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Dexmedetomidine in the Care of Critically Ill Patients from 2001 to 2007

An Observational Cohort Study

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ABSTRACT

Background: Dexmedetomidine is a novel sedative agent that causes anxiolysis without respiratory depression in critically ill patients. We sought to examine patient and hospital variation in dexmedetomidine use and adoption patterns of dexmedetomidine over time.

Methods: We performed a retrospective cohort study of all patients who received intravenous infusion sedation in 174 intensive care units contributing data to Project IMPACT from 2001 through 2007. Sedation use was defined as having received an intravenous sedative infusion (dexmedetomidine, midazolam, lorazepam, or propofol) for any period during the intensive care stay. The primary outcome was use of dexmedetomidine in the intensive care unit.

Results: Of 58,391 patients who received intravenous infusion sedation, 2,535 (4.3%, 95% confidence interval [CI], 4.2–4.5) received dexmedetomidine. Overall use was highest in cardiac surgery patients (11.7%, 10.8–12.7) and was similar in other surgical patients (4.3%, 4.0–4.6) and medical patients (3.4%, 3.2–3.6, $P < 0.001$). Use of dexmedetomidine increased from 2.0% (1.6–2.4) of patients receiving intravenous infusion sedation in 2001 to 7.2% (6.6–7.9) in 2007 ($P < 0.001$), primarily because of an increase in use in cardiac surgery patients (1.4%, 0.0–2.8, in 2001 *vs.* 20.2%, 17.6–22.8 in 2007, $P < 0.001$). Of the patients who received dexmedetomidine, 31.5% (29.6–33.3) received the infusion for more than 1 day, and 10.9% were not mechanically ventilated.

Conclusion: Use of dexmedetomidine in critically ill patients has increased over time, primarily as a result of an increase in use among cardiac surgery patients. A substantial portion of dexmedetomidine was administered outside of the regulatory approval guidelines at the time.

What We Already Know about This Topic

- Dexmedetomdine was approved for sedation in critical care patients over 10 yr ago, but its routine clinical application has not been described

What This Article Tells Us That Is New

- In over 58,000 critical care patients in 174 intensive care units, dexmedetomidine was administered for sedation in a small proportion (4.3%) of those receiving intravenous sedatives, most commonly in patients after cardiac surgery

PATIENTS in intensive care units (ICUs) may experience anxiety, agitation, and pain as a result of invasive monitoring and support or recovery from major surgery.[1,2] Intravenous sedation is considered integral to the care of these patients, especially for those requiring mechanical ventilation.[3,4] Recent sedation guidelines make no clear recommendations as to the choice of sedative to use for a given patient, citing propofol, midazolam, lorazepam, and halo-

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peridol as medications that can all be given as intravenous infusions.[4]

In 1999, an α-2 agonist, dexmedetomidine, was approved by the U.S. Food & Drug Administration for sedation up to 24 h in patients who are mechanically ventilated at the start of the infusion period.[5,6] Dexmedetomidine is similar in structure and action to clonidine, but is seven times more selective for the α-2 receptor. It provides potent anxiolysis and some analgesia without causing respiratory depression,[7–9] and it therefore represents a form of sedation very different from γ-aminobutyric acid receptor agonists such as benzodiazepines and propofol. The majority of early safety and efficacy trials of dexmedetomidine were done in critically ill postsurgical patients, and some specifically focused on cardiac surgery patients.[7,10,11] Since 2000, there has been an increase in research into dexmedetomidine along with the publication of several high-profile randomized controlled trials.[12–14] Still, there is little information on whether this increase in scholarly activity has been matched by an increase in its use in the ICU or an increase in use outside of regulatory guidelines.

Because dexmedetomidine has been approved only in the past 10 years for use in the United States, and at the end of 2009 for use in Canada, it has not been systematically examined in previous studies of sedation practice.[15–17] The purpose of this study was to systematically assess the use of dexmedetomidine in the ICU. Specifically, because it is a novel sedation agent, we sought to examine the patterns of use over time to better understand how a new medication gets adopted by ICU practitioners. We used a large, multicenter U.S. database that captures detailed clinical and demographic data as well as intravenous infusion medications given during the stay in intensive care. Our primary goals were to describe the characteristics of patients receiving dexmedetomidine, the types of hospitals and ICUs where dexmedetomidine is used, and the changes in the use of dexmedetomidine over time.

