further study. Dexmedetomidine has proven effective in treating several withdrawal symptoms in patients addicted to cocaine, narcotics, and benzodiazepines and in intensive care unit patients who received dexmedetomidine during hospital procedures. The value of dexmedetomidine in the management of withdrawal symptoms in children and teenagers has been documented in recent case reports. We also review reports of the use of dexmedetomidine in children undergoing tonsillectomy and other surgical procedures. Although the pharmacokinetics and pharmacodynamics of dexmedetomidine are not completely understood, the drug seems to hold great promise when administered properly, under close clinical scrutiny, for the prevention and treatment of postprocedural agitation in adults and children. At this author's institution, the pharmacy now offers premixed syringes of dexmedetomidine (10 mL with 4 mcg/mL) for use as both a component in a balanced anesthetic and in preventing postanesthesia agitation and delirium. Dexmedetomidine is also used as a rescue drug in the care of these pediatric patients exhibiting such postanesthesia agitation. In both these settings, when used as bolus doses, the drug is most commonly delivered in 0.25-0.5 mcg/kg doses. When bolus doses of more than 0.5 mcg/kg are used, the initial  $\alpha_1$ -agonist effect predominates for the first 5 minutes or so after induction, causing an increase in blood pressure and a decrease in heart rate, which in some patients may be undesirable.

The fourth article reviews the intraoperative use of Hextend, a colloid delivered in a balanced salt solution, and another compound that is a relatively new component for trauma care. Hextend may be simply thought of as a hetastarch in a lactated Ringer's solution. This contrasts to the older Hespan, effectively a hetastarch in 0.9% normal saline. Hespan is accepted to induce coagulopathies when delivered to patients in volumes above 1.5-2 liters. Hextend does not appear, *in vivo*, to precipitate coagulopathies even in doses up to 5 liters. Based on a retrospective review, Drs. Karl Wagner, Ramachandra Avula, and Charles E. Smith, from MetroHealth Medical Center in Cleveland, compare outcomes in two groups of patients who underwent surgery during the first day after admission to a trauma center. Despite the patients in the study receiving Hextend being sicker than those receiving crystalloid infusions when assessed by injury severity scores, there was no difference in morbidity or mortality in the Hextend group. While we await a prospective, randomized, double-blind study on the use of Hextend in the perioperative care of the trauma patients, this article provides us a measure of comfort in using Hextend, in the same fashion as the SAFE (saline vs. albumin) trial established that it is not harmful to use albumin in the critically ill.

In closing, this issue of the journal offers a view of two innovations in trauma care. Dexmedetomidine is, for all practical purposes, a new class of medication, perhaps offering some ideal characteristics for use in the trauma setting: easily arousable sedation and pain control along with a predictable hemodynamic response without significant respiratory depression. Hextend offers a colloid with a balanced salt solution that appears to have no significant deleterious effects, and may perhaps offer an efficient means for volume expansion in the critically injured trauma patient. This author's hope is that the readers of this journal edition will be stimulated to further investigation themselves, and perhaps by pursuing quality research, provide answers to some of the questions elicited by these articles.

# Dexmedetomidine in Trauma Anesthesiology and Critical Care

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**Learning Objectives:** The participant will be familiar with the cellular mechanism of action of dexmedetomidine, its physiologic effects, and its potential applications in the field of trauma anesthesiology and critical care medicine.

## Abstract

Dexmedetomidine (Precedex) is an  $\alpha_2$ -adrenergic agonist that is currently approved by the Food and Drug Administration for the short-term (<24 hours) sedation of adult patients in the intensive care unit. Its clinical effects include sedation, anxiolysis, analgesia, a decrease of the minimum alveolar concentration of inhalational anesthetic agents, blunting of the sympathetic nervous response to surgery, and lowering of heart rate and blood pressure. These beneficial physiologic effects, combined with its relatively low incidence of adverse hemodynamic and respiratory effects, have led to its use in various intraoperative and postoperative clinical scenarios, including sedation during mechanical ventilation, prevention of emergence agitation following general anesthesia, provision of procedural sedation, and prevention of the withdrawal following the prolonged use of opioids and benzodiazepines. This article reviews the basic pharmacology of dexmedetomidine, its end-organ effects including its adverse effect profile, and reports of its use in various clinical scenarios. Its potential applications in the practice of trauma anesthesiology and critical care are explored.

Dexmedetomidine (Precedex), the pharmacologically active dextroisomer of medetomidine, is an  $\alpha_2$ -adrenergic agonist with physiologic effects similar to those of clonidine. The  $\alpha_2$ -adrenergic agonists are subclassified into three groups: imidazolines, phenylethylamines, and oxalozepines. Both dexmedetomidine and clonidine are members of the imidazole compounds, which exhibit a high ratio of specificity for the  $\alpha_2$  versus the  $\alpha_1$  receptor. Clonidine exhibits an  $\alpha_2$ : $\alpha_1$  specificity ratio of 200:1, and that of dexmedetomidine is 1600:1.<sup>1</sup> As such, dexmedetomidine is considered a complete agonist at the  $\alpha_2$ -adrenergic receptor. Another difference between the two agents is that dexmedetomidine has a short half-life (2-3 hours vs. 12-24 hours with clonidine) and is commercially available for intravenous administration as opposed to the epidural formulation for clonidine.

The author has financial interest in one of the products named in this article.

The physiologic actions of dexmedetomidine are mediated via stimulation of postsynaptic  $\alpha_2$ -adrenergic receptors that activate a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein),<sup>2</sup> resulting in inhibitory feedback and decreased activity of adenylyl cyclase.<sup>3</sup> This results in a reduction of intracellular cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase activity, resulting in a dephosphorylation of ion channels.<sup>4</sup> This process subsequently modifies ion translocation and membrane conductance, resulting in decreased neuronal activation and the clinical effects of sedation and anxiolysis.<sup>5</sup> The centrally acting  $\alpha_2$ -adrenergic agonists including dexmedetomidine also activate receptors in the medullary vasomotor center, reducing norepinephrine turnover and decreasing central sympathetic outflow, resulting in decreased heart rate and blood pressure. Additional effects result from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus ceruleus in the brainstem. The latter effect plays a prominent role in the sedation and anxiolysis produced by these agents as decreased noradrenergic output from the locus ceruleus allows for increased firing of inhibitory neurons including the  $\alpha$ -amino butyric acid (GABA) system.<sup>6-8</sup>

The activation of  $\alpha_2$ -adrenergic receptors in the dorsal horn of the spinal cord inhibits the release of substance P, resulting in primary analgesic effects as well as potentiation of opioid-induced analgesia. The latter effect has been shown in clinical trials to result in opioid-sparing and analgesia in acute pain syndromes and during intraoperative anesthetic care (see following discussion). The interactions with  $\alpha_2$ -adrenergic receptors throughout the central nervous system and spinal cord result in physiologic effects in various organs systems including sedation, anxiolysis, analgesia, a decrease of the minimum alveolar concentration of inhalational anesthetic agents, decreased renin and vasopressin levels leading to diuresis, blunting of the sympathetic nervous response to surgery, and lowering of heart rate and blood pressure.<sup>9,10</sup>

Currently, the only Food and Drug Administration (FDA)-approved indication for dexmedetomidine is the provision of sedation in adult patients in the intensive care unit (ICU) setting for up to 24 hours.<sup>11</sup> However, given its favorable physiologic effects as well as its limited adverse effect profile, there is increasing interest in the use of this agent in patients of all ages and various clinical scenarios. This article reviews the basic pharmacology of dexmedetomidine, its end-organ effects and adverse effect profile, and reports from the literature regarding its use in various clinical scenarios.

## Pharmacokinetics

Based on data from healthy volunteers, the pharmacokinetic profile of dexmedetomidine includes a rapid distribution phase with a distribution half-life of approximately 6 minutes, an elimination half-life of approximately 2 hours, and a steady-state volume of distribution of approximately 118 liters.<sup>12</sup> Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when delivered via intravenous infusion for up to 24 hours. It is 94% protein-bound to serum albumin and  $\alpha_1$ -glycoprotein. It undergoes extensive hepatic metabolism with very little unchanged drug excreted in the urine and feces.

The pharmacokinetic profile of dexmedetomidine following intravenous administration has been investigated in patient populations with comorbid features including hepatic or renal dysfunction. Cunningham et al<sup>13</sup> evaluated dexmedetomidine pharmacokinetics following the administration of 0.6 mcg/kg infused during 10 minutes in five individuals with severe hepatic failure and compared the results to five age-matched controls with normal hepatic function. Patients with hepatic dysfunction had a significantly increased volume of distribution at steady state (3.2 vs. 2.2 L/kg,  $P <$

0.05), an increased elimination half-life (7.5 vs. 2.6 hours,  $P < 0.05$ ), and a decreased clearance (0.32 vs. 0.64 L/hr/kg;  $P < 0.05$ ) when compared with age-matched controls. De Wolf et al<sup>14</sup> compared the pharmacokinetics of a 0.6 mcg/kg bolus dose of dexmedetomidine in six patients with severe renal disease versus that of six volunteers with normal renal function. The subjects with severe renal disease had a prestudy 24-hour creatinine clearance of 30 mL/min or less, and stable renal disease with no prior dialysis. They noted no statistically significant differences between the renal disease and control groups in the volume of distribution at steady state ( $1.81 \pm 0.55$  vs.  $1.54 \pm 0.08$  L/kg) or the elimination clearance ( $12.5 \pm 4.6$  vs.  $8.9 \pm 0.7$  mL/min/kg). However, the elimination half-life was decreased in the renal disease group ( $113.4 \pm 11.3$  minutes vs.  $136.5 \pm 13.0$  minutes,  $P < 0.05$ ). Despite the shorter elimination half-life, they also noted prolonged sedation in patients with renal failure. Patients with renal failure had a 1-hour postinfusion visual analogue score of sedation (scale of 0 to 100) of  $49.2 \pm 25.4$  versus  $26.2 \pm 18.3$  in patients with normal renal function ( $P < 0.05$ ). The authors postulated that the increased level of sedation was related to decreased protein binding in patients with renal impairment, resulting in an increased free fraction of the drug. Venn et al<sup>15</sup> evaluated the potential impact of critical illness on dexmedetomidine pharmacokinetics in 10 adult patients requiring mechanical ventilation following complex abdominal or pelvic surgical procedures. Dexmedetomidine was administered as a loading dose of 0.4 mcg/kg during 10 minutes followed by an infusion of 0.7 mcg/kg/hr. No difference in half-life, volume of distribution, or clearance was noted when compared with data from healthy volunteers.

## End-organ Effects of Dexmedetomidine

### Cardiovascular and Hemodynamic Effects

**Heart rate, blood pressure, and cardiac output.** Hypotension and bradycardia have been reported with dexmedetomidine administration in adults, particularly in patients with preexisting cardiac disease, with the concomitant administration of medications with negative chronotropic effects or with large bolus doses. The hemodynamic effects following the intravenous administration of dexmedetomidine have been studied in healthy adult volunteers.<sup>16</sup> There is a biphasic effect with an immediate increase in systolic blood pressure (BP) and a reflex decrease in heart rate (HR) during initial administration, followed by a stabilization of systolic BP and HR at a value that is below the baseline. The initial increase in BP is mediated by stimulation of peripheral postsynaptic  $\alpha_{2B}$ -adrenergic receptors, which results in vasoconstriction, and the subsequent decrease in BP and HR is caused by central presynaptic  $\alpha_{2A}$ -adrenergic receptor-stimulated sympatholysis. The central presynaptic  $\alpha_{2A}$ -adrenergic receptor is a negative feedback receptor, so its stimulation results in decreased catecholamine release from the nerve terminal.

In healthy volunteers, dexmedetomidine in doses of 0.25, 0.5, 1.0, and 2.0 mcg/kg administered during 2 minutes resulted in a decrease of the mean arterial pressure (MAP) of 14%, 16%, 23%, and 27% from baseline at 60 minutes. With a dose of 1 mcg/kg, cardiac output (measured by thoracic bioimpedance) was  $81\% \pm 13\%$  of baseline at 1 minute,  $88\% \pm 14\%$  of baseline at 10 minutes, and  $91\% \pm 11\%$  of baseline at 60 minutes. With a dose of 2 mcg/kg, cardiac output was  $58\% \pm 32\%$  of baseline at 1 minute,  $76\% \pm 33\%$  of baseline at 10 minutes, and  $85\% \pm 28\%$  of baseline at 60 minutes.

The potential clinical impact of the cardiovascular effects of dexmedetomidine are illustrated by the study of Venn et al<sup>11</sup> in an adult ICU population of 98 cardiac and general surgery patients who received dexmedetomidine for sedation during mechanical ventilation. Dexmedetomidine was administered as a bolus dose of 1

mcg/kg during 10 minutes, followed by an infusion of 0.2-0.7 mcg/kg/hr. Hypotension (MAP  $\leq 60$  mm Hg or a  $\geq 30\%$  decrease from baseline) occurred in 18 of 66 patients receiving dexmedetomidine. Eleven of the episodes occurred during the bolus infusion. Six of 66 patients manifested hypertension during the loading dose related to the effects of dexmedetomidine on peripheral  $\alpha_{2A}$ -adrenergic receptors on the vasculature. Although no morbidity or mortality was reported related to the hemodynamic effects of dexmedetomidine, these episodes necessitated temporary ( $n = 3$ ) or permanent ( $n = 3$ ) cessation of the infusion and treatment with atropine ( $n = 2$ ) or temporary cardiac pacing ( $n = 4$ ).

In addition to hypotension, bradycardia or sinus arrest has been reported with dexmedetomidine.<sup>17,18</sup> In a study evaluating the effects of dexmedetomidine on dose requirements of propofol to induce anesthesia, Peden et al<sup>17</sup> reported that two of the first four patients had brief and self-limited sinus arrest after laryngoscopy. These patients received propofol in addition to dexmedetomidine, which was administered as a bolus dose of 1 mcg/kg during 15 minutes followed by an infusion of 0.4 mcg/kg/hr for a total mean dose of 1.47 mcg/kg. The adverse effects resulted in the authors amending their protocol with a decrease of the dexmedetomidine dose to bolus doses of 0.7 mcg/kg during 15 minutes followed by an infusion of 0.27 mcg/kg/hr. No other problems were noted after changing the infusion protocol.

We have previously reported bradycardia in a 5-week-old infant with trisomy<sup>21</sup> who was receiving dexmedetomidine for sedation during mechanical ventilation.<sup>19</sup> Concomitant medications included digoxin for the treatment of chronic congestive heart failure caused by an unrepaired atrioventricular canal defect. Twelve hours after the initiation of the dexmedetomidine infusion, the infant's HR decreased to 40-50 beats/minute with a stable BP. No therapy other than discontinuation of the dexmedetomidine infusion was required and the HR returned to baseline within 1 hour.

Scheinin et al<sup>20</sup> studied 192 patients with American Society of Anesthesiologists (ASA) scores of I and II who were premedicated with either intramuscular dexmedetomidine and intravenous saline, intramuscular dexmedetomidine and intravenous fentanyl, or intramuscular midazolam and intravenous fentanyl. Anesthesia was then maintained with 70% nitrous/30% oxygen, fentanyl, and either enflurane or isoflurane. There was a significant increase in the incidence of transient intraoperative bradycardia and hypotension in the dexmedetomidine groups when compared with the midazolam group. There was one patient who developed severe bradycardia (HR 35 beats/minute), which required therapy. Khan et al,<sup>21</sup> in their study of nine male volunteers assessing the effects of low (0.3 ng/mL) and high (0.6 ng/mL) dexmedetomidine plasma concentrations on isoflurane requirements, reported five hypotensive events in the low dexmedetomidine group and seven in the high dexmedetomidine group. Five subjects required interventions with crystalloid alone, crystalloid end-tidal isoflurane  $\geq 1\%$ .

