The Role of the α_2-Adrenoceptor Agonist Dexmedetomidine in Postsurgical Sedation in the Intensive Care Unit

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Dexmedetomidine was evaluated for sedation of 401 postsurgical patients in this double-blind, randomized, placebo-controlled, multicenter trial. Dexmedetomidine or saline was started on arrival in the intensive care unit (ICU) (1.0 mcg/kg for 10 minutes), then titrated at 0.2 to 0.7 mcg/kg/h to effect. Patients could be given propofol if necessary. Morphine was administered for pain. Sixty percent of the dexmedetomidine patients required no other sedative to maintain an RSS ≥ 3; 21% required < 50 mg propofol. In contrast, 76% of the control group received propofol; 59% required ≥ 50 mg. Dexmedetomidine patients required significantly less morphine for pain relief ($P < .001$). Continuously given throughout the ICU stay, dexmedetomidine had no effect on respiratory rate, oxygen saturation, duration of weaning, or times to extubation. Nurses judged the dexmedetomidine patients were easier to manage. Later, fewer dexmedetomidine patients remembered pain or discomfort. The majority of dexmedetomidine patients maintained blood pressures within normal range, without rebound. Hypertension, atelectasis, and rigors occurred more frequently in the control group, while hypotension and bradycardia occurred more frequently in the dexmedetomidine group. Preoperative cardiovascular conditions were not risk factors for dexmedetomidine patients.

Key words: *α_2-adrenoceptors, imidazoles, sympatholysis, anxiety, cardiac artery bypass graft, respiratory system*

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Ideally, postsurgical patient care in the intensive care unit (ICU) should minimize stress and sympathetic nervous system responses, relieve pain and anxiety, facilitate diagnostic and therapeutic procedures, and permit communication with patients without interrupting sedation—all without compromising hemodynamic or respiratory stability or prolonging time in the ICU [1-3]. Although new sedation protocols continue to improve the quality of ICU sedation and outcomes, fundamental problems remain that are inherent to the agents commonly used. Propofol and midazolam can depress respiratory drive [4-6]. For this reason, both are usually stopped before extubation. Whereas midazolam reduces opioid use, propofol has no analgesic properties. The combination of propofol or midazolam with opioids can result in a disoriented and unresponsive patient, at risk for hypoxemia or respiratory depression [7,8].

Recently, the α_2-adrenoceptor agonist dexmedetomidine was approved in the United States for short-term sedation of ICU patients. Drugs of this class bind to transmembrane G-protein-binding receptors, rapidly initiating a cascade of physiological events. When the α_{2a}-adrenoceptors, which modulate wakefulness in the locus coeruleus are activated, a dose-dependent hypnotic sedation results. Stimulation of presynaptic α_{2a}-adrenoceptors reduces sympathetic tone and increases parasympathetic tone, resulting in a decrease in myocardial oxygen requirements [9]. Predictably, this class of drugs reduces blood pressure and heart rate. Clonidine has been used for many years to reduce blood pressure, opioid use, and the hemodynamic stresses associated with surgery [10,11]. Another important benefit of this class of drugs is that they have no significant effect on respiratory drive, even when used with opioids [9,12]. A number of studies have verified these benefits of dexmedetomidine when used for sedation in critically ill patients

[9,13]. Because dexmedetomidine has a higher α_{2a} to α_1 binding affinity (1300:1) than clonidine (39:1), some of the adverse effects associated with α_1 stimulation may be avoided [14]. Studies have shown that dexmedetomidine reduces plasma catecholamine concentrations and hemodynamic stress responses to endotracheal insertion, surgical stress, awakening from anesthesia, and extubation [15-19]. During short-term sedation, it does not inhibit adrenal steroidogenesis [20]. Although propofol is an effective sedative, it has no analgesic effect, and the adequately sedated patient is unresponsive. In contrast, the dexmedetomidine-sedated patient is easily awakened to participate in diagnostic and therapeutic procedures without stopping the sedative [21,22]. Although there are many demonstrated advantages to the use of dexmedetomidine, more large randomized studies are necessary to determine its value in the clinical setting.