Materials and Methods

We performed a retrospective cohort study of the use of dexmedetomidine in patients in the Project IMPACT database (Cerner Corporation, Kansas City, MO). Project IMPACT is a large clinical registry of ICU patients. Originally developed by the Society of Critical Care Medicine in 1996, Project IMPACT provides regular performance audits and feedback to participating ICUs. Participation is voluntary, and participating organizations pay for the service. Data are collected at each institution by on-site data collectors who are certified in advance by Project IMPACT to assure standardization and uniformity in data definitions and entry.[18]

Patients and Variables

We included patients from calendar years 2001 through 2007. Data were from either consecutive admissions to each ICU or a random sample of admissions to that ICU. The latter sites collected information on 50 or 75% of all patients; the percentage was determined quarterly before data collection commenced, and random sampling then proceeded accordingly using a random number generator at the time of ICU admission. We excluded readmissions to the ICU during the same hospitalization (28,833), patients less than 18 yr old (2,700), and patients missing information on age, gender, hospital mortality, or length of stay (2,014). We examined patients who received some intravenous infusion sedation at any time during their ICU stay, defined as midazolam, lorazepam, propofol, or dexmedetomidine. Diazepam was not included because it is not usually administered as a continuous infusion and is not included as a possible infusion in the 2002 Society of Critical Care Medicine guidelines on sedation;[4] ketamine was not included because it is rarely used and is also not include in the guidelines. Complete data were not available on medications administered by bolus or intermittent intravenous doses, so only intravenous infusion sedation was examined. Information was missing on intravenous infusion medications in 1,835 (1.7% of the total), and we assumed that patients with missing infusion data received none of these medications. We *a priori* divided patients into two groups: those who received dexmedetomidine and those who did not. Patients who received dexmedetomidine may have received other sedatives as well.

Severity of illness was measured using the Mortality Probability Model on ICU admission (MPM_0-III), which incorporates specific patient characteristics on admission to ICU and was generated and validated using Project IMPACT data.[19] Hospital type was defined as academic if university-affiliated and community if non–university-affiliated. Hospital locations were defined as either urban, suburban, or rural according to Centers for Medicare & Medicaid designation.

Statistics

We performed three primary analyses designed to best understand patterns of dexmedetomidine use: an evaluation of patient, ICU, and hospital-level factors associated with dexmedetomidine use; an evaluation of dexmedetomidine use over time; and an evaluation of the timing and duration of dexmedetomidine use in individual patients. We examined cardiac surgery patients and non–cardiac surgery patients separately, because the cardiac surgery population had an especially high rate of dexmedetomidine use. We defined cardiac surgery patients as those who were admitted to a cardiac-thoracic ICU or who underwent heart valve surgery or coronary artery bypass grafting and were admitted to any ICU. We report summary statistics as proportions, means with SD or medians with interquartile ranges. To assess univariate differences in patient, ICU, and hospital characteristics associated with dexmedetomidine use, we used a chi-square test, a *t* test, or the Kruskal-Wallis test, as appropriate.

We used multivariable logistic regression to determine patient, ICU, and hospital level characteristics independently associated with receiving dexmedetomidine *versus* other intravenous infusion sedation. For modeling medical/

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surgical patients, we included ICUs with 150 or more admissions that were in hospitals with more than 250 ICU admissions in the cohort. We excluded patients who were not eligible for calculation of the MPM_0-III score (n = 4,188), which included patients who had acute myocardial infarction, burns, or were missing one or more variables required for calculation of the score.[19] Patient-level factors evaluated in the model included age, race, gender, patient type (elective surgical, emergency surgical, medical), diagnostic category (respiratory, cardiovascular, gastrointestinal, or other), location before admission (same hospital, other hospital, other ICU), cardiopulmonary resuscitation within 24 h before admission, MPM_0-III score, ventilation status on or within 60 min of admission to ICU, and duration of first episode of mechanical ventilation (examined using cubic splines split at the fifth, 27.5th, 50th, 72.5th, and 95th percentiles). To examine ICU and hospital level characteristics, we used a hierarchical mixed model to account for both ICU and hospital effects. ICU variables included were staffing model (discretionary *vs.* mandatory intensivist consult), and type of ICU (medical, surgical, or mixed medical-surgical). Hospital level variables included region of the country, location (urban, suburban, or rural), and the number of operational hospital beds (300 or fewer, 301–450, 451–800, more than 800). Variables were selected *a priori* for the model if they were known to have a potential association with outcome,[20,21] and retained in the model using stepwise elimination with a $P < 0.10$ to remain. Hospitals and ICUs nested within hospitals were random effects, and all other variables were fixed effects. Measures of the final model's calibration and discrimination are reported. We repeated the analysis for the cardiac surgery group, but because of the much smaller sample size, we included hospitals with more than 125 rather than more than 250 ICU admissions. In this smaller cohort, use of dexmedetomidine was highly colinear with hospital, so we ran a mixed effects model that included hospital as a random effect with all other variables considered to be fixed effects. We did not generate models to examine whether use of dexmedetomidine use was associated with specific outcomes because of the likelihood of large, and potentially unmeasured, indication bias.