Despite reports of hemodynamic compromise related to the bradycardia induced by dexmedetomidine, a lowering of HR and thereby myocardial oxygen consumption may be viewed as desirable in patients with coronary artery disease. Talke et al<sup>22</sup> randomized 24 adult patients undergoing vascular surgery to receive either placebo or dexmedetomidine administered by a computer-controlled program to achieve a target plasma concentration of 0.15 ng/mL (low dose), 0.3 ng/mL (medium dose), or 0.45 ng/mL (high dose). The infusion was started 1 hour prior to anesthetic induction and continued for 48 hours. Intraoperatively, there was an increased need for vasoactive medications (atropine and phenylephrine) in patients receiving dexmedetomidine. Postoperatively, no such differences were noted and there was more tachycardia (minutes/monitored hour) in the placebo group (23 min/hr) than in the low-dose (9 min/hr,  $P = 0.006$ ), medium-dose (0.5 min/hr,  $P = 0.004$ ), and high-dose (2.3

min/hr,  $P = 0.004$ ) dexmedetomidine groups. Anecdotally, the negative chronotropic effect of dexmedetomidine has also been used as a therapeutic maneuver when a patient is tachycardic during off-pump coronary artery bypass grafting and is unresponsive to  $\alpha_2$ -adrenergic blockade.<sup>23</sup>

In the majority of patients, the decrease in BP and HR that occur with dexmedetomidine are modest and require no therapy. The current clinical experience and the literature suggest that the potential for negative chronotropic effects may be greater when dexmedetomidine is administered with other medications that have negative chronotropic effects (propofol, succinylcholine, digoxin, pyridostigmine) or during vagotonic procedures such as laryngoscopy.<sup>17-19</sup>

In summary, the effects of dexmedetomidine on cardiac output are related to: (1) bradycardia, (2) an increase in systemic vascular resistance from peripheral  $\alpha_{2B}$ -induced vasoconstriction, (3) alteration in endogenous catecholamine levels, and (4) decreased peripheral oxygen requirements. Animal studies have not demonstrated direct effects on myocardial performance or intracellular calcium regulation.<sup>24</sup> When studied in isolated right ventricular papillary muscles of ferrets, dexmedetomidine has been shown to have no effect on amplitude and time variables of isometric, isotonic, and zero-loaded clamped twitches. Additionally, no effects were noted in the intracellular calcium transients, thereby suggesting that dexmedetomidine has no intrinsic or direct effects on myocardial contractility.

**Sympathetic nervous system.** The effects of dexmedetomidine on the sympathetic nervous system are illustrated by the study of Talke et al,<sup>25</sup> who evaluated the sympatholytic effects of dexmedetomidine in eight female patients following transphenoidal pituitary hypophysectomy for a pituitary microadenoma. Dexmedetomidine was infused postoperatively by a computer-controlled infusion protocol for 60 minutes to achieve a plasma concentration of 600 pg/mL. The plasma norepinephrine concentration decreased from  $2.1 \pm 0.8$  to  $0.7 \pm 0.3$  nmol/L, the plasma epinephrine concentration decreased from  $0.7 \pm 0.5$  to  $0.2 \pm 0.2$  nmol/L, HR decreased from  $76 \pm 15$  to  $64 \pm 11$  beats/minute, and systolic BP decreased from  $158 \pm 23$  to  $140 \pm 23$  mm Hg. The same group of investigators evaluated changes in plasma and urinary catecholamines in 41 adult patients undergoing vascular surgery.<sup>26</sup> Dexmedetomidine was started intraoperatively and continued for the initial 48 postoperative hours. Plasma norepinephrine concentrations were 2-3 times greater in the placebo group at the time of tracheal extubation and 60 minutes after arrival in the postanesthesia care unit (PACU) when compared with patients receiving dexmedetomidine. Urinary norepinephrine levels increased significantly from baseline preoperative values in the placebo group, and no change was noted in patients receiving dexmedetomidine.

**Cardiovascular function during hypovolemia.** Although the sympatholytic effects of dexmedetomidine are generally viewed as beneficial by attenuating the potential deleterious effects of the surgical stress response, the sympathetic response may be protective in certain clinical scenarios including hemorrhage, hypovolemia, and heart failure. In these settings, the normal hemodynamic response mediated by baroreceptors and the sympathetic nervous system includes vasoconstriction to maintain BP at near-normal levels. At a critical level of intravascular blood volume, vasoconstriction fails with a fall in BP and cardiac output. Blake et al<sup>27</sup> evaluated the effects of dexmedetomidine on the BP response to incremental decreases in intravascular blood volume in instrumented dogs. Gradual inflation of an inferior vena cava cuff reduced cardiac index by 8% per minute with a progressive increase in HR and peripheral vasoconstriction to maintain MAP. When cardiac index was approximately 40% of baseline, there was a sudden decompensation with failure of vasoconstriction and a fall in MAP. Dexmedetomidine

administration via an intravenous route or directly into the fourth ventricle of the central nervous system resulted in a decrease of both HR and MAP from baseline as well as an earlier decompensation with the simulation of intravascular hypovolemia by inflation of the inferior vena cava cuff. Similar findings were reported in animals (rabbits) that had been treated with doxorubicin to induce a chronic congestive heart failure-like state prior to the induction of intravascular hypovolemia by inflation of an inferior vena cava cuff.<sup>28</sup> Of note was the fact that the investigators did not notice a difference in the HR and BP response with the administration of dexmedetomidine to rabbits with doxorubicin-induced congestive heart failure and the control group prior to the inflation of the inferior vena cava cuff.

**Additional cardiovascular effects.** Despite the potential for adverse hemodynamic effects including bradycardia and hypotension, additional potentially beneficial effects of dexmedetomidine on myocardial performance and function have been reported. Preliminary clinical data suggest that the perioperative administration of dexmedetomidine may decrease the risk of adverse cardiac events including myocardial ischemia.<sup>29</sup> Clinical trials with mivazerol, another  $\alpha_2$ -adrenergic agonist, have demonstrated improved outcome with a decreased incidence of emergence-related ST depression and fewer postoperative deaths in a high-risk surgical cohort.<sup>30</sup> These clinical trials are supported by animal studies providing some insight into the mechanisms of the protective effect of the  $\alpha_2$ -adrenergic agonists. In an animal model of coronary artery stenosis, Roekaerts et al<sup>31</sup> investigated the effects of dexmedetomidine on blood flow to ischemic and nonischemic areas of the myocardium. Dexmedetomidine reduced blood flow in the nonischemic myocardium and in the ischemic epicardial layer, but had no effect on blood flow in the ischemic midmyocardial and subendocardial layers, thereby increasing the ischemic-nonischemic blood flow ratio. Additionally, myocardial oxygen demand decreased with dexmedetomidine, thereby further reducing the oxygen deficiency of the ischemic myocardium.

Similar findings were reported by Willigers et al<sup>32</sup> in their animal study of the effects of dexmedetomidine during coronary stenosis. Graded coronary occlusion was applied until lactate production was noted from the poststenotic myocardium. In the dexmedetomidine group, the cumulative lactate release during emergence was 46% less and the endocardial/epicardial blood flow ratio increased by 35% compared with the control group. The anti-ischemic effects of dexmedetomidine were also noted prior to emergence as lactate release in none of the eight dogs receiving dexmedetomidine versus four of seven in the control group ( $P = 0.03$ ). The authors postulated that the anti-ischemic effects were related to decreased levels of plasma epinephrine (158 vs. 1909 pg/mL), norepinephrine (126 vs. 577 pg/mL), and decreased HR ( $123 \pm 6$  vs.  $160 \pm 10$  beats/minute).

Additional protective effects of dexmedetomidine on myocardial performance include preservation of myocardial function following ischemia and prevention of catecholamine-induced arrhythmogenesis.<sup>33,34</sup> Hypoxia and subsequent reoxygenation can expose the myocardium to oxidative stress, which can result in a cascade of events leading to tissue injury, tissue death, and myocardial dysfunction. In a rat model of hypoxic injury to the myocardium (exposure to 60 minutes of hypoxia), dexmedetomidine administered prior to, but not after, hypoxia significantly improved the development of left ventricular pressure after reoxygenation.<sup>33</sup> This effect was blocked by the administration of yohimbine, an  $\alpha_2$ -adrenergic antagonist. In a separate study, dexmedetomidine increased the dysrhythmogenic dose of epinephrine in halothane-anesthetized dogs (mean dose of 3 mcg/kg/min in control animals vs. 6 mcg/kg/min in animals receiving dexmedetomidine).<sup>34</sup>

One area of significant controversy, and one that may have significant clinical impact, is the effect on pulmonary vascular resistance (PVR). Despite the relative wealth of information regarding the systemic hemodynamic effects of dexmedetomidine, there is a relative paucity of information regarding its pulmonary vascular effects. In six healthy, instrumented sheep, dexmedetomidine (2 mcg/kg during 1 minute) has been shown to transiently increase mean pulmonary artery pressure (MPAP) and PVR.<sup>35</sup> PVR increased from a baseline value of  $81 \pm 16$  to a maximum of  $141 \pm 27$  dynes/s/cm<sup>5</sup> and MPAP increased from  $15 \pm 1$  to  $18 \pm 0$  mm Hg. A corresponding increase in MAP ( $86 \pm 2$  to  $93 \pm 6$  mm Hg) and systemic vascular resistance ( $1416 \pm 83$  to  $1889 \pm 64$  dynes/s/cm<sup>5</sup>) occurred. No significant change in pulmonary capillary wedge pressure was noted. Similar transient pulmonary hemodynamic changes have been reported in healthy human volunteers with graded dexmedetomidine infusions to achieve a plasma concentration of 1.9 ng/mL.<sup>36</sup> Given the obvious potential clinical impact of these effects, especially in patients with baseline elevations in MPAP or PVR, future studies are needed to delineate these effects and define their clinical significance.

### Respiratory Effects

**Ventilation.** A significant concern with any sedative agent is the potential for direct respiratory depression or potentiation of respiratory depression caused by other agents such as opioids. Belleville et al<sup>10</sup> evaluated the ventilatory effects of increasing doses of dexmedetomidine (0.25, 0.5, 1, and 2 mcg/kg during 2 minutes) in 37 healthy adult volunteers. The ventilatory effects were evaluated by measurement of oxygen saturation (SaO<sub>2</sub>) using pulse oximetry, PaCO<sub>2</sub>, CO<sub>2</sub> response curves during CO<sub>2</sub> rebreathing, and respiratory inductance plethysmography. PaCO<sub>2</sub> increased significantly, with the two highest doses of dexmedetomidine with the maximum effect noted at 10 minutes following the dose. The average PaCO<sub>2</sub> increase from baseline was 5.0 and 4.2 mm Hg with the 1.0 and 2.0 mcg/kg dose, respectively. The effect persisted for 60 minutes following 1 mcg/kg and for 105 minutes following 2 mcg/kg. Resting ventilation was decreased following 1.0 and 2.0 mcg/kg, with the maximal effect noted at 60 minutes following the dose. In patients receiving 2.0 mcg/kg, minute ventilation decreased from  $8.7 \pm 0.7$  to  $6.3 \pm 1.5$  L/min ( $P < 0.05$ ). The decrease was predominantly caused by decreased tidal volume with less of an effect on respiratory rate.

Significant changes were also noted when evaluated using CO<sub>2</sub> response curves as the minute ventilation at an ETco<sub>2</sub> of 55 mm Hg was depressed following the 1.0 and 2.0 mcg/kg doses. Additionally, the authors commented that they noted short episodes of apnea and irregular breathing in some of the subjects. These occurred more commonly with the two highest doses (7 of 10 who received 2 mcg/kg and 5 of 6 who received 1 mcg/kg vs. 1 of 6 with both the 0.5 and 0.25 mcg/kg dose). Respiratory inductance plethysmography tracings of abdominal and thoracic movements indicated that these respiratory problems were obstructive and not central in nature. Although there were decreases in SaO<sub>2</sub> with the obstructive episodes, the mean room air SaO<sub>2</sub> remained above 95% following all of the doses of dexmedetomidine. The SO<sub>2</sub> decrease was greatest at 10 minutes following 1 mcg/kg with a decrease from  $98.5\% \pm 0.7\%$  to  $96.2\% \pm 1.3\%$ , and at 60 minutes following 2.0 mcg/kg with a decrease from  $98.3\% \pm 0.8\%$  to  $95.4\% \pm 1.2\%$ . Similar respiratory effects have been demonstrated in experimental animals, although a paradoxical effect has been noted with less of an effect on ventilation when evaluating 1 versus 10 mcg/kg in one study and 10 or 30 mcg/kg versus 50 mcg/kg in another.<sup>37-39</sup>

Somewhat conflicting results are reported in a study comparing the respiratory effects of dexmedetomidine with remifentanyl in a cohort of six healthy adult volunteers.<sup>40</sup> Compared with baseline,

remifentanyl infusions to achieve a step-wise plasma concentration of 1, 2, 3, and 4 ng/mL resulted in significant respiratory depression with a decrease in respiratory rate and minute ventilation, increased PaCO<sub>2</sub>, blunting of the CO<sub>2</sub> response curve, and apnea resulting in oxygen desaturation. In contrast, during step-wise dexmedetomidine infusions to achieve plasma concentrations of 0.6, 1.2, 1.8, and 2.4 ng/mL, there was an increase in respiratory rate, a decrease in the hypopnea/apnea index when compared with baseline, and no change in the ETco<sub>2</sub>. With dexmedetomidine, the authors also noted in some patients a periodic increase in minute ventilation during CO<sub>2</sub> response curves (hypercapnic arousal), which correlated with changes in the Bispectral Index. The authors relate that similar changes occur during natural sleep and that these findings may relate to the mechanism of action of dexmedetomidine in the locus ceruleus and its convergence on the natural sleep pathway. The authors conclude that dexmedetomidine stands apart from other sedatives in that it seemed clinically safe from a respiratory point of view, even in doses high enough to cause unresponsiveness.

Furst and Weinger<sup>41</sup> found similar effects when evaluating the respiratory effects of dexmedetomidine (10 and 30 mcg/kg) and alfentanil in rats. When compared with saline control, dexmedetomidine in either dose had no effect on PaO<sub>2</sub>, PaCO<sub>2</sub>, and pH, whereas the administration of alfentanil resulted in a decrease in pH and PaO<sub>2</sub> and an increase in PaCO<sub>2</sub>. The administration of dexmedetomidine had no additional effect in rats that had received alfentanil and, in fact, the higher dose of dexmedetomidine (30 mcg/kg) decreased the acidosis and hypercapnia, which occurred following alfentanil, and did not appear to potentiate opioid-induced respiratory depression. Despite these findings, ongoing monitoring of respiratory function appears warranted, especially in high-risk patients or those receiving other agents that may depress respiratory function, especially given the report, albeit anecdotal, of central apnea after a general anesthetic that included dexmedetomidine.<sup>42</sup>

**Airway reactivity.** Dexmedetomidine may provide some protection in patients at risk for airway reactivity and bronchoconstriction. In a study in mongrel dogs, the intravenous, but not the inhaled, administration of dexmedetomidine prevented histamine-induced bronchoconstriction.<sup>43</sup> The effect of aerosolized histamine on airway bronchoconstriction was evaluated using high-resolution computed tomography. Aerosolized histamine constricted the airways to  $66\% \pm 27\%$  of baseline compared with  $87\% \pm 30.4\%$  of baseline, when the animals were pretreated with intravenous dexmedetomidine.

### Central Nervous System Effects

**Sedation.** Clinical studies in humans and experimental trials in both humans and animals have demonstrated the sedative effects of dexmedetomidine.<sup>9,10,36,44,45</sup> In 10 healthy male volunteers, sequential 40-minute infusions of dexmedetomidine were administered to achieve plasma concentrations of 0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 ng/mL.<sup>36</sup> The visual analogue sedation score (0 = very alert and 100 = very sedated) increased by  $36 \pm 27$  and  $62 \pm 18$  from a baseline of 0 with the first two targeted infusions. The two volunteers who received the highest incremental dose could not be aroused, even with vigorous shaking. Picture recall and recognition were preserved during the first incremental infusion, but were 0% (0 of 10) and 20% (2 of 10), respectively, with the third incremental infusion level.