The objective of this double-blind randomized study was to evaluate the efficacy and safety of dexmedetomidine for short-term sedation of postsurgical, ventilated patients compared to a placebo control. Patients received identical infusions of dexmedetomidine or saline from their entry into the ICU through a minimum of 6 hours before extubation, and at least 6 hours postextubation. They were given propofol if their sedation levels were considered inadequate by Ramsay sedation score (RSS) [23]. The primary endpoint for the study was the total dose of propofol required to maintain sedation at an RSS ≥ 3 during assisted ventilation. Secondary endpoints were the dose of morphine for analgesia, weaning duration, time to extubation, and nurses' assessments of patient management.

Materials and Methods

Subjects for this study were scheduled for major surgical procedures that were expected to require a minimum of 6 hours of postsurgical assisted ventilation. A total of 401 patients were enrolled in 34 sites in Europe and Canada.

Excluded from this study were females if pregnant or lactating and patients whose condition or responses could be difficult to evaluate in a blinded trial (eg, had serious central nervous system trauma or intracranial surgery), patients who had unstable or uncontrolled diabetes, patients who were grossly obese, and patients who were hospitalized for a drug overdose. Discontinued from the study were patients who developed excessive bleeding that required a return to surgery; patients who received neuromuscular blocks, epidural, or spinal analgesia during their ICU stay; and patients who had clinically significant arrhythmia or any other cardiac condition or other factor that, in the investigator's opinion, might increase the risk to those patients or preclude obtaining satisfactory study data.

Table 1. Ramsay Sedation Scale

Score	Observation
1	Anxious, agitated, or restless
2	Cooperative, oriented, and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

The protocol, amendments, informed consent form, and all other forms of patient information related to the study were reviewed and approved by an independent ethics committee that complied with Food and Drug Administration regulations and each country's regulatory requirements. A voluntary, written informed consent form was signed by each patient (or representative) after the nature of the study was explained and prior to any study-related procedure.

Dexmedetomidine HCl (100 mcg/mL base) in 0.9% NaCl and the 0.9% NaCl solutions were supplied by Abbott Laboratories. Each site provided propofol, morphine, and all other supplies and equipment. The site pharmacist prepared the correct dilutions of dexmedetomidine (4 mcg/mL, or 8 mcg/mL in 0.9% sodium chloride) and labeled the syringes according to the randomization code. Both solutions were identical in appearance and viscosity. All laboratory staff, all CRO staff, and all Abbott Laboratory personnel involved with the conduct and/or analysis of this study were blinded to the randomization code. Patient assignments remained blinded until after the study was completed, all clinical data had been screened, and all patients were evaluated. In the event of an emergency, the investigator could open the sealed blind-breaker envelope.

Study Design

Patients randomized to group A received dexmedetomidine intravenously; group B patients received 0.9% saline (see Fig 1 for the study design). Both solutions were called "study drug."