To examine the use of dexmedetomidine over time, we graphically examined the percentage of patients who received dexmedetomidine each year and assessed temporal variation using logistic regression with indicator covariates for year. For this analysis, we also stratified patients by whether or not they received care in an academic ICU and then by type of patient (medical, surgical, or cardiac surgery), fitting interaction terms between ICU type/patient type and time.

To assess the timing and duration of use of dexmedetomidine for individual patients, we quantified the percentage of patients who received dexmedetomidine on the first day in the ICU and also examined the overall length of the intravenous infusion. A small percentage of patients (4.5%) received separate discontinuous intravenous infusions of dexmedetomidine. For these patients, only the length of time of the first infusion was used. We did not have information on actual start and stop time within days, so we were unable to assess the exact number of hours a patient received dexmedetomidine. It is possible, therefore, that some patients classified as receiving dexmedetomidine for 1 day may have received the sedative for more or less than 24 h. We considered a *P* value less than 0.05 to be statistically significant. Database management and statistical analysis were performed using Excel (Microsoft Corp., Redmond, WA), Stata 10.0 (StataCorp LP, College Station, TX), and SAS 9.1.3 (SAS Institute, Carey, NC).

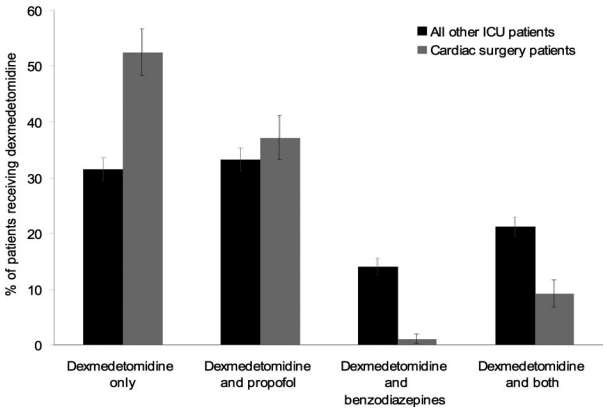

Fig. 1. The distribution of the use of other intravenous infusion sedatives in patients who received dexmedetomidine, for medical/surgical patients and cardiac surgery patients (with 95% confidence intervals). ICU = intensive care unit.

Results

Characteristics and Outcomes of Patients Who Received Dexmedetomidine

There were 296,935 ICU admissions during the study period. Of these, 58,391 (19.7%) patients received intravenous infusion sedation, and dexmedetomidine was administered to 2,535 (4.3%). Patients most frequently received dexmedetomidine in conjunction with other sedative agents (fig. 1). In general, among medical/surgical patients, those who received dexmedetomidine were less likely to have received mechanical ventilation (table 1). Patients who received dexmedetomidine had a lower severity of illness as described by the MPM_0-III mortality probability and subsequently had lower hospital mortality. ICU and hospital length of stay were consistently longer for patients who received dexmedetomidine, whether or not they survived until hospital discharge, suggesting that patients selected to receive dexmedetomidine represent an atypical group of ICU patients. Cardiac surgery patients who received dexmedetomidine were also slightly younger than those who received other intravenous infusion sedation but, unlike other patients, were equally likely to be mechanically ventilated while in the ICU. The ICU length of stay ($P = 0.71$), hospital length of stay ($P = 0.15$), and hospital mortality ($P = 0.12$) were not different between cardiac surgery patients who received dexmedetomidine and for those who received other sedation.

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Table 1. Characteristics and Outcomes for Patients Who Did and Did Not Receive Dexmedetomidine (n = 58,391)

