

Monitored Anesthesia Care with Dexmedetomidine: A Prospective, Randomized, Double-Blind, Multicenter Trial

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BACKGROUND: Dexmedetomidine (DEX) is increasingly being used as a sedative for monitored anesthesia care (MAC) because of its analgesic properties, “cooperative sedation,” and lack of respiratory depression. In this randomized, multicenter, double-blind, Phase III Food and Drug Administration study, we evaluated the safety and efficacy of two doses of DEX for sedation of patients undergoing a broad range of surgical or diagnostic procedures requiring MAC.

METHODS: Three hundred twenty-six patients were randomized 2:2:1 to DEX 0.5 $\mu\text{g}/\text{kg}$, DEX 1 $\mu\text{g}/\text{kg}$, or saline placebo initial loading dose, followed by a maintenance infusion of 0.2–1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of DEX (or equivalent volume of saline) titrated to a targeted level of sedation (≤ 4 on the Observer’s Assessment of Alertness/Sedation Scale [OAA/S]). Study drug was started at least 15 min before placement of regional or local anesthetic block. Midazolam was given for OAA/S > 4 and fentanyl for pain. The primary end-point was the percentage of patients not requiring rescue midazolam.

RESULTS: Significantly fewer patients in the 0.5- and 1- $\mu\text{g}/\text{kg}$ DEX groups required supplemental midazolam compared with placebo (59.7% [80/134], 45.7% [59/129] vs 96.8% [61/63], respectively; $P < 0.001$) and at lower doses to achieve an OAA/S ≤ 4 before and during surgery compared with the saline group (1.4 and 0.9 mg vs 4.1 mg, respectively; $P < 0.001$, each group compared with placebo). Both DEX groups required significantly less fentanyl (84.8 and 83.6 μg vs 144.4 μg , respectively; $P < 0.001$, for both DEX groups versus placebo) for all surgical subtypes. Anesthesiologists indicated significantly increased ease of achieving and maintaining targeted sedation in both DEX groups compared with placebo with midazolam ($P < 0.001$). Patient satisfaction was significantly higher with DEX ($P \leq 0.009$, both groups versus placebo). Common adverse events with DEX were protocol-defined bradycardia and hypotension that were predominately mild to moderate in severity. The incidence of clinically significant respiratory depression (defined as a respiratory rate of < 8 or an oxygen saturation of $< 90\%$) was lower in DEX-treated patients ($P = 0.018$, for both groups versus placebo).

CONCLUSIONS: DEX is an effective baseline sedative for patients undergoing MAC for a broad range of surgical procedures providing better patient satisfaction, less opioid requirements, and less respiratory depression than placebo rescued with midazolam and fentanyl.

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The most commonly used medications for monitored anesthesia care (MAC) are midazolam, propofol, and fentanyl. Each of these drugs, however, causes respiratory depression.^{1,2} The most commonly reported adverse effects of midazolam are variability of patient

response and respiratory complications.² Combining midazolam with fentanyl or other opioids for MAC increases the risk for hypoxemia and apnea.¹ The addition of propofol may further exacerbate respiratory depression.³ A 2006 review of closed malpractice claims in the American Society of Anesthesiologists’ Closed Claim Database revealed oversedation leading to respiratory depression played a pivotal role in patient injuries during MAC.⁴ The adverse respiratory profile of benzodiazepines, propofol, and opioids, along with the stress response to surgery, create the need for a sedative drug

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that can be used safely during MAC in both healthy and high-risk patients, with limited adverse effects.

Dexmedetomidine (Precedex[®], Hospira, Lake Forest, IL) is a centrally acting α -2 receptor agonist that can be titrated to the desired level of sedation without significant respiratory depression.⁵⁻⁷ Dexmedetomidine has an analgesic-sparing effect, significantly reducing opioid requirements both during and after surgery.^{3,8-12} In addition, dexmedetomidine has a sympatholytic effect that can attenuate the stress response to surgery, mitigating tachycardia and hypertension.^{8,11} Because of its analgesic properties, "cooperative sedation," and lack of respiratory depression, dexmedetomidine is increasingly being used as a sedative for MAC.⁶ There have been several reports on the successful use of dexmedetomidine as the primary sedative drug for orthopedic, ophthalmic, dental, and plastic surgery, and for diagnostic procedures.¹¹⁻¹⁶

The safety and efficacy of dexmedetomidine in nonintubated patients undergoing MAC have not been rigorously evaluated in a large clinical study. We present the results of a prospective, multicenter trial that evaluated the safety and efficacy of dexmedetomidine as the primary sedative drug for nonintubated patients having MAC.