Qualitatively, dexmedetomidine induces a sedative response that exhibits properties similar to natural sleep.<sup>44,45</sup> Studies using functional magnetic resonance imaging indicate that the blood oxygen level-dependent signal, which correlates with local brain activity, changes with dexmedetomidine-induced sedation in a similar fashion to that seen during natural sleep compared with the markedly different pattern that occurs with midazolam.<sup>45</sup> Nelson et

al<sup>45</sup> assessed c-fos expression in sleep-promoting brain nuclei in rats using immunohistochemistry and in situ hybridization.

Dexmedetomidine induced a qualitatively similar pattern of c-fos expression in rats as that seen during nonrapid eye movement sleep (a decrease in the locus ceruleus and tuberomammillary nucleus and an increase in the ventrolateral nucleus). These effects were attenuated by atipamezole and did not occur in rats that lack  $\alpha_2$ -adrenergic receptors.

**Intracranial pressure and cerebral perfusion pressure.** Major concerns of any sedative agent in the trauma patient are potential effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Several studies have attempted to evaluate the effects of dexmedetomidine on ICP, CPP, as well as cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMRO<sub>2</sub>). Talke et al<sup>46</sup> evaluated the effects of dexmedetomidine on ICP and CPP in 16 adults (7 dexmedetomidine and 9 placebo patients) following transphenoidal resection of a pituitary tumor. Postoperatively, dexmedetomidine was administered by a computer-controlled infusion to achieve a plasma concentration of 600 pg/mL. ICP was measured from a lumbar intrathecal catheter. No change in ICP was noted in patients receiving dexmedetomidine. The highest ICP values in the dexmedetomidine patients were 19 and 20 mm Hg. Although no change in CPP occurred over time in the placebo patients, there was a decrease in CPP in patients receiving dexmedetomidine ( $95 \pm 8$  to  $78 \pm 6$  mm Hg,  $P < 0.05$ ).

Similar effects on ICP were noted in an animal study with escalating doses of dexmedetomidine (20, 80, and 320 mcg/kg).<sup>47</sup> There were no effects on ICP in animals in the baseline state and also in animals with intracranial hypertension (mean baseline ICP, 16.8 mm Hg) induced by a cryogenic lesion. Dexmedetomidine has also been shown to lower intraocular pressure in animals with both normal and elevated intraocular pressure.<sup>48</sup>

Both animal and human studies have demonstrated a reduction in cerebral blood flow (CBF) following the administration of dexmedetomidine.<sup>49,50</sup> Karlsson et al<sup>49</sup> demonstrated a reduction of CBF following the administration to dogs anesthetized with 0.9% halothane; however, the authors noted that because of their study design, they could not determine if dexmedetomidine has a direct cerebral-vasoconstricting effect or if it merely cancelled the cerebral vasodilatation induced by halothane. Prielipp et al<sup>50</sup> used positron emission tomography scans to evaluate changes in CBF with dexmedetomidine in nine healthy adult volunteers.

Dexmedetomidine was administered as a bolus dose of 1 mcg/kg followed by an infusion of either 0.2 (low dose) or 0.6 mcg/kg/hr. Global CBF (mL/100 g/min) decreased from a mean baseline value of 91 to 64 (low dose) and 61 (high dose).

**Seizure threshold.** Another issue of importance in the patient with traumatic brain injury may be the relative anticonvulsant or proconvulsant effect of agents used for sedation or analgesia. To date, the literature regarding these effects of dexmedetomidine are mixed, with four different reports examining the relative proconvulsant and anticonvulsant effects of dexmedetomidine when coadministered with other medications.<sup>51-54</sup> Mirski et al<sup>51</sup> demonstrated a proconvulsant effect of dexmedetomidine (doses of 100 and 500 mcg/kg, but not 20 mcg/kg) in rats treated with pentylenetetrazol and showed that the effect was blocked by the  $\alpha_2$ -adrenergic antagonist, atipamezole. They suggested that their data were consistent with previous data demonstrating that inhibition of central noradrenergic transmission facilitates seizure expression. Similar results were reported by Miyazaki et al,<sup>52</sup> who demonstrated that dexmedetomidine (doses of 10 and 100 mcg/kg, but not 1 mcg/kg) reduced the seizure threshold during enflurane anesthesia in cats. Anticonvulsant properties of dexmedetomidine were demonstrated by two other groups of investigators. Whittington et al<sup>53</sup> demonstrated that dexmedetomidine (20 mcg/kg followed by an

infusion of 1 mcg/kg/min) significantly increased the dose of cocaine required to cause seizures in Sprague-Dawley rats. Cocaine was infused at 1.25 mg/kg/min and the investigators noted that rats treated with dexmedetomidine manifested seizures at  $49.3 \pm 14.8$  minutes versus  $25.0 \pm 7.7$  minutes in the control animals. Likewise, an anticonvulsant effect of dexmedetomidine was demonstrated by Tanaka et al<sup>54</sup> in Sprague-Dawley rats in their model of local anesthetic toxicity. The dose of either levobupivacaine or bupivacaine required to cause seizures was greater in rats treated with dexmedetomidine than in control animals. Although this may initially seem to be a beneficial effect, one must wonder as to whether this would eliminate an early warning sign of local anesthetic toxicity, with the first manifestation being the difficult-to-treat cardiotoxicity rather than the generally more treatable central nervous system (CNS) toxicity.

**Neuroprotection.** One of the more intriguing aspects of dexmedetomidine is its potential to ameliorate CNS sequelae during ischemic injury. Its efficacy in this regard was originally thought to relate to the deleterious CNS effects of endogenous catecholamines, which are released during ischemic injury to the CNS, and the ability of dexmedetomidine to blunt this catecholamine surge. Various animal models with complete and incomplete as well as transient and permanent ischemic injury have attempted to define the protective effects of dexmedetomidine during such injury. Hoffman et al<sup>55</sup> evaluated the effect of dexmedetomidine on neurologic and histopathologic outcome from incomplete cerebral ischemia in rats anesthetized with 70% nitrous oxide and fentanyl. Dexmedetomidine was administered in a dose of either 10 or 100 mcg/kg intraperitoneally 30 minutes prior to ischemia, which was produced by 30 minutes of unilateral carotid occlusion combined with hypotension induced by phlebotomy. After 30 minutes, the carotid occlusion was removed and the withdrawn blood was reinfused. Dexmedetomidine blunted the endogenous release of epinephrine and norepinephrine as well as improved both histopathologic and the neurologic outcome scores when compared with control animals and those animals that received dexmedetomidine plus atipamezole. Also of note, serum glucose concentrations were significantly higher in animals receiving dexmedetomidine. The authors relate this to  $\alpha_2$ -adrenergic inhibition of insulin release.

Kuhomen et al<sup>56</sup> evaluated the potential neuroprotective effects of dexmedetomidine in gerbils exposed to 5 minutes of bilateral carotid occlusion. Dexmedetomidine (3 or 30 mcg/kg) was administered prior to and then for 48 hours after the injury or only following the injury. Histopathologic outcome of neuronal cells in the CA1 and CA3 regions of the hippocampus and the dentate gyrus was examined at 1 week postinjury. None of the treatments had any effect on the histopathologic outcome in the CA1 region, while there was a significant decrease in the number of ischemic cells in the CA3 region in rats that received 3 mcg/kg of dexmedetomidine prior to the injury, but not in rats receiving 30 mcg/kg of dexmedetomidine prior to the injury, or in either dose if administered after the injury. In the dentate hilus, decreased numbers of ischemic cells were noted in rats that received 3 mcg/kg of dexmedetomidine prior to the injury and those that received 30 mcg/kg of dexmedetomidine after the injury. The authors concluded that low-dose dexmedetomidine had neuroprotective effects if administration was started prior to the ischemic insult and continued for 48 hours following it.

Additional information is provided by the same group of investigators in a model comparing transient (90 minutes) and permanent ischemia using occlusion of the middle cerebral artery (MCA) in rats.<sup>57</sup> Dexmedetomidine was administered after MCA occlusion as a bolus of 3 mcg/kg followed for 120 minutes by an infusion of either 3 or 6 mcg/kg/hr. The authors noted a statistically significant increase in the infarct size when comparing transient versus permanent ischemia. No effect of dexmedetomidine was

noted in the animals subjected to a permanent ischemic injury and the authors suggested that, although it was not statistically significant, there was a trend toward decreased infarct size following transient ischemia in animals treated with the higher dose of dexmedetomidine. The infarct volumes in both the cortex and the brainstem were 20%-30% less in dexmedetomidine-treated animals compared with the control animals.

The neuroprotective effects of dexmedetomidine may also have clinical applications in the neonatal arena. Dexmedetomidine decreased infarct size and histopathologic evidence of neuronal death in term, 5-day old mice that received an intracerebral injection of the *N*-methyl-D-aspartate (NMDA) agonist, ibotenate.<sup>58</sup> An NMDA agonist was chosen because of the evidence implicating the excessive release of glutamate as a causative factor in the development of hypoxic-ischemic encephalopathy and periventricular white matter lesions in premature infants.

The mechanism of action for the neuroprotective effect of dexmedetomidine was presumed to relate to its control of endogenous catecholamine release during ischemia. However, recent evidence has questioned this theory. Although dexmedetomidine has been shown to suppress circulating catecholamine concentrations during cerebral ischemia in rats, it does not suppress brain norepinephrine and glutamate levels, thereby suggesting another mechanism for its neuroprotective effects.<sup>59</sup> Currently, it has been postulated that the effect is mediated by increased expression of active (autophosphorylated) focal adhesion kinase (FAK), a nonreceptor tyrosine kinase that plays a role in cellular plasticity and survival as well as a reduction in caspase-3 expression (a proapoptotic factor).<sup>60</sup>

**Miscellaneous.** Additional effects related to the central and peripheral nervous system include antishivering and prevention of opioid-induced muscle rigidity, the latter being demonstrated in an animal model using hindlimb electromyographic activity in which dexmedetomidine abolished increased electromyographic activity associated with alfentanil administration.<sup>41</sup> Another unique property of the  $\alpha_2$ -adrenergic agonists is their ability to prevent or treat shivering in various clinical scenarios.<sup>61,62</sup> Jalonen et al<sup>61</sup> randomized 80 patients scheduled for coronary artery bypass grafting to receive either saline placebo or dexmedetomidine starting after the induction of anesthesia. Dexmedetomidine decreased the incidence of fentanyl-induced muscle rigidity (15/40 vs. 33/40 patients) and postoperative shivering (13/40 vs. 23/40 patients).

When compared with meperidine in healthy adult volunteers, the shivering threshold was  $36.0^\circ\text{C} \pm 0.5^\circ\text{C}$  with dexmedetomidine ( $P < 0.001$  compared with control),  $35.5^\circ\text{C} \pm 0.6^\circ\text{C}$  with meperidine ( $P < 0.001$  compared with control),  $34.7^\circ\text{C} \pm 0.6^\circ\text{C}$  with dexmedetomidine and meperidine ( $P < 0.001$  compared with control), and  $36.7^\circ\text{C} \pm 0.3^\circ\text{C}$  in control patients.<sup>62</sup> These effects may make dexmedetomidine a useful agent for sedation as well as the prevention of shivering in patients with closed-head injury or those who are postasphyxial arrest in whom hypothermia is used as a therapeutic agent.

### Miscellaneous Effects

**Gastrointestinal motility.** Alterations in gastrointestinal (GI) motility and delays in gastric emptying are of particular concern in the perioperative period and in critically ill ICU patients, in whom it may interfere with enteral feeding, lead to bacterial overgrowth, and promote bacterial translocation. Given these concerns, the effects of sedative and analgesic agents on GI motility must be entertained when decisions are made regarding the optimal sedation regimen. In a whole-animal model (rat), Asai et al<sup>63</sup> compared the effects of clonidine, dexmedetomidine, and morphine on GI transit time and

gastric emptying using radio-labelled sodium chromate. All three agents strongly inhibited GI transit time in a dose-dependent manner. Clonidine and dexmedetomidine weakly inhibited gastric emptying time and morphine's effect was greater. Gastric emptying, defined as the percentage of radioactivity that had entered the small intestine at 30 minutes, was 88.2% in the control group, 70.9% with clonidine, 78% with dexmedetomidine, and 23% with morphine. Herbert et al<sup>64</sup> compared the effects of clonidine and dexmedetomidine in an in vitro segment of guinea pig ileum. In isolated segments of the ileum, the pressure required to induce peristalsis was measured. Inhibition of GI motility as manifested by the requirement for an increased pressure to stimulate peristalsis was noted for both clonidine and dexmedetomidine, but was markedly greater with dexmedetomidine.

**Adrenocortical function.** Imidazole compounds such as etomidate have been shown to inhibit adrenocortical function and are no longer recommended for prolonged infusions in the ICU setting. Like etomidate, dexmedetomidine is an imidazole compound and therefore, appropriately so, there may be concerns regarding its effect on steroidogenesis. This issue has been addressed in a combined in vitro and animal study as well as a clinical trial. In a series of in vitro and animal studies, Maze et al<sup>65</sup> investigated the effects of dexmedetomidine on steroidogenesis, on binding to glucocorticoid receptors, and on adrenocorticotrophic hormone (ACTH)-stimulated release of corticosterone. The authors concluded that in concentrations that are used clinically to provide sedation or anesthesia, dexmedetomidine does not cause the clinically significant depression of adrenocortical function that occurs with etomidate, and an important biologic effect on steroidogenesis probably will not occur. However, the studies did demonstrate that high doses of dexmedetomidine are capable of inhibiting steroidogenesis.

In a clinical trial, Venn et al<sup>66</sup> randomized 20 adult patients who required sedation during mechanical ventilation to receive either propofol or dexmedetomidine. There was no difference in cortisol, ACTH, prolactin, and glucose concentrations between the two groups. However, some of the dexmedetomidine patients had abnormal ACTH stimulation tests, although these were attributed to their acute surgical illness and not the dexmedetomidine. None of the patients were believed to be at risk for adrenocortical failure, or manifested symptoms related to adrenal dysfunction according to the authors. The failure to meet the criteria for an acceptable ACTH stimulation test varied according to the criteria used. If an acceptable response was a peak cortisol level following ACTH administration of  $\geq 400$  nmol/L, 9 of 10 patients had a normal response. If the peak cortisol level following ACTH administration was  $\geq 550$  nmol/L, 8 of 10 had a normal response. However, if there was a requirement to increase the serum cortisol by 200 nmol/L, only 5 of 10 met the criteria. Despite these findings, the authors concluded that dexmedetomidine does not inhibit adrenal steroidogenesis when used for short-term sedation after surgery, and that the pattern of serum cortisol and ACTH levels was not similar to what was reported with etomidate administration.

### White blood cell function and inflammatory response.

Previous studies have suggested that several anesthetic agents may inhibit various aspects of white blood cell (WBC) function, including chemotaxis, phagocytosis, and intracellular killing.<sup>67</sup> In an in vitro study, dexmedetomidine was found to have no effect on WBC chemotaxis, phagocytosis, or superoxide anion production, leading the authors to conclude that there is no concern regarding the use of this agent in patients with acute infectious processes.<sup>68</sup> However, the authors also cautioned that their data also suggest that there are no beneficial effects of dexmedetomidine in disease processes that involve auto-tissue injury caused by neutrophils. Despite these findings, there are preliminary data to suggest that dexmedetomidine may act to modify the mediators of the

inflammatory response. In the previously mentioned study of Venn et al,<sup>66</sup> which randomized patients to receive either propofol or dexmedetomidine for sedation during mechanical ventilation, there was a decrease in interleukin-6 levels from baseline in patients receiving dexmedetomidine with no change in patients receiving propofol. A similar effect has been demonstrated in laboratory animals.<sup>65</sup> Additional work has demonstrated that the ability of dexmedetomidine to control the systemic inflammatory response may be beneficial during endotoxemia.<sup>69</sup> Taniguchi et al<sup>68</sup> randomized rats to (1) endotoxin administration, (2) saline control, (3) dexmedetomidine, or (4) endotoxin + dexmedetomidine. Mortality rates at 8 hours after the administration of endotoxin were 94%, 10%, 0%, and 44%, respectively, in the four groups. Hypotension, increases in tumor necrosis factor and interleukin-6 concentrations, and the infiltration of neutrophils in the airspaces and vessel walls were less in the rats that received dexmedetomidine after endotoxin than in rats that received endotoxin alone.