Characteristics and Outcomes	Intravenous Infusion Sedation			
	Medical/Surgical Patients		Cardiac Surgery Patients	
	Dexmedetomidine (n = 1,971)	No Dexmedetomidine (n = 51,088)	Dexmedetomidine (n = 564)	No Dexmedetomidine (n = 4,768)
Total, %	3.7	96.3	10.6	89.4
Age, mean ± SD	53.0 ± 17.9	56.5 ± 18.3*	59.9 ± 13.6	64.2 ± 12.9*
Male, %	63.9	59.3*	64.9	68.0
Race, %				
Caucasian	75.1	78.4*	79.4	86.5*
African American	19.0	14.1	16.0	6.8
Hispanic	4.0	5.6	2.3	4.5
Other	2.0	1.9	2.3	2.2
Patient type, %				
Medical	61.4	66.8*	5.1	6.0
Elective surgical	17.3	13.9	73.4	75.1
Emergent surgical	21.3	19.3	21.5	18.9
Mechanically ventilated on admission to ICU, %	61.5	71.1*	92.7	92.3
Ever mechanically ventilated in ICU, %	86.3	96.8*	98.8	99.3
Duration of 1st episode of mechanical ventilation (days), median (IQR)	3.9 (1.5–8.6)	2.3 (0.8–6.1)*	0.6 (0.3–1.1)	0.6 (0.3–1.0)
CPR in 24 h before admission, %	2.5	3.8*	10.6	9.8
MPM_0-III mortality probability, mean ± SD†	14.1 ± 14.7	19.5 ± 19.0*	NA	NA
ICU LOS (days), median (IQR)				
All	7.9 (3.8–14.2)	4.8 (2.2–10.1)*	2.1 (1.1–5.0)	2.1 (1.1–4.8)
Survivors	7.8 (3.7–13.6)	4.6 (2.2–9.8)*	2.0 (1.0–4.7)	2.1 (1.1–4.1)
Nonsurvivors	10.9 (5.0–17.4)	5.4 (2.1–11.1)*	8.6 (5.2–15.0)	6.5 (3.0–14.0)
Hospital LOS (days), median (IQR)				
All	15 (8–26)	11 (6–21)*	9 (6–15)	9 (6–14)
Survivors	15 (9–26)	12 (7–22)*	9 (6–15)	9 (6–14)
Nonsurvivors	14 (7–25)	9 (3–17)*	13 (9–29)	12 (5–25)
Hospital mortality, %	12.7	23.7*	5.5	7.3

* $P < 0.05$ for comparison of dexmedetomidine group with other sedation group. Tests were separate for medical/surgical patients and cardiac surgery patients. † The MPM_0-III score was calculated on n = 48,870. The score is not calculated on patients missing one or more required variable, on patients with burns, or on those who had an acute myocardial infarction or are post-cardiac surgery.[19]

CPR = cardiopulmonary resuscitation; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; MPM = mortality probability model; NA = not applicable.

Hospital and ICU-level Factors Associated with Dexmedetomidine Use

Overall, 48.4% of hospitals (60 of 124) and 48.0% of ICUs (83 of 173) used dexmedetomidine in at least one ICU patient between 2001 and 2007. A much greater percentage of patients in cardiothoracic ICUs received dexmedetomidine compared with patients in other ICUs (table 2). Cardiac surgery patients were much more likely to receive dexmedetomidine ($P < 0.001$) in ICUs with a mandatory intensivist staffing model than in ICUs with a discretionary intensivist consult model, but this difference was not replicated in general ICU patients. For general patients as well as cardiac surgery patients, those cared for in government-owned hospitals were less likely to receive dexmedetomidine ($P < 0.001$). Cardiac surgery patients in urban hospitals received dexmedetomidine more frequently than those in suburban or rural hospitals. Both groups of patients had an appreciably higher likelihood of receiving dexmedetomidine if they received care in large (more than 800 beds) hospitals.

Independent Factors Associated with Receiving Dexmedetomidine

After multivariable adjustment in medical/surgical patients, the prior location of the patient, duration of mechanical ventilation, decreasing severity of illness, and cardiopulmonary resuscitation

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Table 2. Dexmedetomidine Use by Hospital and ICU Level Characteristics

	Medical/Surgical Patients			Cardiac Surgery Patients		
	Number of ICUs	n	% Receiving Dexmedetomidine	Number of ICUs	n	% Receiving Dexmedetomidine
Type of ICU (total, n = 173)	169			91		
Medical	35	7,341	3.3	11	31	51.6
Surgical	39	14,013	4.6	26	1,466	1.9
Mixed medical/surgical	93	31,576	3.4	50	2,226	7.1
Cardiothoracic	NA	NA	NA	4	1,609	22.5
Neurologic	2	129	3.1	NA	NA	NA
Staffing model (coverage)						
Mandatory intensivist	47	24,028	3.9	26	2,415	16.7
Discretionary intensivist	113	27,978	3.8	60	2,678	6.0
None	6	933	0.2	3	236	0
Unknown	3	120	7.5	2	3	0
Hospital type (total, n = 124)						
Academic	21	18,320	3.4	17	2,823	13.5
Community	96	32,597	4.1	54	2,468	7.3
Government	5	2,133	1.1	3	40	2.5
Hospital location						
Urban	60	29,266	3.9	42	3,035	17.3
Suburban	44	12,100	5.5	20	600	5.0
Rural	17	11,564	1.4	12	1,697	0.5
Unknown	1	129	0	NA	NA	NA
Hospital beds						
0–300	27	6,325	2.4	12	1,021	9.8
301–450	41	19,538	3.3	26	1,665	3.5
451–800	42	17,759	2.8	27	1,409	6.6
>800	11	9,359	7.1	9	1,237	25.3
Unknown	1	78	0	NA	NA	NA

$P < 0.001$ for all tests of statistical significance between all patients.
ICU = intensive care unit; NA = not applicable.

within the 24 h before admission were significantly associated with receiving dexmedetomidine (table 3). Very short duration of mechanical ventilation was associated with a very small decrease in the probability of receiving dexmedetomidine, followed by a sharp, nonlinear association for longer duration up to day 6 (see appendix). No ICU or hospital level factors were independently associated with dexmedetomidine use in the final model.