METHODS

This was a prospective, randomized, double-blind, placebo-controlled, Phase III study conducted at 26 investigational sites in the United States (ClinicalTrials.gov; NCT00398827). A placebo-controlled design was selected to comply with Food and Drug Administration requirements. The protocol was approved by the IRB of the study centers, and all patients provided written informed consent. Patients scheduled for elective surgeries and procedures performed in an operating room or procedure room and requiring MAC with an anesthesiologist in attendance were eligible for enrollment. Surgeries/procedures were expected to last at least 30 min and included orthopedic, ophthalmic, plastic, vascular stents, breast biopsies, hernias, arteriovenous fistulas, and excision of lesions. Eligible patients were ≥ 18 yr old, ASA physical status of I-IV, and required a local anesthetic block. Patients were excluded if they had received general anesthesia within 7 days before study entry, any experimental drug within 30 days before study drug administration, an α -2-agonist or antagonist within 14 days before the scheduled surgery/procedure, an IV opioid within 1 h, or an oral or IM opioid within 4 h of the start of study drug administration. Patients were also excluded if they required epidural or spinal anesthesia, or had any of the following: acute unstable angina, acute myocardial infarction documented by laboratory findings in the past 6 wk, heart rate (HR) < 50 bpm, systolic blood pressure (SBP) < 90 mm Hg, or third-degree heart block unless the patient had a pacemaker.

Patients were randomized in a 2:2:1 ratio to dexmedetomidine 0.5- $\mu\text{g}/\text{kg}$ load arm, 1- $\mu\text{g}/\text{kg}$ load arm, or saline placebo using a computer-generated randomization schedule. Two different loading groups were used for the main purpose of maintaining the blinding of the investigators with reference to the placebo group. The respective initial loading doses of 0.5 or 1.0 $\mu\text{g}/\text{kg}$ of dexmedetomidine or placebo were administered over 10 min followed by a maintenance infusion beginning at a rate of 0.6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Fifteen minutes after starting study drug, patients were assessed for level of sedation using the Observer's Assessment of Alertness/Sedation Scale (OAA/S)¹⁷ and any patient having a score > 4 received IV midazolam in 0.5 mg doses, repeated until OAA/S was ≤ 4 . After the initial loading dose, study drug was titrated from 0.2 to 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of dexmedetomidine or saline equivalent volume to maintain score ≤ 4 . All subjects received a local anesthetic block before surgery/procedure (at least 15 min after beginning the drug infusion and when an OAA/S score ≤ 4 was observed). If a patient was not adequately sedated through titration, rescue midazolam could be administered as single IV boluses of 0.5 mg, repeated as needed to achieve an OAA/S score ≤ 4 . IV fentanyl, 25 μg boluses and repeated as necessary, could be given if a patient expressed a pain score of ≥ 3 during study drug infusion and ≥ 4 in the postanesthesia care unit (PACU) on a scale of 0-10 (0 = no pain, 10 = worst pain), or the investigator determined the presence of pain when verbal communication was not possible. At any time, if clinically indicated, the patient could be converted to an alternative sedative or anesthetic therapy and the study drug discontinued. OAA/S scores and all standard vital signs were obtained every 5 min throughout the study drug infusion and before the administration of any rescue midazolam. Study drug was discontinued when the patient left the operating room. Subjects remained in the PACU for a minimum of 1 h after discontinuation of study drug. Vital signs were recorded every 5 min for the first 15 min, then every 15 min for the next 45 min. The OAA/S and pain scores were assessed every 15 min while the patient was in the PACU.

Immediately after transfer to the PACU, the anesthesiologist rated the ease of maintenance of intraoperative sedation, respiratory stability, hemodynamic stability, and patient cooperation using visual analog scale scores. The patient's level of anxiety experienced before, during, and after the study drug infusion was assessed using the Anxiety Assessment Scale; scores range from 0 (no anxiety) to 10 (extreme anxiety). Patients were discharged when the Aldrete Score¹⁸ was ≥ 9 . Twenty-four hours after discontinuation of study drug, patients were visited or contacted by telephone to assess satisfaction with their anesthetic using the Iowa Satisfaction with Anesthesia Scale.¹⁹ The schematic of the overall study design is provided in Figure 1.