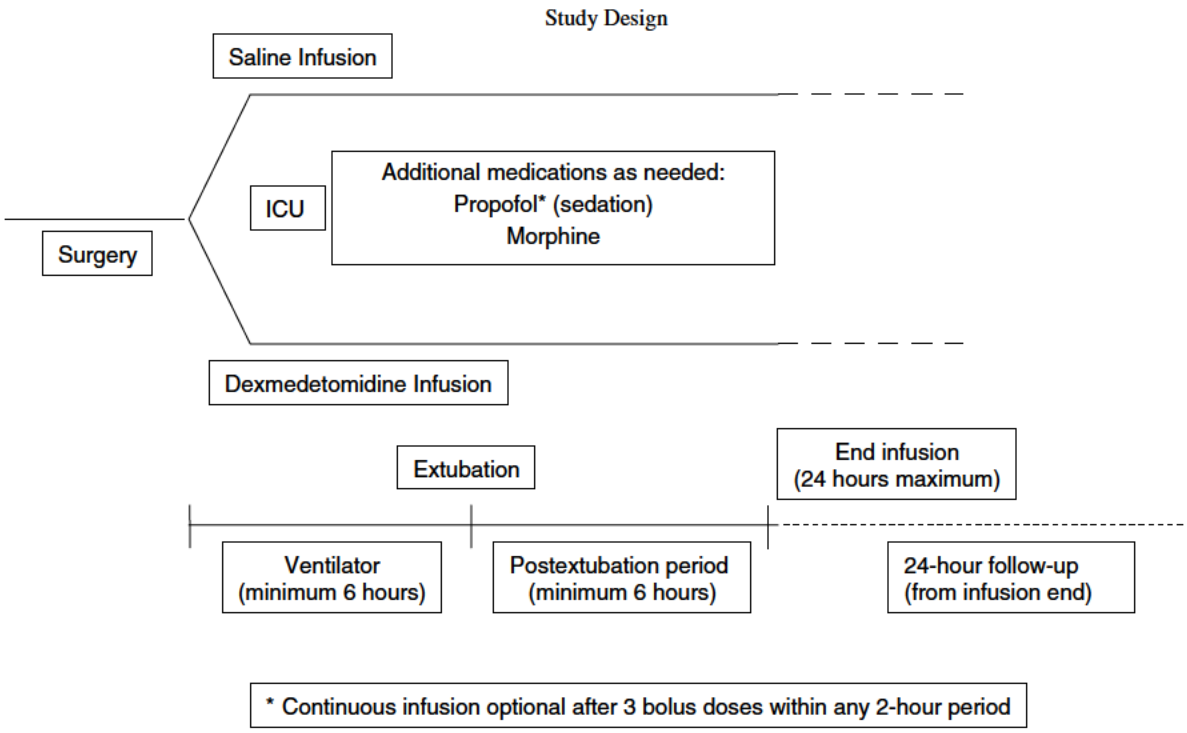

Fig 1. Study design. Study drug infusions began within 1 hour after the patients entered the intensive care unit (ICU) and continued uninterrupted for up to 24 hours. Study protocols required a minimum of 6 hours of assisted ventilation before extubation and a minimum of 6 hours with study drug administration after extubation.

There were no restrictions on intraoperative drug use. If a patient required sedation to assist in the transport from the operating room to the ICU prior to the start of study drug, a 0.2-mg/kg bolus of propofol could be given. Study drug infusions were started as soon as possible after the patient entered the ICU, but within 1 hour. Baseline values were the last measurements recorded before the start of study drug infusion. The infusion pump was set to give 1.0 mcg/kg (dexmedetomidine or saline) for 10 minutes (loading dose) and then was reduced to 0.4 mcg/kg/h. The latter rate could be adjusted within the range of 0.2 to 0.7 mcg/kg/h as necessary to achieve and maintain an RSS ≥ 3 while the patient was on the ventilator. If sedation could not be maintained within the protocol-defined range and the infusion rate was at the maximum of 0.7 mcg/kg/h, patients could be given a bolus of 0.2 mg/kg propofol intravenously. If sedation was still considered inadequate after 3 bolus doses, a continuous infusion of propofol was started (at a rate of 0.5 to 4.0 mg/kg/h). Following extubation, the infusion rate was to be adjusted to achieve a Ramsay score ≥ 2.

Incremental (2 mg) doses of morphine were given intravenously to patients in both groups as necessary for pain relief at any time during the study. No pain scale was used. The need for analgesia was assessed individually, either by direct communication or based on indirect symptoms of pain (eg, sweating, tachycardia, hypertension, or excessive movement).

All patients were kept on the ventilator for a minimum of 6 hours after entry into the ICU. Infusions of dexmedetomidine or saline were continued without interruption while in the ICU, through weaning and extubation, and for a minimum of 6 hours postextubation; total time was < 24 hours. Blood samples for hematology, blood gases, and blood chemistry assessments were collected before dosing and approximately 24 hours after the end of study drug infusion. Systolic and diastolic arterial blood pressure, heart rate, and respiratory rate were recorded at protocol-specified time points (Table 2). SpO_2 was monitored continuously.

Efficacy was evaluated by measuring the amount of propofol, in addition to dexmedetomidine or saline (placebo), that was required to achieve and maintain an RSS ≥ 3 during assisted ventilation. Secondary efficacy variables were as follows.