**Neuromuscular blockade.** An animal study and a human study have evaluated the effects of dexmedetomidine on neuromuscular blockade.<sup>69,70</sup> In a rat a model, vecuronium was administered by continuous infusion to produce a depression of T1 of the train-of-four (TOF) to  $53\% \pm 2\%$  of baseline.<sup>69</sup> Dexmedetomidine was administered as a bolus dose (10, 30, or 100 mcg/kg) and the T1 was measured for the ensuing 60 minutes. No change occurred in the T1 height during the 30 minutes following any of the three doses of dexmedetomidine. Although at later times there were minor differences between the groups, the authors concluded that these effects were unlikely to be of clinical significance. Similar findings were reported by Talke et al<sup>70</sup> in a study involving 10 healthy adult volunteers anesthetized with alfentanil and propofol. Rocuronium was administered by continuous infusion to produce a 50% decrease from baseline of the T1 value. Dexmedetomidine was administered by a computer-controlled infusion to produce a plasma concentration of 0.6 ng/mL for 45 minutes. T1 values decreased from  $51\% \pm 2\%$  to  $44\% \pm 9\%$  ( $P < 0.0001$ ). There was also a statistically significant increase in plasma rocuronium concentrations during the dexmedetomidine infusion. The authors concluded that dexmedetomidine does not have direct effects at the neuromuscular junction, but rather that it alters rocuronium pharmacokinetics. The authors also emphasized, as in the previous study, that this effect is unlikely to be of clinical significance.

## Clinical Applications

### Perioperative Applications

Clinical trials have demonstrated several of the potential perioperative effects of dexmedetomidine including a reduction of the requirements for both intravenous and inhalational anesthetic agents, improved hemodynamic stability, decreased requirements for  $\beta_2$ -adrenergic antagonists in patients with cardiovascular disease, and a decreased emergence delirium following general anesthesia in pediatric patients.<sup>11,15,17,20,21,22,26,60</sup> Dexmedetomidine has been used as a premedication, as an intraoperative infusion, by intraoperative bolus dosing, and for postoperative sedation in both intubated and nonintubated patients.

**Preoperative administration (premedication).** Jaakola et al<sup>71</sup> randomized 20 adults undergoing hysterectomy to receive either dexmedetomidine, 2.5 mcg/kg intramuscularly 60 minutes prior to surgery and intravenous saline, or intramuscular midazolam and intravenous fentanyl. Both premedication regimens resulted in sedation and anxiolysis. Intraoperatively, systolic and diastolic BP were 15% and 13% lower in patients who received dexmedetomidine and HR was an average of 9 beats/minute less. Supplemental

fentanyl was required more often in patients premedicated with midazolam-fentanyl versus dexmedetomidine (3.5 vs. 2.5 supplemental doses), with the total amount of fentanyl being 57% less in patients premedicated with dexmedetomidine.

Dexmedetomidine premedication decreases the induction dose requirements for barbiturates and the response to endotracheal intubation.<sup>72</sup> Twenty-four adults of ASA I or II class were randomized to receive dexmedetomidine 0.6 mcg/kg or placebo 10 minutes prior to anesthetic induction. Dexmedetomidine decreased thiopentone requirements ( $4.4 \pm 0.9$  vs.  $6.9 \pm 1.6$  mg/kg,  $P < 0.001$ ), attenuated the cardiovascular responses (HR and BP) to endotracheal intubation, blunted the intraoperative increase in plasma norepinephrine concentrations, decreased intraoperative fentanyl requirements, and decreased postoperative oxycodone needs.

Jaakola et al<sup>73</sup> randomized 30 adult patients to placebo or dexmedetomidine (1 mcg/kg) prior to intravenous regional anesthesia for hand surgery. Following dexmedetomidine, there was a 16%-20% decrease from baseline of HR and BP. Dexmedetomidine decreased the need for intraoperative supplemental intravenous fentanyl (12 of 15 in the placebo group vs. 4 of 15 who received dexmedetomidine,  $P = 0.009$ ). Dexmedetomidine also blunted the increase in plasma concentration of norepinephrine and epinephrine that occurred with tourniquet inflation. These data suggest the potential role of dexmedetomidine as a component of sedation during regional anesthesia.

Similar results were demonstrated in a study of 96 women undergoing abdominal hysterectomy.<sup>74</sup> The patients were randomized to receive saline, dexmedetomidine (0.3 or 0.6 mcg/kg), or fentanyl (2 mcg/kg) as a single bolus dose 10 minutes prior to anesthetic induction. Although HR and BP increased in all groups following endotracheal intubation, the HR and BP response was significantly less with high-dose dexmedetomidine compared with placebo, and the HR response was significantly less with high-dose dexmedetomidine versus fentanyl (HR increase of  $18 \pm 3$  vs.  $26 \pm 3$  beats/minute). Intraoperatively, the isoflurane requirement was decreased with high-dose dexmedetomidine (0.35%) compared with saline (0.47%) and fentanyl (0.48%).

Intraoperative administration (balanced anesthetic technique). Jalonon et al<sup>61</sup> randomized 80 adults scheduled for coronary artery to placebo or dexmedetomidine. Dexmedetomidine was administered at 50 ng/kg/min for 30 minutes prior to anesthetic induction, followed by an intraoperative infusion. In addition to decreasing the incidence of fentanyl-induced muscle rigidity (15/40 vs. 33/40 patients) and postoperative shivering (13/40 vs. 23/40 patients), dexmedetomidine decreased the intraoperative requirements for fentanyl and enflurane.

Several other studies have demonstrated the ability of dexmedetomidine to decrease anesthetic requirements as well as improve intraoperative stability.<sup>75-77</sup> In a volunteer study, dexmedetomidine was administered to achieve a plasma concentration of either 0.3 or 0.6 ng/mL.<sup>75</sup> The end-tidal isoflurane concentration at which 50% of the participants responded to a titanic stimulus was 1.05% during the control state, 0.72% with low-dose dexmedetomidine, and 0.52% with high-dose dexmedetomidine. Additionally, the authors noted that isoflurane did not alter the pharmacokinetics of dexmedetomidine. Additional information regarding the ability of dexmedetomidine to decrease inhalational anesthetic requirements is provided by Aho et al<sup>76</sup> in their study of 20 women undergoing gynecologic surgery. Maintenance anesthesia consisted of 70% nitrous oxide, fentanyl 2 mcg/kg, and isoflurane titrated according to hemodynamic response. Dexmedetomidine, administered as a bolus (170 ng/kg) prior to anesthetic induction and then continued intraoperatively as an infusion of 10 ng/kg/min, reduced isoflurane requirements by more than 90%. Five of 10 patients in the dexmedetomidine group did not require isoflurane

compared with 2 of 10 in the control group. A postoperative interview conducted on day 1 revealed no evidence of recall.

Dexmedetomidine has also been shown to reduce the requirements of IV anesthetic agents including thiopental and propofol.<sup>78-80</sup> Women scheduled for dilation and curettage were randomized to receive a single bolus dose of dexmedetomidine (0.5 mcg/kg) or saline placebo 15 minutes prior to transport to the operating room.<sup>78</sup> There was a 30% reduction of the thiopental dose required to complete the procedure in patients who received dexmedetomidine ( $316 \pm 79$  mg vs.  $456 \pm 151$  mg). A subsequent study evaluated the thiopental dose required to achieve burst suppression on the electroencephalogram in healthy adult volunteers.<sup>79</sup> As with the previous study, dexmedetomidine-treated patients required 30% less thiopental; however, the authors also evaluated pharmacokinetic parameters and found that dexmedetomidine decreased distribution volumes and distribution clearances of thiopental, thereby demonstrating that the mechanism of dexmedetomidine in reducing thiopental requirements may be at least in part the result of a pharmacokinetic effect.

Dutta et al<sup>80</sup> studied the interaction of propofol and dexmedetomidine. They noted that dexmedetomidine reduced the propofol plasma concentrations required to prevent a motor response to an electrical stimulus, the ability to hold a syringe, and maintain the eyelid reflex. The plasma concentration of propofol at which 50% of patients did not move to an electrical stimulus was 6.63 mcg/mL in the control patients and 3.89 mcg/mL during the administration of dexmedetomidine.

**Intraoperative administration (monitored anesthesia care and primary anesthetic technique).** Given its favorable physiologic effects, dexmedetomidine may find a role as part of monitored anesthesia care (MAC) combined with a regional anesthetic technique.<sup>71,81</sup> Arain and Ebert<sup>81</sup> randomized 40 adults receiving regional anesthetic techniques to MAC with dexmedetomidine (1 mcg/kg followed by an infusion of 0.4-0.7 mcg/kg/hr) or propofol (12.5-75 mcg/kg/hr). The sedative infusion was titrated to achieve a Bispectral Index of 70-80. Although sedation was achieved more rapidly with propofol (10 minutes vs. 25 minutes), after 25 minutes, no differences were noted between the two groups. The average MAP was higher with dexmedetomidine than with propofol ( $86 \pm 3$  vs.  $75 \pm 3$  mm Hg). Dexmedetomidine patients had a lower visual analog sedation scale, lower pain scores, and required less morphine in the postanesthesia care unit. No difference was seen in regard to recovery and discharge times. Additional intraoperative applications of dexmedetomidine have included sedation during awake craniotomy in both adults and pediatric patients.<sup>82,83</sup> One case series describes the use of dexmedetomidine in doses up to 10 mcg/kg/hr as the sole anesthetic in three adult patients with the maintenance of spontaneous ventilation, although one patient did require a chin lift for upper airway obstruction.<sup>84</sup>

**Postoperative analgesic effects.** The analgesic effects of dexmedetomidine have been demonstrated in both clinical and experimental trials.<sup>85-88</sup> Dexmedetomidine (1 mcg/kg) administered 10 minutes prior to anesthetic induction reduced morphine PCA requirements following abdominal surgery in adults by 28% during the first 24 hours postoperatively.<sup>86</sup> Similar findings were reported by Arain et al,<sup>87</sup> who randomized 34 adult patients who would require at least a 24-hour postoperative hospital admission to receive either placebo or an intraoperative infusion of dexmedetomidine (1 mcg/kg followed by 0.4 mcg/kg/hr for 4 hours). Patients who received dexmedetomidine required less morphine in the PACU ( $4.5 \pm 6.8$  vs.  $9.2 \pm 5.2$  mg). After 60 minutes in the PACU, 6 of 17 patients who received dexmedetomidine required morphine versus 15 of 17 in the control group.

Dexmedetomidine may also be a useful adjunct to epidural analgesia. Following thoracotomy, Wahlander et al<sup>89</sup> randomized patients to receive either dexmedetomidine (0.5 mcg/kg followed by an infusion of 0.4 mcg/kg/hr) or placebo in addition to thoracic epidural analgesia. Although there was no difference in the pain scores between the two groups, patients receiving dexmedetomidine required less supplemental analgesia with epidural fentanyl and had lower PaCO<sub>2</sub> values ( $40.3 \pm 4.1$  vs.  $43.9 \pm 4.3$  mm Hg). Adverse hemodynamic effects that required therapy were noted with dexmedetomidine, including bradycardia in one patient who was treated with atropine, and hypotension in four patients who responded to fluid. No sequelae of these hemodynamic changes were noted.

**Prevention of emergence delirium.** Three reports outline the successful use of dexmedetomidine to prevent emergence delirium following general anesthesia with sevoflurane or desflurane.<sup>90-92</sup> Ibacache et al<sup>90</sup> randomized 90 children to placebo or one of two doses of dexmedetomidine (0.15 or 0.3 mcg/kg) during general anesthesia with sevoflurane. There was no difference in the time to awakening and tracheal extubation. The incidence of emergence delirium was 37% with placebo, 17% with 0.15 mcg/kg dexmedetomidine, and 10% with 0.3 mcg/kg dexmedetomidine. Similar efficacy with the use of dexmedetomidine to prevent emergence agitation was demonstrated in the studies of both Hanafy et al<sup>91</sup> and Guler et al.<sup>92</sup> Hanafy et al randomized 46 children (4 to 12 years of age) undergoing adenotonsillectomy to dexmedetomidine (0.5 mcg/kg) or placebo administered during general anesthesia with desflurane. Patients who received dexmedetomidine had less agitation in the PACU (2/23 vs. 18/23,  $P < 0.05$ ), were less likely to require treatment for agitation (0/23 vs. 8/23,  $P < 0.05$ ), and had lower pain scores. No difference in time to emergence, time to tracheal extubation, PACU discharge time, or hemodynamic and respiratory variables were noted.

The third trial of the use of dexmedetomidine to prevent emergence agitation included 60 children (3 to 7 years of age) who were randomized to receive dexmedetomidine (0.5 mcg/kg) or placebo with maintenance anesthesia provided by sevoflurane.<sup>92</sup> As opposed to the two previous studies, Guler et al<sup>92</sup> administered dexmedetomidine 5 minutes prior to the completion of the surgery instead of after anesthetic induction. Dexmedetomidine decreased the incidence of emergence agitation (5/17 vs. 17/30,  $P < 0.05$ ). The incidence of severe pain was 7 of 30 (23%) with dexmedetomidine versus 16 of 30 (53%) with placebo ( $P < 0.05$ ). They also noted that the incidence of severe coughing on emergence and in the PACU was decreased with dexmedetomidine (0/30 vs. 6/30,  $P < 0.05$ ). However, there was a modest delay in the time to emergence ( $5.03 \pm 2.3$  vs.  $3.30 \pm 1.3$  minutes,  $P < 0.05$ ) and extubation ( $9.30 \pm 2.9$  vs.  $7.20 \pm 2.7$  minutes,  $P < 0.05$ ) with dexmedetomidine versus placebo, respectively.

### Procedural Sedation

Given its limited effects on hemodynamic and respiratory function, dexmedetomidine may be an effective agent for sedation during nonpainful procedures such as computed tomography and magnetic resonance imaging and radiation therapy. Preliminary data were provided by Nichols et al,<sup>93</sup> who used dexmedetomidine for "rescue sedation" during radiologic imaging in five pediatric patients, ranging in age from 11 months to 16 years, when chloral hydrate and midazolam were ineffective. Effective sedation was achieved using dexmedetomidine (loading dose of 0.3-1.2 mcg/kg followed by an infusion of 0.5-0.7 mcg/kg/hr) and allowed for the completion of the examination without adverse effects.

Two prospective trials have evaluated the efficacy of dexmedetomidine for sedation during radiologic imaging in pediatric patients. Koroglu et al<sup>94</sup> randomized 80 children (1 to 7 years of age)

to either dexmedetomidine or midazolam for sedation during magnetic resonance imaging. Dexmedetomidine was administered as a loading dose of 1 mcg/kg during 10 minutes followed by an infusion of 0.5 mcg/kg/hr, and midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 mcg/kg/hr. Inadequate sedation, defined as inability to complete the scan, was treated by a bolus dose of either midazolam or propofol. The quality of sedation was better and the need for rescue sedation was less (8 of 40 vs. 32 of 40) with dexmedetomidine compared with midazolam. No significant adverse effects on hemodynamic or respiratory function were noted in either group.