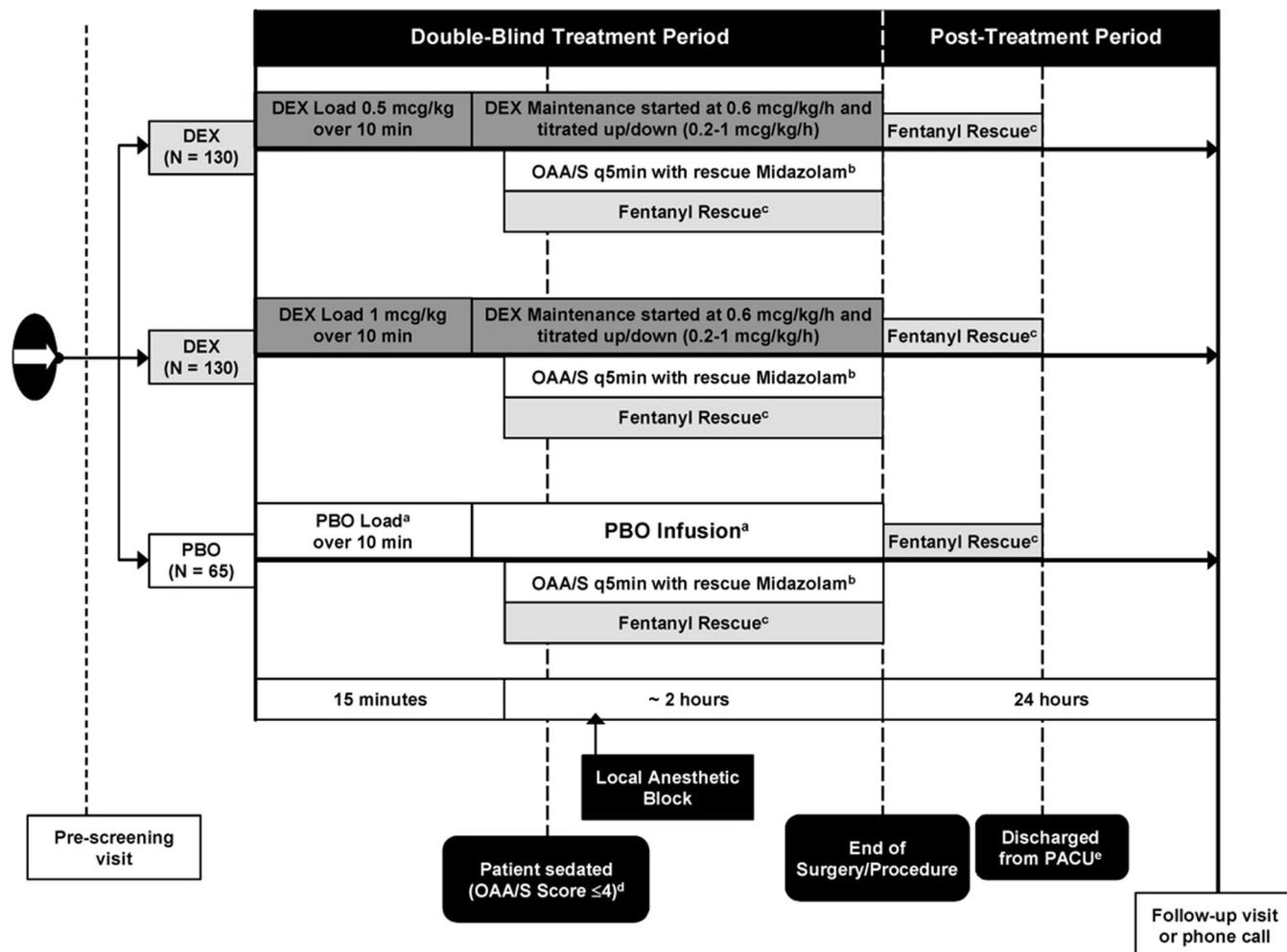


Figure 1. Study schema. ^aPlacebo group received sodium chloride at an infusion rate equivalent to the DEX groups. ^bBeginning 15 min after the start of study drug infusion and continuing throughout the surgery/procedure, rescue boluses of midazolam 0.5 mg were given for OAA/S >4 after titration of study drug. ^cBeginning 15 min after study drug infusion until the patient was discharged from the PACU, rescue boluses of fentanyl 25 μ g IV were given as needed for pain based on protocol-specified pain assessments. ^dThe patient was sedated (OAA/S \leq 4) before entry into the operating room, procedure room, or block room and before administration of local anesthetic block. ^eAt least 1 h after study drug had been discontinued. DEX = dexmedetomidine; PBO = placebo; OAA/S = Observer's Assessment of Alertness/Sedation Scale; PACU = postanesthesia care unit.

The primary efficacy end-point was the percentage of patients not requiring midazolam for rescue sedation based on achieving and/or maintaining an OAA/S score \leq 4. Secondary end-points included total amount of rescue midazolam, time from onset of study drug infusion to first dose of rescue midazolam, percentage of patients who converted to alternative sedative and/or anesthetic therapy because of treatment and rescue failure, time to recovery and readiness for discharge from the PACU, total amount of fentanyl required for pain control, incidence of postoperative nausea and vomiting in the PACU, protocol-defined hemodynamic stability (SBP time outside range + HR time outside range/study drug infusion period), and overall patient and anesthesiologist satisfaction. Safety was evaluated by monitoring adverse events, cardiac hemodynamic variables, laboratory tests, vital signs, and concomitant medications. Protocol-defined relative changes in arterial blood pressure (30% or more change from baseline, which was

determined as the average of three measurements 3 min apart), HR (30% or more change from baseline determined as for arterial blood pressure), and absolute respiratory depression (defined as respiratory rate of <8 or an oxygen saturation of <90%) were also assessed.

Statistical Analysis