After multivariable adjustment in cardiac surgery patients, age, admission type, duration of mechanical ventilation, ventilation on or within the first 60 min of admission, year, and admission to an ICU with a mandatory intensivist model were significantly associated with receiving dexmedetomidine (table 4). Although statistically significant, these effects were of minimal clinical significance.

Use of Dexmedetomidine Over Time

For all ICU patients from 2001 through 2007, the majority received propofol for sedation (fig. 2A and B). Use of dexmedetomidine tripled from 2.0% (1.6–2.4) of patients receiving intravenous infusion sedation in 2001 to 7.2% (6.6–7.9) in 2007 ($P < 0.001$), primarily because of an increase in use in cardiac surgery patients (1.4%, 0.0–2.8, in 2001 *vs.* 20.2%, 17.6–22.8, in 2007, $P < 0.001$). The overall increase in the use of dexmedetomidine was due both to an increase in the percentage of ICUs using dexmedetomidine (18.8% in 2001, and 49.4% in 2007) and to an increase in the percentage of patients receiving dexmedetomidine in the ICUs where it was already in use (4.1% of patients in ICUs using dexmedetomidine in 2001 and 9.4% in 2007). The rate of increase was similar in academic and nonacademic ICUs, except from 2005 to 2007, when dexmedetomidine use increased rapidly in academic ICUs, contributing to an overall difference in the cohort ($P < 0.001$ for interaction term between type of ICU and time, fig. 3A). Stratified by type of patient, there was a more rapid increase in dexmedetomidine use in cardiac surgery patients compared with medical patients ($P < 0.001$) (fig. 3B). Other surgical patients had a slightly increasing probability, over time, of receiving dexmedetomidine that was similar to that seen in medical patients ($P < 0.001$).

Length of Dexmedetomidine Infusions

In 32.4% of patients who received dexmedetomidine, the infusion started on the first day of admission to the ICU (table 5). Cardiac surgery patients were more likely to receive dexmedetomidine on the first day in the ICU (63.0%) than other patients (23.4–29.8%). The mean infusion duration was 1.5 ± 2.0 days. Cardiac surgery patients had a shorter duration (mean, 0.7 ± 1.2 days). A substantial portion of

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Table 3. Patient, ICU, and Hospital Level Factors Associated with Receiving Dexmedetomidine *vs.* Other Intravenous Infusion Sedation (Excluding Cardiac Surgical Patients)

n = 48,235	Odds Ratio (95% CI)	*P* Value
Sex		
Male	1.00	—
Female	0.83 (0.68–1.03)	0.08
Prior location of patient		
Same hospital	1.00	—
Other hospital	0.44 (0.27–0.71)	< 0.001
Other ICU	0.62 (0.38–0.97)	0.04
Duration of first episode of MV	—†	< 0.001
MPM_0-III probability‡	0.82 (0.77–0.88)	< 0.001
CPR within first 24 h prior to ICU admission	1.37 (1.05–1.79)	0.07

Other variables that were examined but were not included in the multivariable model due to $P > 0.10$ in the univariate analysis: intensive care unit (ICU) staffing model (discretionary critical care consult *vs.* mandatory, ICU type (mixed, medical, surgical), region of hospital, location (rural, outer urban, large urban), number of hospital beds, academic status of the hospital, race, diagnostic category, age, patient type, year. Hosmer-Lemeshow Statistic = 10.91 ($P = 0.21$), Shapiro-Wilk test = 0.78, Brier Score = 0.036, area under the receiver operating characteristic curve = 0.67.

† Splined variable; odds ratio depends on value of duration of mechanical ventilation. Please see appendix for further information on model results for length of mechanical ventilation. ‡ The odds ratio for each 10% increase in MPM_0-III probability of mortality.

CI = confidence interval; CPR = cardiopulmonary resuscitation; MPM = mortality probability model; MV = mechanical ventilation; NS = not significant.