In an open label trial, Berkenbosch et al<sup>95</sup> evaluated the use of dexmedetomidine for sedation during magnetic resonance imaging in a cohort of 48 pediatric patients ranging in age from 5 months to 16 years. Dexmedetomidine was administered as a loading dose of 0.5 mcg/kg during 5 minutes and repeated as needed to achieve an acceptable level of sedation. Once adequate sedation was achieved, a continuous infusion was started that was equivalent in micrograms per kilogram per hour to the initial loading dose. Fifteen of the patients received dexmedetomidine after other agents had failed, and the other 33 received dexmedetomidine as the primary agent. Sedation was induced with a loading dose of  $0.92 \pm 0.36$  mcg/kg followed by an infusion of  $0.69 \pm 0.32$  mcg/kg/hr. Effective sedation was achieved in all patients. Although there was a statistically significant decrease in HR and BP, no values were outside of the normal range for age.  $ETCO_2$  measured from the nasal cannula exceeded 50 mm Hg in 7 of the 404 (1.7%) measurements. Recovery time was longer in patients who had received other agents prior to dexmedetomidine than in those who received dexmedetomidine as a primary agent ( $117 \pm 41$  vs.  $69 \pm 34$  minutes). Additional anecdotal reports have demonstrated the efficacy of dexmedetomidine for sedation in various clinical scenarios in pediatric patients, including cardiac magnetic resonance imaging and radiation therapy.<sup>96-98</sup>

Despite the successes outlined here, dexmedetomidine has not been effective as the sole agent for painful, invasive procedures. Tobias et al<sup>99</sup> noted that, although successful in other scenarios (sedation during mechanical ventilation and as an adjunct to controlled hypotension), dexmedetomidine did not provide effective sedation during gastroduodenoscopy in an 11-year-old patient. Likewise, Jalowiecki et al<sup>100</sup> found dexmedetomidine to be ineffective during colonoscopy in adults. Sixty-four patients were randomized to receive dexmedetomidine (1 mcg/kg during 15 minutes followed by 0.2 mcg/kg/hr), meperidine (1 mg/kg) plus midazolam (0.05 mg/kg) or fentanyl (100-200 mcg on demand). Supplemental analgesia with fentanyl was available as needed. The authors had planned to study 90 patients, but terminated the study early because of the inefficacy and high adverse effect profile that they noted in the dexmedetomidine group. With dexmedetomidine, 2 of 19 patients developed bradycardia with a HR less than 40 beats/minute, and 4 of 19 had hypotension (BP less than 50% of baseline). Supplemental fentanyl was required in 47% of patients receiving dexmedetomidine versus 42.8% of those receiving meperidine/midazolam. Time-to-home readiness was also longer with dexmedetomidine than with meperidine/midazolam or fentanyl.

Given its limited analgesic effects when used as the sole agent, dexmedetomidine is not an ideal agent for painful procedures if used alone. Anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be an effective combination in these scenarios.<sup>101,102</sup> Scher and Gitlin<sup>101</sup> reported the successful use of dexmedetomidine as a bolus of 1 mcg/kg followed by an infusion of 0.7 mcg/kg/hr combined with ketamine (15 mg followed by an infusion of 20 mg/hr) for procedural sedation (awake fiberoptic intubation in an adult patient). We have previously reported our experience with a combination of ketamine and dexmedetomidine for sedation during magnetic resonance imaging in three children

with trisomy 21 and obstructive sleep apnea.<sup>102</sup> Additionally, we have found that this combination provides effective sedation during cardiac catheterization in children (unpublished data). The combination of dexmedetomidine with ketamine makes pharmacologic sense as these two medications may prevent each other's adverse effects, in addition to having limited effects on respiratory function and providing adequate sedation. Dexmedetomidine may prevent the tachycardia, hypertension, salivation, and emergence phenomena from ketamine, and ketamine prevents the bradycardia and hypotension that has been reported with dexmedetomidine.<sup>103</sup>

### **Sedation During Mechanical Ventilation**

Sedation for up to 24 hours in initially intubated and mechanically ventilated adults is the only FDA-approved indication for dexmedetomidine. In one of the earlier studies, Venn et al<sup>11</sup> randomized adult patients who required mechanical ventilation following cardiac and general surgical procedures to receive dexmedetomidine in a dose of 1 mcg/kg during 10 minutes followed by an infusion of 0.2-0.7 mcg/kg/hr or placebo. Patients receiving dexmedetomidine required 80% less midazolam and 50% less morphine than placebo patients. Similar results were reported in a comparison of adults following cardiac and general surgical procedures who were randomized to dexmedetomidine or placebo with supplemental analgesia provided by morphine and propofol.<sup>104</sup> Patients receiving dexmedetomidine required approximately 50% less morphine and propofol.

A subsequent study by Venn and Grounds<sup>105</sup> randomized 20 adult patients who required mechanical ventilation for at least 8 hours following surgery to receive either dexmedetomidine or propofol. Depth of sedation, measured using the Bispectral Index monitor, was equivalent between the two groups; however, patients receiving dexmedetomidine required less supplemental sedation/analgesia with alfentanil (2.2-2.9 mg/hr vs. 0.65-1.2 mg/hr,  $P = 0.004$ ). No adverse effects were noted in either group. There was no difference in MAP between the groups, and the HR was lower with dexmedetomidine. Time to extubation was likewise similar between the two groups.

Similar efficacy when comparing a continuous infusion of propofol to dexmedetomidine was noted in a randomized trial of Herr et al<sup>106</sup> in 295 adults who received sedation following coronary artery bypass grafting surgery. Twenty-eight percent of the patients receiving dexmedetomidine required supplemental morphine analgesia during mechanical ventilation compared with 69% of the patients receiving propofol ( $P < 0.001$ ). Propofol patients required 4 times as much morphine as the patients receiving dexmedetomidine. A 5% incidence of ventricular tachycardia was noted with propofol versus 0% with dexmedetomidine ( $P = 0.007$ ). No clinically significant differences were noted in respiratory parameters or hemodynamic function. Fewer dexmedetomidine patients received  $\beta_2$ -adrenergic antagonists, nonsteroidal anti-inflammatory agents, antiemetics, and high-dose diuretics.

However, all of the literature does not favor dexmedetomidine. Corbett et al<sup>107</sup> randomized 89 adult patients to receive either dexmedetomidine or propofol for sedation following coronary artery bypass grafting surgery. They noted no difference in length of ICU stay or time until to extubation. Using postoperative satisfaction surveys, they noted a higher incidence of discomfort, pain, and sleeping difficulties in patients receiving dexmedetomidine compared with propofol. They concluded that dexmedetomidine does not offer any significant advantages over propofol.

To date, there is only one prospective trial regarding the use of dexmedetomidine during mechanical ventilation in infants and children. Tobias and Berkenbosch<sup>108</sup> randomized 30 infants and

children who required sedation during mechanical ventilation to receive either a continuous infusion of midazolam starting at 0.1 mg/kg/hr or a continuous infusion of dexmedetomidine starting at either 0.25 or 0.5 mcg/kg/hr. The efficacy of sedation was assessed using the Ramsay sedation score and the Bispectral Index with supplemental analgesia/sedation provided by intermittent doses of morphine as needed, with an increase of the midazolam or dexmedetomidine infusion in 20% increments if repeated doses of morphine were required. Dexmedetomidine at 0.25 mcg/kg/hr was as effective as midazolam at 0.22 mg/kg/hr, and a higher dose of dexmedetomidine (0.5 mcg/kg/hr) was more effective. The improved efficacy of the higher dose of dexmedetomidine was demonstrated by equivalent sedation scores and Bispectral Index with a decreased need for supplemental morphine (0.28 ± 0.12 mg/kg/24 hours with dexmedetomidine vs. 0.74 ± 0.5 mg/kg/24 hours with midazolam) as well as fewer patients (2/10 vs. 6/10) who manifested a Ramsay score of 1 at any time during the study protocol. Additionally, there were a decreased total number of Ramsay scores of 1 (5 with dexmedetomidine at 0.5 mcg/kg/hr vs. 14 with midazolam at a mean dose of 0.22 mg/kg/hr). The authors speculated that dexmedetomidine may be less effective in younger patients as five of the six patients who manifested a Ramsay score of 1 in either of the two dexmedetomidine groups (0.25 or 0.5 mcg/kg/hr) were less than 12 months of age.

A second report in infants and children regarding the use of dexmedetomidine during mechanical ventilation used dexmedetomidine as part of a rotating sedation regimen in an effort to prevent the development of tolerance and eliminate issues of withdrawal following prolonged sedation with a single agent.<sup>109</sup> The cohort for the study included patients who required 5-6 days of sedation and mechanical ventilation following laryngotracheoplasty, and included two patients, a 10- and a 14-month-old infant. Both patients were admitted to the pediatric ICU and received a continuous infusion of cis-atracurium titrated to maintain one twitch of the train-of-four. The sedation regimen included midazolam 0.1-0.2 mg/kg/hr with as needed doses of morphine on day 1, fentanyl 2-3 mcg/kg/hr with as needed doses of lorazepam on day 2, and dexmedetomidine 0.25-0.5 mcg/kg/hr with as needed doses of morphine on day 3. Midazolam and morphine were used on day 4 and fentanyl/lorazepam again on day 5. The authors noted no tolerance as there was no difference in the midazolam doses on day 1 versus day 4 or the fentanyl doses on day 2 versus day 5. Additionally, no patient developed signs of withdrawal and they were discharged from the hospital sooner when compared with a cohort of five historical control patients (day 6-7 vs. day 8-10) who had received a midazolam infusion with as needed morphine for the entire 5-day course.

To date, there are limited reports in adult or pediatric patients regarding the use of dexmedetomidine for more than 24-48 hours as a sedative during mechanical ventilation. Shehabi et al<sup>110</sup> retrospectively reviewed their experience with "long-term" dexmedetomidine infusions in 12 critically ill adult ICU patients. The median infusion time was 71.5 hours, with a range of 35 to 168 hours. Adequate sedation defined as a Ramsay sedation score of 2-5 was observed during 83% of the observation points. Sixteen of the patients required minimal supplementation sedation with midazolam (median dose of 4 mg/day) and 10 required minimal supplemental analgesia with morphine (median dose of 2 mg/day). They noted no evidence of hemodynamic rebound after abrupt cessation of dexmedetomidine. Hammer et al<sup>111</sup> reported the use dexmedetomidine for sedation for 4 days following tracheal resection in a 9-year-old boy. Dexmedetomidine was started when fentanyl and midazolam infusions in escalating doses were ineffective. Effective sedation was provided with a maximum dexmedetomidine dose of 0.5 mcg/kg/hr until postoperative day 4 when the patient was taken to the operating

room and his trachea was extubated.

### **Treatment of Withdrawal**

Various scenarios may arise in the ICU setting in which the patient manifests withdrawal symptoms. Tolerance and subsequent withdrawal may be iatrogenic, related to the prolonged use of opioids, benzodiazepines, or other agents for the provision of sedation and analgesia during mechanical ventilation, or may be the result of the use of illicit medications, ethanol, tobacco, or cannabinoids. Regardless of the agent responsible for withdrawal symptoms, the literature has demonstrated the efficacy of  $\alpha_2$ -adrenergic agonists such as clonidine in the treatment of such problems. The potential efficacy of dexmedetomidine in treating these issues is supported by animal studies, and anecdotal clinical reports have shown this agent to be effective in treating withdrawal symptoms from various agents including opioids and benzodiazepines.<sup>112-116</sup> The various anecdotal reports and case series have shown that dexmedetomidine is effective in both the adult and pediatric populations in the control of withdrawal that has occurred following the appropriate use of benzodiazepines and opioids for sedation in the ICU setting as well as withdrawal symptoms that have occurred from the use illicit substances including alcohol and cannabinoids. The advantages of dexmedetomidine over other  $\alpha_2$ -adrenergic agonists such as clonidine include its shorter half-life, allowing for easier titration and availability for IV administration.

### **Summary**

Dexmedetomidine (Precedex) is an  $\alpha_2$ -adrenergic agonist that shares physiologic similarities with clonidine. It is currently approved by the FDA for continuous infusions for up to 24 hours in adult ICU patients who are initially intubated and receiving mechanical ventilation. As with any sedative agent, the potential exists for adverse end-organ effects, although the current literature suggests that these events are generally uncommon with dexmedetomidine. Reported adverse cardiovascular effects include occasional episodes of bradycardia, with rare reports of sinus pause or cardiac arrest. Hypotension has been reported, as well as hypertension, the latter caused by peripheral  $\alpha_{2B}$ -agonism with peripheral vasoconstriction. Hypotension and bradycardia appear to be more common with the initial loading dose, in patients with comorbid cardiovascular disease, and when coadministered with other medications that have negative chronotropic effects. Although dexmedetomidine has no direct effects on myocardial function, decreased cardiac output may result from changes in HR and/or increases in afterload. Despite the potential for adverse consequences of the decreased HR and BP, preliminary perioperative data suggest a decreased incidence of ischemic episodes as well as the potential for decreased morbidity and mortality in patients with comorbid cardiovascular disease. Dexmedetomidine has been shown to modulate the sympathetic nervous system with blunting of the sympathetic stress response and decreased levels of endogenous epinephrine and norepinephrine. Animal data suggest an improvement of myocardial blood flow during ischemia as well as protection against postischemic depression of left ventricular function and catecholamine-induced arrhythmogenesis. Its effects on pulmonary vascular resistance remain somewhat controversial and require further study, although the preliminary data suggest the potential to increase pulmonary artery pressure and PVR via a mechanism similar to its effects on the peripheral vasculature and agonism at the  $\alpha_{2B}$ -adrenergic receptor of the vasculature.

There are somewhat conflicting reports in the literature regarding the effects of dexmedetomidine on ventilatory function, with some studies (both human and animal) suggesting some degree

of respiratory depression with mild increases of PaCO<sub>2</sub> (4-5 mm Hg), decreased minute ventilation, and decreased response to CO<sub>2</sub> challenge during performance of CO<sub>2</sub> response curves following bolus doses of 1 or 2 mcg/kg. Additionally, there is one case report of postoperative apnea that may be linked to dexmedetomidine. Despite these reports, other animal and human studies have shown no effect on respiratory function, and one anecdotal adult report outlines the maintenance of spontaneous ventilation with doses up to 10 mcg/kg/hr. Dexmedetomidine has been shown to protect against bronchoconstriction from a provocative inhalational challenge in an animal model.

The CNS effects include sedation and analgesia with prevention of recall and memory at higher doses. These effects are mediated via its central mechanism of action in the locus ceruleus. Animal data suggest that dexmedetomidine may induce a sleep-like state with electroencephalographic characteristics of nonrapid eye movement sleep. These properties may allow avoidance of the interruption of normal sleep cycles that is seen with other sedative agents and perhaps a decreased incidence of ICU delirium, thereby giving dexmedetomidine a significant advantage of other commonly used agents such as benzodiazepines.<sup>117</sup>

Despite its lack of direct effects on ICP, its hemodynamic effects may result in a decreased CPP. Both animal and human studies have demonstrated cerebral vasoconstriction with a decrease of CBF. Mixed results have been noted in animal studies regarding the anticonvulsant or proconvulsant effects of dexmedetomidine, with studies suggesting a proconvulsant effect when coadministered with either enflurane or pentylenetetrazol and an anticonvulsant effect when seizures are provoked by either cocaine or local anesthetic agents. Another intriguing CNS effect of dexmedetomidine is its potential neuroprotective activity during periods of ischemia. Although there are some discrepancies in the literature related to the mechanism of ischemia, its duration, the animal model used, and the dosing regimen of dexmedetomidine, the majority of the data tend to support the potential neuroprotective effects of dexmedetomidine when given prior to a transient ischemic injury. The neuroprotective effect appears to be lost if dexmedetomidine is given after the ischemic injury or with a permanent versus a transient injury. It has also been shown that this effect is provided despite the fact that serum glucose concentrations may increase following dexmedetomidine administration because of decreased endogenous insulin release. Although the neuroprotective effects were originally ascribed to control of the catecholamine surge that occurs with ischemia, this mechanism has now been questioned, with recent evidence favoring increased expression of active FAK, a nonreceptor tyrosine kinase that plays a role in cellular plasticity and a reduction in caspase-3 expression.