1. *The total dose of morphine administered for pain.* Morphine use was compared between groups during the first 6.5 hours of study drug infusion (when all patients received assisted ventilation and the period of most intense analgesic requirements) and from 6.5 hours after the start of study drug

Table 2. Study Procedures and Schedule of Assessments

Assessment	Screening (≤ 7 Days Before Dosing)	Baseline (Prior to Start of Study Drug Infusion)	First Hour of Study Drug Infusion	After First Hour to Stop of Study Drug Infusion	Prior to Discharge (24 Hours Postinfusion Stop)
Informed consent/medical history	X				
Laboratory testing		X			X
Physical examination	X				X
12-lead electrocardiogram	X				X
Cardiac telemetry monitoring		X	Continuous		
SBP, DBP, HR, RR	X	X	q10 min[a]	q60 min[b]	X[c]
CVP		X	q10 min[a]	q60 min[b]	
SpO_2		X	q10 min[a]	q60 min[b]	X[c]
Temperature	X	X		q6 hours	X[c]
Blood gases		X		At end of infusion	
Ramsay		X	q10 min[a,b]	q60 min[b,d]	
Pain assessments		X	PRN	PRN	X

Cardiac output and central venous pressure (CVP) were assessed as clinically indicated and only at a subgroup of sites. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, SpO_2 = oxygen saturation by pulse oximeter, PRN = as needed.

a. Assessed every 10 ± 2 minutes for 30 minutes after the start of the study drug infusion and at 60 minutes after the start of study drug.

b. Assessed every 60 ± 5 minutes from 1 hour after the start of the study drug infusion to the end of study drug infusion.

c. Assessed every 3 hours until study completion.

d. Also assessed prior to and 10 minutes after any rate change in study drug or administration of additional sedative.

(postextubation for most patients) to the end of study drug infusion.

2. *The duration of weaning (the difference between initiation of weaning from the ventilator and readiness for extubation).* Guidelines for weaning were as follows. After the patient was stabilized in the ICU, the fraction of inspired oxygen (FiO_2) was to be decreased no more frequently than every 30 minutes by 0.10 decrements (if SpO_2 exceeded 92%) to a goal FiO_2 of no more than 0.40. Patients were weaned from the ventilator when they were responsive, were hemodynamically stable, had no shivering or bleeding requiring treatment, and registered a temperature above 36°C.
3. *Time to extubation (the difference between ICU arrival and when the patient was considered ready for extubation).* The endotracheal tube could be removed if the following criteria were met and the investigator deemed it appropriate: (1) the patient was awake or arousable, neurologically intact, cooperative, and comfortable and (2) the patient had an FiO_2 value ≤ 0.4, positive end-expiratory pressure (PEEP) < 5 cm H_2O, and pressure support ≤ 10 cm H_2O. The patient's lung mechanics were as follows: minute ventilation expired > 4 L/min but < 15 L/min, tidal volume > 5 mL/kg, and spontaneous respiratory rate < 25 breaths/min.
4. *Nurses' assessments (see the appendix).* For any nursing shift that started or ended during assisted ventilation, nurses recorded their ratings of the quality of sedation, the ability of the patient to tolerate the endotracheal tube/ventilator and the ICU, the ease of communication with the patient, and ease of management. Scores from each of these assessments were summed to arrive at a composite score defined as the Patient Management Index. We used the Cochran-Mantel-Haenszel statistic to test the significance of the differences between each assessment, simultaneously adjusting for site-specific nursing practices.
5. *Patient questionnaires (see the appendix).* At the end of their stay in the ICU, each patient was asked about their recall of their ICU experience, discomfort, and overall satisfaction.

Throughout the study, the investigator closely monitored each patient for clinical or laboratory evidence of an adverse event (AE). The investigator rated the severity of each AE as mild (transient and easily tolerated), moderate (causing discomfort), or severe (causing considerable interference with the patient's usual activities, incapacitating, or life threatening). If life-threatening or prolonging hospitalization, the severe AE was also rated serious. Before breaking the blind, the investigator also assessed the possible relationship of an AE to study drug (both dexmedetomidine and saline were called study drug to maintain the study blind). Hypertension and hypotension were defined by each investigator according to his or her evaluation of each patient's age, history, and condition, as well as the absolute change in blood pressure. These were further rated in terms of severity—mild, moderate, or severe.