Table 4. Patient, ICU, and Hospital Level Factors Associated with Receiving Dexmedetomidine *vs.* Other Intravenous Infusion Sedation for Cardiac Surgical Patients

N = 5,332	Odds Ratio (95% CI)	*P* Value
Age*	0.99 (0.98–0.99)	< 0.001
Patient type		
Medical	1.00	—
Elective surgical	1.13 (1.08–1.18)	< 0.001
Emergent surgical	1.13 (1.07–1.17)	< 0.001
Ventilated at admission or within 60 min	0.92 (0.88–0.96)	< 0.001
Duration of first episode of MV (days)	1.01 (1.00–1.01)	0.03
ICU model		
Mandatory	1.00	—
Discretionary	0.96 (0.93–0.99)	0.02
Year		
2001	1.00	—
2002	1.02 (0.96–1.08)	0.50
2003	1.06 (1.01–1.12)	0.03
2004	1.05 (0.99–1.11)	0.09
2005	1.01 (0.96–1.07)	0.75
2006	1.01 (0.96–1.07)	0.70
2007	1.12 (1.06–1.18)	< 0.001

Other variables that were examined but were not included in the multivariable model due to $P > 0.10$: intensive care unit (ICU) type (mixed, medical, surgical), region of hospital, location (rural, outer urban, large urban), number of hospital beds, academic status of the hospital, race, sex, cardiopulmonary resuscitation within 24 h before admission, location prior to admission (same hospital, other hospital, other ICU). Hosmer-Lemeshow Statistic = 36.61 ($P < 0.01$), Shapiro-Wilk test = 0.71, Brier Score = 0.064, area under the receiver operating characteristic curve = 0.90.

* For every 10-yr increase in age.

CI = confidence interval; MV = mechanical ventilation.

patients (31.5%) received a dexmedetomidine infusion for more than 1 day.

Use of Opiates

We also examined the use of intravenous infusions of opiates in patients who received dexmedetomidine *versus* patients who received other sedation. Slightly more patients who received dexmedetomidine received no intravenous infusion of opiates compared with patients who received other sedatives (65.4 *vs.* 62.3%, $P = 0.002$), but the overall distribution of types of intravenous infusions of opiates was similar in the two groups (fig. 4), demonstrating no large change in patterns of use of infusions of opiates with dexmedetomidine.

Discussion

The percentage of patients who received intravenous infusion sedation who were sedated with dexmedetomidine more than tripled from 2001 to 2007, with the most substantial increases among cardiac surgery patients. At the time of the study, the Food and Drug Administration approved indications for dexmedetomidine infusion required that it be administered only to patients mechanically ventilated at the start of the infusion for a duration not exceeding 24 h. The Food and Drug Administration indications may explain these usage patterns, because cardiac surgery patients are more predictably extubated within 24 h after admission to an ICU than are other types of critically ill patients. Moreover, some of the earlier published dexmedetomidine studies were conducted in patients undergoing cardiac surgery.[7,10]

We did find considerable "off-label" use of dexmedetomidine. In particular, many patients received an infusion for more than 1 day, and 10% were never mechanically ventilated. The 2002 Clinical Practice Guidelines published by the Society of Critical Care Medicine did not make direct recommendations about the use of dexmedetomidine, concluding that "the role of this new agent in the sedation of ICU patients remains to be determined."[4] Data also suggest that clinicians do not always follow guidelines, even when they are clear.[22] Our results regarding clinician use of dexmedetomidine are similar to a smaller study examining prescribing patterns in 10 ICUs between 2001 and 2002; approximately one third of the patients in that study received dexmedetomidine for greater than 24 h, and 15% were never mechanically ventilated.[23]

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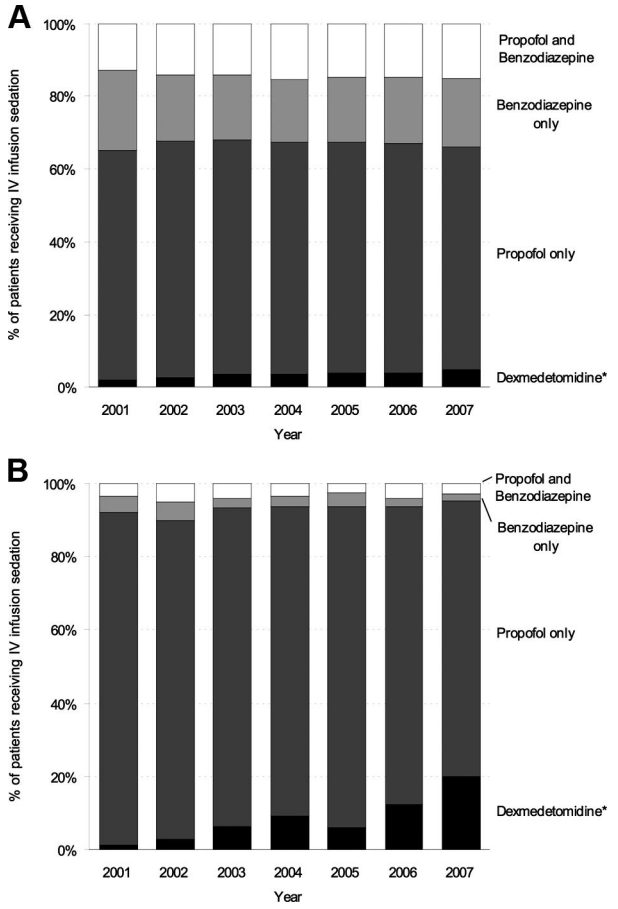