Although not FDA-approved for other clinical scenarios, given its beneficial physiologic effects and its limited adverse effect profile, there are numerous additional applications of dexmedetomidine that have been reported in the literature. It has seen great use in the perioperative arena, with several clinical trials demonstrating significant benefits from its preoperative, intraoperative, or postoperative administration, including preoperative sedation, prevention of opioid-induced muscle rigidity, reduction of intraoperative requirements for both inhalational and intravenous anesthetic agents, blunting of the surgical stress response with decreased endogenous catecholamine release, control of the hemodynamic response to endotracheal intubation, and decreased perioperative tachycardia. Preliminary data suggest that the control of perioperative tachycardia may result in a decreased incidence of perioperative cardiovascular morbidity in patients with coronary artery disease. It has been used for monitored anesthetic care in combination with regional anesthetic techniques. Postoperative benefits include a decreased incidence of postanesthesia shivering, a

decreased incidence of emergence delirium in pediatric patients after general anesthesia with sevoflurane or desflurane, and the potentiation of opioid and epidural analgesia.

Additional clinical applications include prevention or treatment of substance withdrawal, both iatrogenic and that related to illicit drug abuse, and for the provision of procedural-sedation during nonpainful radiologic imaging. However, the current literature suggests that it is not effective as a sole agent for painful procedures. For that indication, there may be a role for the combination of dexmedetomidine with analgesic agents such as ketamine for painful procedures. When used in this combination, the adverse effects of the two medications (salivation, hypertension, tachycardia, and emergence hallucinations with ketamine and hypotension and bradycardia with dexmedetomidine) may be avoided.

Dexmedetomidine is available in a 2-mL vial of a 100 mcg/mL solution. For continuous infusions, it is generally reconstituted in normal saline to a 4 mcg/mL solution, which can be administered via a peripheral or central vein. Acquisitions costs vary from \$50-\$80 per vial. Given its favorable sedative and anxiolytic properties combined with its limited effects on hemodynamic and respiratory function, there is growing interest in its use in various clinical scenarios and patient populations. It appears to be an agent that may be well suited in several areas for the care of the adult and pediatric trauma patient.

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## 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 al<sup>1</sup> 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](http://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 difficult<sup>2</sup>: age over 55 years, body mass index exceeding 26 kg/m<sup>2</sup>, 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,<sup>3</sup> with a version also in development that is specifically related to the trauma patient.<sup>4</sup>

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**

<b>Clinical history</b>	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.
<b>Mouth opening</b>	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.
<b>Mallampati view of oropharynx</b>	Rated from class I to IV.
<b>Thyromental distance</b>	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.
<b>Teeth</b>	Edentulous patients are always easier to intubate. Patients with poor teeth or prominent teeth may be more difficult to intubate.
<b>Tongue</b>	Tongue should not be large, immobile, or edematous.
<b>Head mobility</b>	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.”
<b>Trauma-related</b>	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"> <li>• Obesity with resulting redundant oropharyngeal tissue</li> <li>• Diagnosis of obstructive sleep apnea</li> <li>• Tonsillar hypertrophy (especially lingual tonsils)</li> <li>• Glottic/supraglottic/laryngeal edema</li> <li>• Vocal cord pathology (e.g., vocal cord polyps)</li> <li>• Maxillary or mandibular hypoplasia</li> <li>• Bulbar muscle weakness (e.g., myasthenia gravis)</li> <li>• Upper airway tumors or foreign bodies</li> <li>• Nasal obstruction (e.g., nasal polyps, deviated septum)</li> <li>• Trauma-related problems             <ul style="list-style-type: none"> <li>• Hematomas compressing the airway</li> <li>• Fractured larynx</li> <li>• Fractured maxilla</li> <li>• Fractured mandible</li> </ul> </li> </ul>
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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  $\alpha_2$ -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,<sup>3</sup> 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.<sup>5</sup> Careful attention to head and neck positioning and cervical immobilization are especially important components of patient care in patients with possible cervical trauma.<sup>6</sup> The acute management of a patient with spinal cord injury begins at the scene of the accident.<sup>7</sup> 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.<sup>8-10</sup> Clinical criteria for cervical spine clearance in the out-of-hospital setting have not been well validated<sup>11</sup> 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.<sup>12-18</sup> Lennarson et al<sup>17</sup> 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 al<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup>

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.<sup>22</sup> 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,<sup>23</sup> sufentanil,<sup>22</sup> and remifentanil<sup>24-29</sup> 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.<sup>30,31</sup> Neuroleptanalgesia using droperidol with fentanyl has also been suggested for sedation in awake intubations<sup>32,33</sup>; 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.<sup>34</sup> 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.<sup>35</sup>

## Dexmedetomidine: A Novel $\alpha_2$ -Receptor Agonist

Clinicians have used  $\alpha_2$ -receptor agonists since the 1970s to treat hypertension and withdrawal from long-term drug or alcohol abuse.<sup>36</sup> The prototype  $\alpha_2$ -agonist, clonidine, has since been recognized as a useful adjunct to anesthesia and analgesia. The newer  $\alpha_2$ -agonist, dexmedetomidine, is a more selective  $\alpha_2$ -agonist, with 8 times greater affinity for the  $\alpha_2$ -receptor than clonidine and is 1,620 times more potent as an  $\alpha_2$ -agonist than an  $\alpha_1$ -agonist.<sup>36,37</sup>

The effects of  $\alpha_2$ -agonists are mediated through transmembrane receptors, which belong to the G protein-coupled receptor superfamily.<sup>36</sup> The effector mechanisms of these G proteins are diverse and include adenylate cyclase, N-type voltage-gated calcium channels, potassium channels, Na<sup>+</sup>/H<sup>+</sup> exchange, and polyphosphoinositide hydrolysis. Such diversity may account for the different physiologic and clinical effects elicited by these receptors.<sup>38</sup>

$\alpha_2$ -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  $\alpha_2$ -receptors results in inhibition of noradrenalin release and neuronal firing.<sup>39</sup> A decrement in sympathetic activity, especially at the locus ceruleus, leads to sedation and hypnosis.<sup>40</sup> At the level of the medulla,  $\alpha_2$ -agonist activity at the dorsal motor nucleus of the vagus nerve may lead to bradycardia and hypotension.<sup>41</sup> In the spinal cord,  $\alpha_2$ -adrenoreceptors are found to be concentrated in the intermediolateral cell column and substantia gelatinosa.<sup>41</sup> The analgesic activity of  $\alpha_2$ -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.<sup>42,43</sup>

The actions of the  $\alpha_2$ -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,  $\alpha_2$ -agonists also lead to transient vasoconstriction and an increase in blood pressure with subsequent decrease in heart rate and cardiac output.<sup>44</sup>

Within the respiratory system, activation of  $\alpha_2$ -receptors leads to bronchodilation and attenuation of response to  $\text{CO}_2$  increase.<sup>38</sup>

In 1999, the recently released  $\alpha_2$ -agonist, dexmedetomidine, was approved by the Food and Drug Administration for short-term (<24 hours) sedation of the critically ill patient.<sup>45</sup> 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.<sup>46-48</sup>

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.<sup>49,50</sup>

Unlike clonidine, dexmedetomidine has a shorter half-life, making titration as an intravenous infusion possible.<sup>36,43</sup> 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.<sup>51-53</sup> Context-sensitive half-life after infusions of different durations is not known. Talke et al<sup>52</sup> 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.<sup>44,52</sup> Such consistent hemodynamic changes have not been found to increase morbidity and can be managed by increased IV fluids.<sup>54</sup> 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.<sup>44,50</sup>

Dexmedetomidine appears to have a clinically insignificant effect on respiratory function and gas exchange.<sup>55</sup> Arterial oxygen saturation does not decrease less than 90% and  $\text{PaCO}_2$  does not increase differently than that seen during normal sleep.<sup>44,56</sup> Although obstructive apnea has been associated with dexmedetomidine,<sup>57</sup> Hall et al<sup>55</sup> suggest that this is more related to rapid loading doses (during 2 minutes). Because  $\alpha_2$ -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.<sup>50,55</sup>

## 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  $\alpha_2$ -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,<sup>57,8</sup> and arterial  $\text{PCO}_2$  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.<sup>59</sup>

Novel uses of dexmedetomidine are not restricted to clinical airway management. Hofer et al<sup>60</sup> 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 al<sup>61</sup> 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  $2.6 \pm 0.83$  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 al<sup>62</sup> 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.

Dexmedetomidine, a selective  $\alpha_2$ -adrenergic receptor agonist, exhibits sympatholytic, sedative, and analgesic effects. It acts at presynaptic and postsynaptic adrenergic sites. Dexmedetomidine inhibits the release of norepinephrine and terminates the propagation of pain signals by activation of the presynaptic  $\alpha_2$ -adrenoceptor. Additionally, dexmedetomidine inhibits sympathetic activity with a resultant decrease in blood pressure and heart rate by postsynaptic activation of these receptors in the central nervous system. Together, these effects produce sedation, anxiolysis, sympatholysis, and analgesia.<sup>1</sup> Although dexmedetomidine may be initiated with a loading dose of 0.5 mcg/kg infusion during 10–20 minutes, more commonly, therapy begins with a modest infusion of 0.3–1 mcg/kg/hr titrated to the desired effect.

Dexmedetomidine has several advantages over traditional medications such as narcotics, benzodiazepines, or propofol for use as a sedative in the ICU. Dexmedetomidine produces minimal respiratory depression, which facilitates sedation in the nonintubated patients and allows extubation without the need to discontinue the drug infusion. Dexmedetomidine sedation may be continued during the postextubation period, providing flexibility in the timing of tracheal extubation and making the drug useful during the ventilator weaning process. A further advantage of dexmedetomidine is relative ease of arousability in the treated patients, i.e., they can typically be calmly and easily awakened, facilitating ease of patient evaluation and care. Additionally, patients receiving dexmedetomidine demonstrate a lower sympathetic tone. Dexmedetomidine has been described to be effective in treating four patients with agitation and hyperadrenergic states refractory to haloperidol.<sup>2</sup> Elevated sympathetic tone contributes to morbidity and mortality in the trauma patient and is an additional problem in caring for the agitated and/or delirious patient.

In view of these attributes, dexmedetomidine may be of great benefit in treating and preventing agitation and delirium in perioperative and ICU patient care. Additionally, dexmedetomidine may be a useful additional tool in a number of other trauma situations that may cause agitation and confusion, such as traumatic brain injury.

### Withdrawal Symptoms

Withdrawal symptoms from benzodiazepines or narcotics occurs not infrequently in trauma and ICU patients. In addition to those who experience withdrawal from medications taken at home, including alcohol and illicit drugs, some may withdraw from medications initiated in the hospital or ICU. This is particularly true for those receiving high dosages of benzodiazepines or narcotics over prolonged periods. Symptoms and signs of withdrawal include agitation, hypertension, tachycardia, and diaphoresis. These symptoms may easily be overlooked because of their similarity to other manifestations of critical illness. The majority of these hyperadrenergic-state withdrawal symptoms can be relieved by dexmedetomidine.

Ethanol withdrawal symptoms are frequently managed with benzodiazepines or even intravenous ethanol. Dexmedetomidine was shown to be as effective as diazepam in relieving the ethanol withdrawal reaction in rats.<sup>3</sup> Compared with placebo, administration of dexmedetomidine diminished the severity of the ethanol withdrawal reaction as measured by the sum score of the three most specific withdrawal signs (rigidity, tremor, and irritability) in ethanol-intoxicated rats.<sup>4</sup> Interestingly, dexmedetomidine has also been shown to relieve ethanol-induced neuronal loss in the locus ceruleus.<sup>5</sup> Votava et al<sup>6</sup> tested in rats whether dexmedetomidine inhibits behavior uniformly or with respect to particular stimuli or situations. They found a dose-dependent, antiaggressive effect in

aggressive mice. Nonetheless, while dexmedetomidine has been shown to be effective in such setting in rats, its effectiveness at treating or preventing delirium tremens in humans has not been fully elucidated, and therefore, while promising as a component in the care of withdrawal of the patient with alcohol and/or benzodiazepine dependency, particularly regarding the hyperadrenergic state, dexmedetomidine cannot be recommended to be the sole agent for these patients at this time.

In humans, dexmedetomidine has been reported to be useful in preventing and treating drug-withdrawal symptoms. Maccioli<sup>7</sup> has reported using dexmedetomidine to treat severe withdrawal symptoms in two ICU patients. One of these patients was a cocaine addict who was effectively sedated with dexmedetomidine. The patient's clinical symptoms improved immediately following the loading dose (1 g/kg). The second patient was successfully treated with dexmedetomidine for 7 days for his narcotic/benzodiazepine withdrawal symptoms. In a double-blind, randomized, and comparative parallel-group study design, dexmedetomidine premeditation was further found to attenuate ketamine-induced postanesthetic delirium. Compared with midazolam, dexmedetomidine proved to have equal sedative and anxiolytic effects after intramuscular administration.<sup>8</sup> Moreover, dexmedetomidine elicited significantly less preoperative psychomotor impairment and less anterograde amnesia than midazolam. Additionally, dexmedetomidine was more effective in reducing adverse ketamine-induced central nervous system effects.

Dexmedetomidine has also been reported to attenuate withdrawal symptoms in pediatric patients. Finkle and Elrefai<sup>9</sup> reported using dexmedetomidine infusion to "detoxify" a 13-kg infant with Hunter syndrome who was sedated for a prolonged time with opioids and benzodiazepines. Additionally, Tobias et al<sup>10</sup> reported using dexmedetomidine successfully in treating a 17-year-old patient who developed withdrawal symptoms in the ICU.

### Emergence Delirium

Emergence delirium (ED) is a frequent challenge in caring for the postoperative pediatric patient recovering from general anesthesia (GA). A variety of medications has been suggested for the treatment/prophylaxis of ED with varying degrees of success.<sup>11–13</sup> Guler et al<sup>14</sup> administered dexmedetomidine (0.5 mcg/kg) to children 5 minutes before extubation following tonsillectomy. They found that children experienced smoother emergence from GA with better pain scores when compared with the placebo group. They also noted a lower frequency of airway difficulties, which they attributed to the lessened degree of laryngeal stimulation as a result of the sedative and analgesic effects of dexmedetomidine. In a similar study, Ibacache et al<sup>15</sup> compared a smaller dose of dexmedetomidine (0.3 mcg/kg) administered at the beginning of the procedure to placebo and found a smoother emergence from GA. These pediatric studies used bolus doses of dexmedetomidine without an infusion and reported stability in the subjects' vital signs during the administration of the drug.

Another study compared the effects of dexmedetomidine infusion (0.2 mcg/kg/h) to a placebo saline infusion on ED in children aged 1 to 10 years.<sup>16</sup> The infusion was started within a few minutes following the induction of GA and was continued through the procedure. The trachea was extubated at the end of the procedure. The infusion of dexmedetomidine was terminated 15 minutes following the postanesthesia care unit admission. Using a blinded observer and compared with the placebo group, the incidence and frequency of ED was lower in the children who received dexmedetomidine. On the other hand, the times to extubation or discharge were the same. A loading dose was not

administered. Dexmedetomidine infusion was safe, with all the patients maintaining stable vital signs. Dexmedetomidine reduces norepinephrine release and sympathetic activity, which may explain its role in achieving superior sedation and preventing ED.<sup>17</sup>

## Conclusion

Dexmedetomidine needs to be studied further with respect to its properties as a sedative and its side effect profile as many of the examples provided in this discussion are the result of either case reports, retrospective evaluations, or anecdotes. For example, the pharmacokinetics and pharmacodynamics of the drug are as yet undescribed in the pediatric population. Furthermore, the safety profile for a dexmedetomidine infusion longer than 24 hours is only beginning to be elucidated. Appropriate patient selection remains important, with patients already having either a low tone state or hypovolemia being relatively excluded from dexmedetomidine use, given its sympatholytic effect.<sup>18,19</sup> Dexmedetomidine is a promising agent in preventing and treating agitation, delirium, and withdrawal while providing a comfortable, cooperatively sedated patient.