Statistical Analyses

To detect a clinically significant difference between the dexmedetomidine and placebo groups in the total dose of propofol administered at the .05 (2-tailed) level with 80% power, the calculated sample

Table 3. Patient Demographics and Disposition

	Dexmedetomidine	Control
Intent-to-treat patients	203	198
Mean age, years (range)	60.2 (17-88)	62.5 (17-87)
Gender n (%)		
Female	62 (31)	64 (32)
Male	141 (69)	134 (68)
Weight (kg ± SD)		
Female	64.3 ± 11.12	64.1 ± 11.61
Male	76.8 ± 12.31	76.5 ± 12.35
Evaluable patients	200	191
Reasons for nonevaluability		
Insufficient time on ventilator	0	1
Received disallowed medication during study drug therapy	3	5
Enrolled twice	0	1

size was 150 patients per treatment group. This was based on the following assumptions: propofol use over 24 hours would be 70 mg/kg for the placebo group and 20 mg/kg for the dexmedetomidine group, the effect size would be 0.35, and 90% of the patients enrolled would be evaluable.

Treatment groups were compared using analysis of variance. Differences in the distributions of patients in each category between groups were tested with a chi-square statistic. Treatment differences for weaning duration and time to extubation were also analyzed by Kaplan-Meier survival curves with log-rank analysis. If a patient was discontinued from the study for any reason, duration of weaning and time to extubation were based on the length of infusion at discontinuation. If extubation had not occurred by 24 hours, extubation time was considered 24 hours. Where indicated in the text, differences were also compared by Fisher's exact test. Statistical software used was SAS version 6.12.

All results in this report are based on the intent-to-treat population (patients who received any amount of study drug).

Results

The intent-to-treat data set consisted of 401 postsurgical patients. There were no significant differences between groups in baseline demographics or clinical characteristics (Table 3). Surgeries were of 4 types: cardiac (45%), laparotomy (30%), head and neck (7%), and other (18%). The majority of the cardiac surgeries were coronary artery bypass grafts (CABGs). Complications resulted in discontinuation from the study for 13 dexmedetomidine and 7 control group patients. Study drug was considered a possibly contributing factor for 4 of 13 dexmedetomidine and 2 of 7 control group patients. Four patients died during the study (3 dexmedetomidine, 1 control). None of the events leading to death were related to study drug. Most complications observed during the study were mild or moderate in severity, and events considered severe occurred at the same rate in both groups (12%).

During assisted ventilation, both groups were sedated to similar levels (3.4 ± 0.04, dexmedetomidine; 3.1 ± 0.04, control). A statistically significant center effect was observed (in magnitude, not direction), but results at all centers were within the range of 3 to 6. Three percent of patients in the dexmedetomidine group had an RSS of 1 at least once compared to 7% in the control group. To maintain the protocol-defined target range RSS of ≥ 3, dexmedetomidine patients required significantly less propofol than did patients in the control group, by mean total dose and mg/h (Table 4). After extubation, the dexmedetomidine patients received 8.4 ± 6.3 mg of propofol compared to 46.6 ± 16.3 mg in the control group (mean total dose ± SEM, P = .028). Sixty percent (122/203) of the dexmedetomidine patients required no propofol, 21% received less than 50 mg, and 19% received ≥ 50 mg. In contrast, 76% of the control group received propofol; 17% received less than 50 mg propofol and 59% received ≥ 50 mg. Differences by country in the use of propofol ranged from all patients in both treatment groups receiving some propofol (Austria) to only control patients receiving propofol (Sweden). In 8 of 11 countries represented in this study, the majority (60% to 85%) of the dexmedetomidine patients received no propofol.

During assisted ventilation (the first 6.5 hours of the study), patients in the dexmedetomidine group received significantly less morphine for pain relief,

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