Fig. 2. Trends over time: the distribution of the use of different types of intravenous (IV) infusion sedatives among all intensive care unit patients who received any IV infusion sedation from 2001–2007 for medical/surgical patients (*A*), and cardiac surgery patients (*B*). *$P = 0.001$ for increase over time using logistic regression.

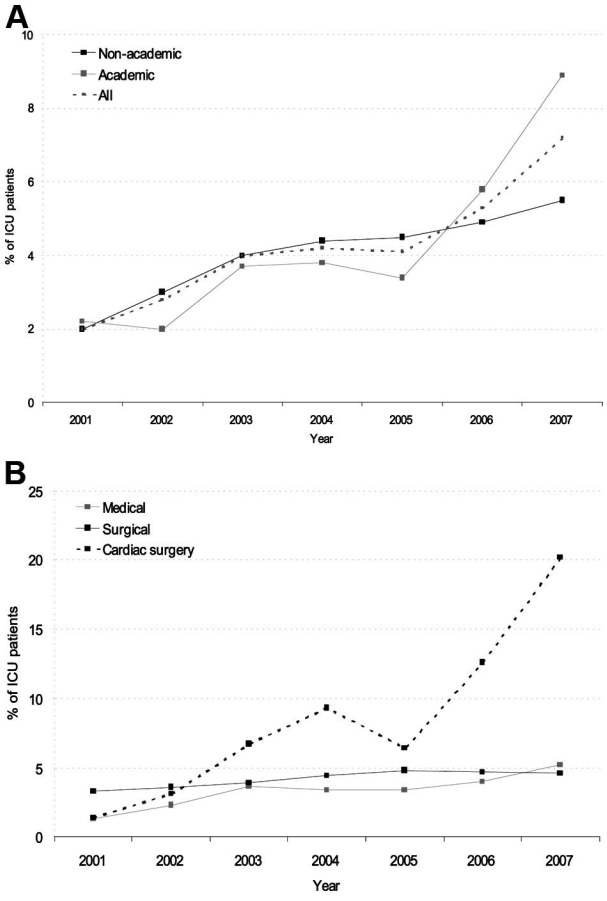

Fig. 3. Trends over time: the percentage of patients who received dexmedetomidine among patients who received any intravenous infusion sedation stratified by care in academic *versus* nonacademic intensive care units (ICUs) (*A*) and stratified by type of patient (medical, general surgical, and cardiac surgical) (*B*).

For medical/surgical patients, we found little difference in use between academic and community hospitals. This finding was surprising, because it is inconsistent with other data suggesting faster adoption of new drugs in academic *versus* nonacademic hospitals.[24] Nondifferential uptake may indicate that, at least with regard to novel pharmaceuticals, U.S. community practitioners and academic practitioners in ICUs are equally likely to adopt new therapies or that adoption was sufficiently slow in both groups because of the absence of current randomized trial data demonstrating superiority of the new drug such that we were unable to detect a difference. However, cardiac surgery patients seen in academic hospitals were more likely to receive dexmedetomidine than patients in nonacademic hospitals. Perhaps with the clearer indication for use among cardiac surgery patients, the more standard patterns of adoption apply.

Cardiac surgery patients who did or did not receive dexmedetomidine were remarkably equivalent with regard to patient characteristics, length of stay, and mortality. The results of the multivariable analysis confirmed this, because few hospital, ICU, or patient-level factors available were determinants of receiving dexmedetomidine in this population. Among general medical/surgical patients, those who received dexmedetomidine had a lower MPM_0-III predicted mortality compared with other patients, suggesting that clinicians tended to select less sick patients for use of dexmedetomidine. This study was not designed to assess outcomes associated with dexmedetomidine *versus* other sedation. The selection biases associated with use are likely to be enormous. Even with rigorous statistical techniques to adjust for differences between groups, results from such an analysis would be difficult to interpret.