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# Retrospective Review of Hextend Use in Trauma Patients Requiring Surgery

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**Learning Objectives:** 1) To determine the effect of intraoperative Hextend on various respiratory parameters, vitals signs, and outcome. 2) To describe the correlation between intraoperative Hextend use, crystalloid fluid use and severity of injury, American Society of Anesthesiologists physical status, and postoperative mechanical ventilation.

## Abstract

In trauma patients who do not need blood products, the choice of resuscitative fluid is unclear. Factors influencing choice of fluid include effects on circulation, hemostasis, organ function, and metabolic state. Hextend is a colloidal plasma volume expander containing 6% hydroxyethyl starch in a physiologically balanced medium of electrolytes, glucose, and lactate. Hextend has been shown to be effective for the treatment of hypovolemia, and has a more favorable side effect profile compared with 6% hetastarch in saline. The purpose of this study was to investigate the intraoperative use of Hextend in trauma patients requiring surgery within 24 hours of admission to a Level 1 trauma center. The anesthesia and trauma surgery database of 512 consecutive trauma patients (age >16 years) was reviewed. Patients were retrospectively divided into two groups: Group A received Hextend as part of their resuscitation and Group B did not. Fluids were infused as necessary to maintain normovolemia. Transfusion of blood products was done as required. The majority of patients in both groups were male undergoing emergency orthopaedic, general, and neurosurgical procedures with general anesthesia and tracheal intubation following blunt trauma. Two patients died in each group. A greater percent of Hextend versus crystalloid patients required mechanical ventilation postoperatively, although the duration of mechanical ventilation was similar between groups. Compared with the crystalloid group, patients receiving Hextend had significantly higher American Society of

Anesthesiologists (ASA) physical status, injury severity, longer and more complex surgery, greater blood loss, and larger fluid volumes infused. There were no differences in postoperative vital signs, alveolar-arterial oxygen gradient, and oxygen index between groups. In the crystalloid group, there was a significant correlation between blood loss, ASA physical status, injury severity, blood transfusion, and postoperative mechanical ventilation. In the Hextend group, there was a significant correlation between ASA physical status, injury severity, and postoperative mechanical ventilation. Hextend administration was not associated with worsened alveolar-arterial oxygen gradient, oxygen index, vital signs, or outcome, although its use was a marker for increased severity of injury, blood loss, and requirement for postoperative mechanical ventilation.

The choice of crystalloid or colloid solutions for intraoperative resuscitation of trauma patients requiring surgery is unresolved. Factors influencing choice of asanguinous fluids include effects on coagulation, metabolic state, alterations in macro and microcirculation, volume distribution, and organ function (e.g., kidney function and splanchnic perfusion).<sup>1,2</sup>

Resuscitation with crystalloid fluids alone may reduce colloid oncotic pressure and promote tissue edema through interstitial expansion with plasma water.<sup>3</sup> Colloid oncotic pressure of the plasma is the osmotic pressure exerted by the macromolecules or colloid molecules, which serves to retain plasma water within the intravascular compartment. Colloid oncotic pressure, together with the fluid filtration coefficient, capillary hydrostatic pressure, interstitial hydrostatic pressure, and reflection coefficient, determines fluid flux at vascular membranes.<sup>2</sup>

It has been suggested that decreased colloid oncotic pressure from infusion of crystalloid solutions would result in adverse pulmonary outcomes because of interstitial pulmonary edema.<sup>4,5</sup>

Hextend is a colloidal plasma volume expander containing 6% hydroxyethyl starch (HES) in a physiologically balanced medium of electrolytes, glucose, and lactate (Hextend: mean molecular HES weight approximately 670 kD; range, 450-800, degree of HES molar substitution 0.75; Abbott Laboratories, North Chicago, IL).

The purpose of this retrospective study was to investigate the intraoperative use of Hextend in trauma patients requiring surgery within 24 hours of admission to a Level 1 trauma center. The hypothesis was that, compared with Hextend, resuscitation with crystalloid fluids would increase the incidence of postoperative respiratory failure requiring mechanical ventilation.

## Methods

We retrospectively reviewed the anesthesia and trauma surgery database of 512 consecutive trauma patients undergoing surgery within 24 hours of admission at MetroHealth Medical Center from June 2003 until August 2004. Inclusion criteria were age  $\geq$ 16 years and requiring an operation within 24 hours of admission to the hospital. Patients were retrospectively divided into two groups: Group A (n = 188) received Hextend as part of their resuscitation and Group B (n = 324) did not. All operations were scheduled and performed as indicated by the surgical team. Anesthetic technique and drugs were at the discretion of the attending anesthesiologist and not dictated by protocol. Fluids available for use in our operating rooms were lactated Ringer's solution, 0.9% saline, and Hextend. There were no guidelines in place for Hextend use. Fluids were

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Implication statement: Hextend administration was not associated with worsened alveolar-arterial oxygen gradient, oxygen index, vital signs, or outcome, although its use was a marker for increased severity of injury, blood loss, and requirement for postoperative mechanical ventilation.

infused as necessary to maintain normovolemia. Transfusion of red blood cells was done intraoperatively to maintain a hematocrit of 20% or greater. Fresh-frozen plasma and platelet concentrates were transfused according to standard coagulation indices or for the subjective assessment of excessive diffuse oozing.

Variables studied included demographics, vital signs on admission to the postoperative anesthetic care unit or intensive care unit, injury severity, anesthesia and surgery times, fluid balance, blood gas analysis, requirement for postoperative mechanical ventilation, and 30-day mortality. Calculated data were alveolar-arterial oxygen gradient [ $P_{A}O_2 = (F_iO_2 \cdot (760 - 47)) - (P_{A}CO_2 / 0.8)$ ], A-a gradient =  $P_{A}O_2 - P_{A}O_2$ ] [ $A\text{-a gradient} = (713 \cdot \text{inspired oxygen concentration}) - (\text{arterial } pCO_2/0.8) - \text{arterial } PO_2$ ], and oxygen index (= arterial  $PO_2/\text{inspired oxygen concentration}$ ). Complexity of surgery was classified as major, moderate, minor, and superficial as follows.

Major: Body cavities or major vessels are exposed to ambient temperature. Examples: major abdominal, thoracic, vascular, thoracic spine surgery, pelvic fracture, hip and femur surgery.

Moderate: Surgery in which body cavities are exposed to a lesser degree. Examples: laparoscopy, craniotomy, other long bone fracture surgery (tibia, fibula).

Minor surgery: Closed reduction of fractures, facial injuries, ophthalmology injuries.

Superficial: Lacerations, debridement.

All statistical analyses were performed using Statistix 8.0 (Analytical Software, Tallahassee, FL). Data were compared between groups using chi square and unpaired Student's *t* test. Pearson's correlations were computed for duration of mechanical ventilation and other variables using a correlation matrix. Multilinear regression was then used to determine the "best" set of independent variables to predict requirement for postoperative mechanical ventilation. A *P* value < 0.05 was considered significant.

## Results

The groups were similar with respect to age, weight, and height (Table 1). The majority of patients (>70%) in both groups were male undergoing emergency orthopaedic, general, and neurosurgical procedures following blunt trauma (Table 2). Tracheal intubation and general anesthesia were employed in 97% of the patients. After completion of surgery, 223 patients in the crystalloid group were admitted to the postanesthesia care unit and 99 to the intensive care unit. Corresponding numbers for the Hextend group were 70 and 116 patients. Two patients died in each group. Data from these two patients are included up until their time of death.

Compared with the crystalloid group, patients receiving Hextend had significantly (*P* < 0.001) higher American Society of Anesthesiologists (ASA) physical status, injury severity, longer and more complex surgery, greater blood loss, and larger fluid volumes infused (Tables 1 and 3). There were no differences in postoperative vital signs, A-a gradient, and oxygen index between groups (Table 4). A greater percent of Hextend versus crystalloid patients required mechanical ventilation postoperatively (52 vs. 24%; *P* < 0.001), although the duration of mechanical ventilation was similar between groups (Table 4, Figure 1).

In the crystalloid group, there was a significant (*P* < 0.001) correlation between blood loss, ASA physical status, injury severity, blood transfusion, and postoperative mechanical ventilation (Table 5). In the Hextend group, there was a significant correlation between ASA physical status, injury severity, and postoperative mechanical ventilation (Table 5; *P* < 0.001).

Best subset regression model showed that in the Hextend group, 15% of the variability in mechanical ventilation days could be

**Table 1. Patient Data\***

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Age (yr)	40 ± 1	38 ± 1
Male	230 (71)	144 (77)
Female	94 (29)	44 (23)
Height (cm)	174 ± 1	173 ± 1
Weight (kg)	82 ± 1	87 ± 2
Mechanism of Injury†		
Blunt	67 (21)	55 (29)
Penetrating	257 (79)	133 (71)
ASA Physical Status‡		
I	20 (6)	4 (2)
II	171 (53)	64 (34)
III	76 (23)	62 (33)
IV	42 (13)	47 (25)
V	16 (5)	11 (6)
Injury Severity Score‡		
Median	10	17
25th–75th quartile	917	9–22

\*Data are means ± SEM or number of patients (%).

†*P* < 0.05 between groups.

‡*P* < 0.001 between groups.

**Table 2. Surgery Data\***

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Service		
Orthopaedics	206 (64)	110 (59)
Trauma, general	63 (19)	49 (26)
Neurosurgery	34 (11)	14 (7)
Plastics	12 (4)	2 (1)
Cardiothoracic	2 (1)	3 (2)
Vascular	7 (2)	10 (5)
Urology	4 (1)	0
Ophthalmology	10 (3)	0
Otolaryngology	10 (3)	2 (1)
Oral maxillofacial	1 (0.3)	0
Complexity of operation†		
Major	148 (46)	145 (77)
Moderate	147 (45)	39 (21)
Minor	24 (7)	3 (1.6)
Superficial	6 (2)	1 (0.5)
Emergent or urgent surgery	239 (74)	144 (77)

\*Data are number of patients (%). There could be more than one surgical service per patient.

†*P* < 0.001 between groups.

**Table 3. Intraoperative Data\***

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Anesthesia time (min)†	184 ± 5	279 ± 11
Surgery time (min)†	123 ± 4	208 ± 10
Crystalloid (mL)†	2218 ± 86	4465 ± 231
Hextend (mL)	0	844 ± 38
Blood products†		
RBC (units)	3 ± 0.3, n = 50 (15%)	5 ± 0.6, n = 88 (47%)
FFP (units)	2 ± 3.7, n = 14 (4%)	3 ± 5, n = 25 (13%)
Platelets (units)	3 ± 2.5, n = 6 (2%)	6 ± 3.3, n = 11 (6%)
Cell saver (mL)	725, n = 2 (0.6%)	707, n = 10 (5%)
EBL (mL)†	311 ± 34	1439 ± 216

\*Data are means ± SEM or number of patients (%). RBC, packed red blood cells; FFP, fresh-frozen plasma; EBL, estimated blood loss.

†*P* < 0.001 between groups.

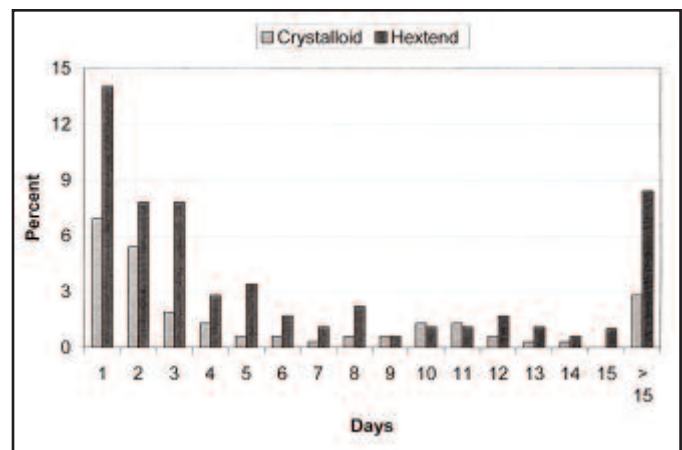
**Table 4. Postoperative Data**

	Crystalloid Group (n = 324)	Hextend Group (n = 188)
Systolic BP (mm Hg)	143 ± 1	145 ± 2
Diastolic BP (mm Hg)	70 ± 1	75 ± 1
Heart rate	99 ± 1	103 ± 1
Respiratory rate	17 ± .3	16 ± .3
Oxygen saturation (%)	97 ± .2	98 ± .2
Temperature (°C)	36.6 ± .05	36.6 ± .08
Mechanical ventilation required†	78 (24)	98 (52)
Duration of ventilation (days)		
Median	2.5	3
25th–75th quartile	1-10	3-10
Range	1-37	1-66
Arterial blood gas analysis‡		
Inspired O <sub>2</sub> (%)	50 ± 2	60 ± 2
pH	7.33 ± .01	7.33 ± .01
pCO <sub>2</sub> (mm Hg)	38 ± .9	38 ± .6
pO <sub>2</sub> (mm Hg)	169 ± 10	171 ± 8
Hemoglobin (g/dL)	11.5 ± .3	10.4 ± .2
Hematocrit (%)	34.2 ± .8	30.9 ± .6
Alveolar—arterial O <sub>2</sub> gradient (mm Hg)	189 ± 13	216 ± 16
Oxygen index	305 ± 13	303 ± 14

Data are means ± SEM or number of patients (%). BP, blood pressure.

† *P* < 0.001 between groups.

‡ Arterial blood analysis was done in 68 crystalloid only patients and 91 Hextend + crystalloid patients.



**Figure 1. Frequency histogram of duration of postoperative mechanical ventilation in patients receiving crystalloid fluids alone (n = 324) or Hextend (n = 188). Mechanical ventilation was required more often in the Hextend compared with the crystalloid alone group (*P* < 0.001), although duration of ventilation was similar between groups.**

predicted by injury severity (Figure 2, Table 6). By adding age to the model, the ability to accurately predict duration of ventilation improved to 17% (Figure 3). In the crystalloid group, 25% of the total variability in duration of ventilation was explained by ASA physical status (Figure 4, Table 6). By adding injury severity to the model, the ability to accurately predict duration of ventilation improved to 31% (Figure 5).

## Discussion

Fluid management is a challenging task in trauma patients undergoing urgent and emergent surgery. The major goal is to stop the bleeding and replete intravascular volume to optimize blood pressure and tissue oxygen delivery. Choice, volume, and timing of intraoperative fluid resuscitation is based on correlates of hypoperfusion such as tachycardia, hypotension, low urinary output, low central venous pressure, and acid-base variables such as pH, base deficit, and lactate.<sup>6-9</sup>

**Table 5. Pearson Correlations Between Duration of Mechanical Ventilation and Variable\***

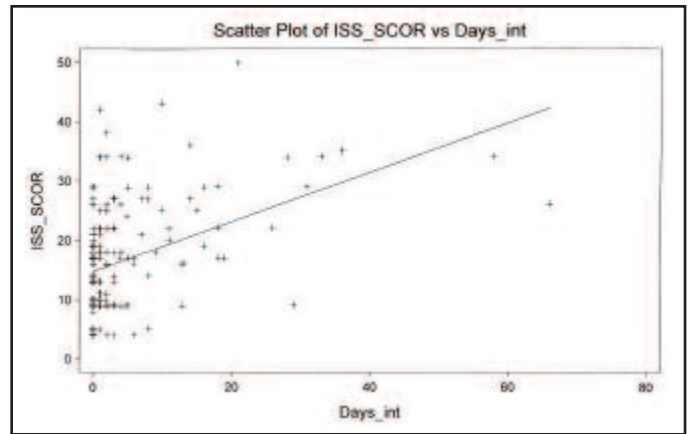
Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA physical status		
Correlation	0.51	0.22
P value	0.0000	0.0055
Injury Severity Score		
Correlation	0.46	0.41
P value	0.0000	0.0000
Estimated blood loss		
Correlation	0.18	0.05
P value	0.0018	NS (0.5)
Age		
Correlation	0.13	0.13
P value	0.025	NS (0.1)
Red blood cell transfusion		
Correlation	0.24	0.12
P value	0.0001	NS (0.1)
Fresh-frozen plasma transfusion		
Correlation	0.26	0.07
P value	0.0000	NS (0.4)

\*ASA, American Society of Anesthesiologists; NS, not significant.

Quantifying the degree of postoperative respiratory failure requiring mechanical ventilation after trauma surgery is difficult. In the present study, use of crystalloid fluids was not associated with increased requirement for postoperative mechanical ventilation or worsened indices of oxygenation. However, increased blood loss and transfusion requirements in the crystalloid group were associated with increased duration of ventilation. Intraoperative use of Hextend was a marker for increased severity of injury, blood loss, duration and complexity of surgery, and requirement for postoperative mechanical ventilation. Patients in the Hextend group received approximately 2.4 times more asanguinous fluids, and were transfused more often compared with the crystalloid group.

It is unlikely that use of Hextend contributed to the increased requirement for mechanical ventilation because multiple regression showed that major predictors for postoperative mechanical ventilation in the Hextend group were increased injury severity and ASA physical status. A previous study<sup>10</sup> comparing 4% albumin to normal saline for fluid resuscitation in the intensive care unit demonstrated equivalent requirements for mechanical ventilation in both groups (4.3 to 4.5 days), although there was increased mortality in head-injured patients randomized to the albumin (59 of 241 patients, 25%) as compared with the saline group (38 of 251 patients, 15%). In the present study, duration of ventilation was considerably shorter (2.5 to 3 days) and mortality was very low (0.6% to 1%) in both groups.

Other factors that may have contributed to mechanical ventilation postoperatively include diminished functional reserve capacity, hemodynamic alterations, atelectasis, decreased lung



**Figure 2. Scatter plot of Injury Severity Score (ISS\_Scor) and duration of postoperative mechanical ventilation days (Days\_int) in the Hextend group (r = 0.40).**

**Table 6. Results of the Multivariate Linear Regression for Duration of Mechanical Ventilation**

Variable	Crystalloid Group (n = 324)	Hextend Group (n = 188)
ASA* physical status		
Coefficient	1.58	0.68
Standard error	0.23	0.37
P value	0.0000	0.07
Injury Severity Score		
Coefficient	0.14	0.15
Standard error	0.03	0.04
P value	0.0000	0.0003

\* American Society of Anesthesiologists.

compliance, increased work of breathing, acute lung injury, and increased extravascular lung water. Acute lung injury and increased extravascular lung water would be expected to worsen A-a gradient and oxygen index, as evidenced in the present study. Despite these abnormalities, there were no differences between groups in oxygenation, acid-base, and other postoperative variables. Elderly patients may be at increased risk for requiring mechanical ventilation after trauma surgery because of alterations in control of respiration, lung structure, mechanics, and pulmonary blood flow. In the present study, age was only slightly predictive for duration of ventilation in the two groups.

The low mortality rate in both groups in the present study supports the effectiveness of both fluid management strategies in maintaining tissue homeostasis. There was no evidence that intraoperative use of colloids increased mortality as has been suggested by a meta-analysis of 24 studies involving 1,419 patients.<sup>11</sup> Of note, there were several patients in both groups who were unexpected survivors as evidenced by ASA physical status 5 and being alive at 30 days. All deaths occurred in ASA 5 patients, as expected.

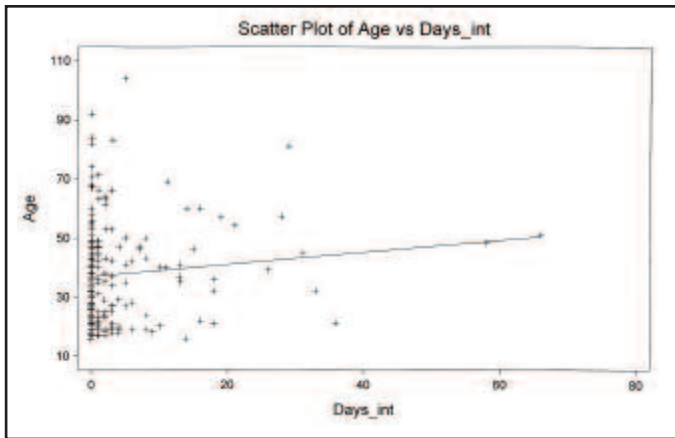


Figure 3. Scatter plot of age (years) and duration of postoperative mechanical ventilation days (Days\_int) in the Hextend group.

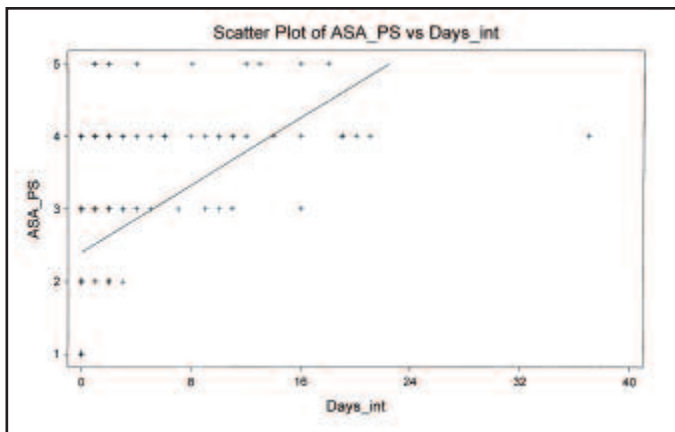


Figure 4. Scatter plot of American Society of Anesthesiologists Physical Status (ASA\_PS) and duration of postoperative mechanical ventilation days (Days\_int) in the crystalloid fluid alone group ( $r = 0.56$ ).

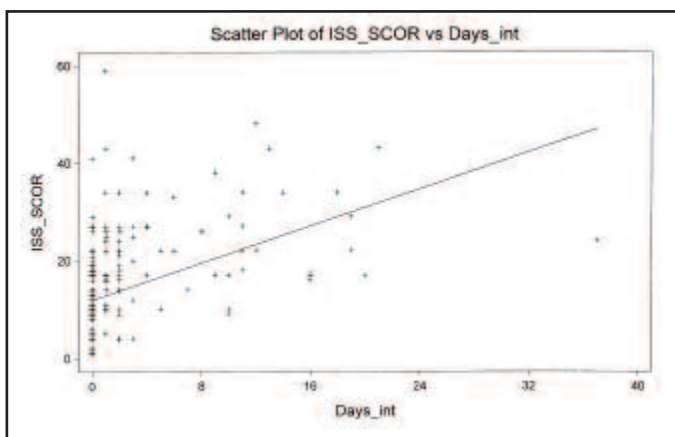


Figure 5. Scatter plot of Injury Severity Score (ISS\_Scor) and duration of postoperative mechanical ventilation days (Days\_int) in the crystalloid fluid alone group.

Although crystalloid solutions such as lactated Ringer's solution and isotonic 0.9% sodium chloride are the preferred nonblood solutions for fluid resuscitation of patients with blunt and penetrating trauma, colloid solutions such as HES are more effective plasma expanders and increase colloid oncotic pressure, which serves to retain plasma water within the intravascular compartment and minimize interstitial edema within vital organs such as the lung, heart, and brain. Intraoperative use of colloid solutions has been associated with improved outcome and decreased hospital stay,<sup>12,13</sup> possibly because of decreased tissue edema, nausea, vomiting, and pain.

Administration of large volumes of HES such as Hespan (6% HES in 0.9% sodium chloride; mean molecular weight approximately 600 kD, degree of molar substitution 0.75; Baxter, Deerfield, IL) causes coagulopathy. Indeed, because of the adverse effects of Hespan on hemostasis, (e.g., impaired platelet aggregation, type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, decreased von Willebrand factor antigen, and factor VIII-related ristocetin cofactor),<sup>14,15</sup> this colloid was withdrawn from our hospital formulary and replaced with Hextend, which is associated with better thromboelastographic parameters of dynamic clot formation compared with Hespan.<sup>7</sup>

Patients receiving Hextend in the present study had increased blood loss and blood transfusion compared with the crystalloid group, likely due to increased injury severity and complexity of surgery. It is recognized that medium-molecular weight HES (130 kD, 200 kD) with lower molar substitution (0.4, 0.5) has less negative effects on coagulation compared with first-generation HES preparations.<sup>16</sup> Nonetheless, there is evidence that, unlike Hespan, Hextend does not inhibit platelet function, which may be related to its solvent containing calcium chloride dihydrate (2.5 mmol/L).<sup>17</sup> Further, Hextend may be the preferred solution for alternative resuscitation strategies such as hypotensive resuscitation in clinical settings that prevent the application of standard Advanced Trauma Life Support care.<sup>18</sup> There is evidence that Hextend may be beneficial after head injury. For example, Hextend as the sole resuscitation fluid after severe traumatic brain injury in pigs, reduced fluid requirement, eliminated the need for mannitol, improved neurologic outcome, and had no adverse effect on the coagulation profile relative to crystalloid fluids plus mannitol standard of care.<sup>19</sup> Compared with normal saline, volume resuscitation with Hextend was associated with less metabolic acidosis and longer survival in an animal model of septic shock.<sup>20</sup>

Storage and accumulation of Hextend in the body does occur. Hextend undergoes slow intravascular catabolism by alpha-amylase. The median serum half-life during 7 days was 38.2 hours.<sup>21</sup> The smaller molecules are rapidly eliminated by glomerular filtration. Hemodilution is observed for 24 to 48 hours after short-term infusion. A varying amount of Hextend is taken up by the reticuloendothelial system. Severe pruritus has been reported.<sup>22</sup> Life-threatening anaphylactic reactions may occur with different kinds of hetastarch preparations but appear to be rare.<sup>23,24</sup>

Limitations of this study include its retrospective nature and the confounding effects of different injuries, surgeries, and fluid management strategies. It is acknowledged that many different HES preparations are available with varying concentration, molecular weight, and molar substitution.<sup>25</sup> Therefore, the applicability of these data to other starch compounds and colloid solutions in trauma patients remains to be determined. A prospective study of Hextend versus crystalloid to minimize posttraumatic respiratory complications appears warranted.

In conclusion, compared with Hextend, resuscitation with crystalloid fluids was not associated with increased duration of mechanical ventilation, or worsened A-a gradient and oxygen index after surgery in trauma patients. Intraoperative use of Hextend was a marker for increased severity of injury, ASA status, blood loss, fluid requirements, surgery complexity, and requirement for postoperative mechanical ventilation. Increasing ASA status and injury severity were associated with increased duration of postoperative mechanical ventilation regardless of fluid group.

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- When the FDA approved the use of dexmedetomidine, there were no limitations to its use.
  - True
  - False
- Dexmedetomidine's mechanism of action is mediated via which receptor type?
  - $\alpha_1$ -adrenergic
  - $\alpha_2$ -adrenergic
  - $\beta_1$ -adrenergic
  - $\beta_2$ -adrenergic
- Adverse effects of dexmedetomidine include all of the following except:
  - Hypertension
  - Hypotension
  - Bradycardia
  - Tachycardia
- Dexmedetomidine's site of action in the central nervous system is:
  - The cerebral cortex
  - The locus ceruleus
  - The reticular activating system
  - The hypothalamus
- Dexmedetomidine is currently FDA-approved for which indication in adults?
  - Sedation during mechanical ventilation
  - Treatment of withdrawal
  - Prevention of emergence delirium
  - Procedural sedation
- Dexmedetomidine's physiologic effects include all of the following except:
  - Sedation
  - Slowing of the heart rate
  - Decrease in the cerebral metabolic rate for oxygen
  - Increase in gastrointestinal motility
- Dexmedetomidine is generally administered in a dose of 0.2-0.7:
  - mcg/kg/min
  - mcg/kg/hr
  - mg/kg/min
  - mg/kg/hr
- Dexmedetomidine's physiologic effects include all of the following except:
  - Potiation of opioid analgesia
  - Neuroprotection during ischemia or hypoxia
  - Potiation of neuromuscular blockade
  - Increase in cerebral perfusion pressure
- Why is awake intubation the method of choice in patients with cervical spine injury?
  - It allows neurologic examination after intubation.
  - Patients can alert the intubating personnel if there is any change in neurologic symptoms.
  - It involves less cervical motion when compared to the use of rigid laryngoscope.
  - All of the above.
- What is the prominent hemodynamic effect of dexmedetomidine?
  - Tachycardia and hypotension
  - Bradycardia and Hypertension
  - Bradycardia and transient hypertension changing to hypotension
  - Tachycardia and hypotension changing to hypertension
- Which is not a characteristic that makes dexmedetomidine suitable for awake intubations?
  - Sedation
  - Definite amnesia
  - Analgesia
  - Minimal effect on respiratory drive

- 12. Symptoms and signs of withdrawal include all the following except:
  - a. Agitation
  - b. Hypotension
  - c. Tachycardia
  - d. Diaphoresis
- 13. Emergence delirium is a frequent phenomenon in children recovering from general anesthesia.
  - a. True                      b. False
- 14. Compared to placebo, children who receive dexmedetomidine a few minutes before extubation following general anesthesia have all the following except:
  - a. Smoother emergence
  - b. Higher pain scores
  - c. Lower frequency of airway problem
- 15. Benzodiazepines and opioids can cause agitation and confusion.
  - a. True                      b. False
- 16. Dexmedetomidine causes all of the following except:
  - a. sedation
  - b. increase in sympathetic activities
  - c. analgesia
  - d. anxiolysis
- 17. The multiple pharmacologic agents usually administered in the ICU do not play a role in agitation.
  - a. True                      b. False
- 18. Compared with patients receiving crystalloid fluid alone, intraoperative Hextend administration was associated with:
  - a. worsened alveolar-arterial oxygen gradient
  - b. altered vital signs
  - c. longer and more complex surgery
  - d. decreased blood loss
- 19. Concerning postoperative mechanical ventilation:
  - a. patients receiving Hextend had a longer duration of mechanical ventilation compared with the crystalloid-only group
  - b. patients receiving Hextend had a shorter duration of mechanical ventilation compared with the crystalloid-only group
  - c. patients receiving Hextend required postoperative mechanical ventilation less frequently than patients in the crystalloid-only group
  - d. patients receiving Hextend required postoperative mechanical ventilation more frequently than patients in the crystalloid-only group
- 20. In the Hextend group there was a significant correlation between which of the following variable(s):
  - a. ASA physical status
  - b. Injury severity
  - c. Postoperative mechanical ventilation
  - d. All the above

**Evaluation Form: Please rate this self-study activity by marking one response for each statement.**

Did the articles meet their stated objectives?     Yes     No

How do you rank the quality of this educational activity?     5 (high)     4     3     2     1 (low)

Comments: \_\_\_\_\_

Did you perceive any evidence of bias for or against any commercial products?     Yes     No    If yes, please explain.

Comments: \_\_\_\_\_

How do you rank the effectiveness of this activity as it pertains to your practice?     5 (high)     4     3     2     1 (low)

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Additional comments about this activity: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Answer Form: Please circle the one best answer for each question.**

TraumaCare Volume 17, Number 1, 2007 issue

Name: _____		
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- 1. a b                      11. a b c d
- 2. a b c d                12. a b c d
- 3. a b c d                13. a b
- 4. a b c d                14. a b c
- 5. a b c d                15. a b
- 6. a b c d                16. a b c d
- 7. a b c d                17. a b
- 8. a b c d                18. a b c d
- 9. a b c d                19. a b c d
- 10. a b c d               20. a b c d

I certify that I have completed the "TraumaCare/Vol. 17, No. 1, 2007 issue" activity as designed and claim 10 credit hours in Category 1 of the Physicians Recognition Award of the American Medical Association.

Signature \_\_\_\_\_ Date \_\_\_\_\_

**Mail answer form and check (\$100, members; \$200, nonmembers) to ITACCS Department of CME Credit, P.O. Box 4826, Baltimore, MD 21211. Allow 4 to 6 weeks for processing.**

*Credit for this activity is offered until June 30, 2008.*

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