The more surprising outcome, perhaps, is that, compared with medical/surgical patients who received other types of intravenous infusion sedation, the patients who received dexmedetomidine had an increased ICU and hospital stay, both for survivors and nonsurvivors. It is noteworthy that a study of the use of dexmedetomidine in general ICU patients reported a relatively high rate of adverse drug reactions (30%), some of which contributed to an increased length of stay.[23] The data set in our study was not designed to capture these reactions, but it seems unlikely that such complications

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Table 5. Timing of Infusions of Dexmedetomidine

	All	Medical	Surgical	Cardiac Surgical
Received dexmedetomidine on first day in ICU (%)	32.4	23.2	29.8	63.0
Length of dexmedetomidine infusion (days), mean ± SD	1.5 ± 2.0	1.6 ± 2.0	1.7 ± 2.3	0.7 ± 1.2
Length of dexmedetomidine infusion, %				
0–1 Day	68.2	62.8	65.5	90.4
2+ Days	31.5	37.2	34.5	9.6

ICU = intensive care unit.

would fully explain the large differences seen in our study. Whether the longer length of stay for these patients is due to a selection bias or to the use of dexmedetomidine warrants further research.

This analysis has a number of important limitations. We have no details on the infusion dose or loading dose of dexmedetomidine. We also do not know exact start and stop times of dexmedetomidine (only the date). Therefore, we were not able to assess the exact number of hours a patient received dexmedetomidine. Therefore, it is possible, on the one hand, that some patients estimated as receiving "1 day" of dexmedetomidine received it only for a few hours overnight or, on the other hand, that some patients received close to 48 h of an infusion. In particular, this affects the reliability of our estimates regarding the percentage of patients who received dexmedetomidine for longer than 24 h.

We also have no data on bolus medications, which is perhaps most pertinent to dosing of benzodiazepines. This prevented us from capturing all patients who received sedation. We could not assess patient satisfaction with dexmedetomidine, but it has not previously been shown to be superior to propofol in this respect.[11,25] There were only 5,332 cardiac surgery patients, which did not give us enough statistical power to detect large effects in a multivariable model. Finally, our data may represent a select group of hospitals and ICUs perhaps more focused on quality improvement than most, as the hospitals that submitted data were all motivated to purchase the Project IMPACT system. Nonetheless, our study cohort included patients from a diverse range of ICUs and hospitals, from many different regions in the United States, with almost 300,000 admissions.

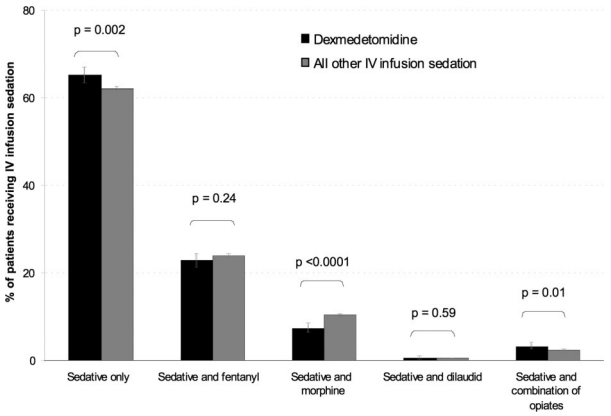

Fig. 4. The distribution of the use of intravenous (IV) infusions of opiates among patients who received dexmedetomidine *versus* other IV infusion sedation (with 95% confidence intervals).

It is rare to be able to track the adoption of a new medication in intensive care units. The randomized controlled trials on which "standard of care" may be based frequently exclude the majority of potential ICU patients. Thus, it remains essential to conduct observational studies to elucidate what types of patients are actually receiving a new medication or technology. This type of information is important for safety, because it helps to elucidate patterns of diffusion of innovation and may inform decisions regarding how to speed adoption of other types of innovation, such as use of thromboprophylaxis and sedation scales.

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Appendix: Modeling of the Length of Mechanical Ventilation as a Predictor of the Use of Dexmedetomidine

Duration of first episode of mechanical ventilation (days) was examined using logarithm and spline terms, at log equivalents of 0.11, 0.81, 2.10, 5.45, 17.50 days (representing the fifth, 27.5th, 50th, 72.5th, and 95th percentiles). In figure 5, we plot the likelihood of receiving dexmedetomidine for a given duration of mechanical ventilation.

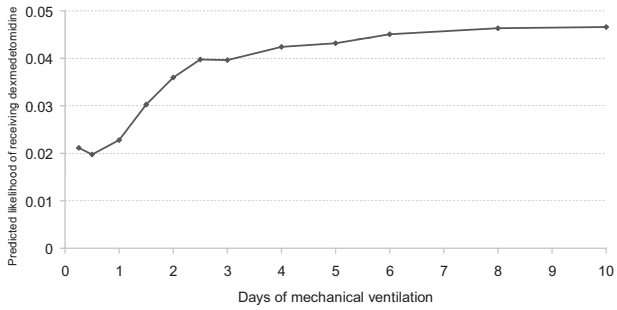

Fig. 5. Likelihood of receiving dexmedetomidine for a given duration of mechanical ventilation (medical/surgical patients).

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