All patients who received randomized study drug and had at least one postbaseline efficacy measurement were included in the intent-to-treat population. Safety analyses were performed on all patients who were randomized and received any study drug. For the primary efficacy end-point, statistical assessments comparing dexmedetomidine, 1- μ g/kg load arm versus placebo (primary analysis), and dexmedetomidine, 0.5- μ g/kg load arm versus placebo, were performed separately using the Cochran-Mantel-Haenszel test adjusting for surgery/procedure type. Statistical assessments comparing each dexmedetomidine group versus placebo for

total amount of rescue midazolam were performed separately using an analysis of variance model adjusted for surgical type. Subgroup analyses were performed according to surgical procedure. χ^2 tests were used to compare treatment differences in the percentage of patients reporting any treatment-emergent adverse event and for each system organ class for each dexmedetomidine arm versus placebo. Vital signs were assessed using a two-sample *t*-test for each dexmedetomidine arm versus placebo. A sample size of 250 patients was required to provide >99% power, assuming >70% of patients in the dexmedetomidine 1- μ g/kg group and <10% in the placebo group did not require rescue midazolam for proper sedation during study drug infusion to detect a difference among treatment groups. All statistical tests were two-sided and a *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Three hundred seventy-one eligible patients were randomized. Of these, 326 patients were included in the intent-to-treat and safety analyses, with 134 in the dexmedetomidine 0.5- μ g/kg arm, 129 in the dexmedetomidine 1- μ g/kg arm, and 63 in the placebo arm (Fig. 2). Baseline characteristics were similar among treatment groups (Table 1). Mean (\pm SD) duration of study drug infusion was 97.0 \pm 52.5, 102.3 \pm 59.7, and 105.6 \pm 47.4 min for the 0.5- μ g/kg, 1- μ g/kg, and placebo arm, respectively.

Efficacy

Significantly more patients in the dexmedetomidine 1- μ g/kg group did not require rescue midazolam to achieve an OAA/S score ≤ 4 compared with the placebo group (54.3% [70/129] vs 3.2% [2/63]; *P* < 0.001; Fig. 3). The number of patients in the dexmedetomidine 0.5- μ g/kg group requiring supplemental midazolam (40.3% [54/134] vs 3.2% [2/63]; *P* < 0.001; Fig. 3) was also significantly higher than for the placebo group (*P* < 0.001). The percentage of patients not requiring rescue midazolam was significantly higher in both dexmedetomidine groups versus placebo according to all surgical subtypes, with the exception of the dexmedetomidine 0.5- μ g/kg pooled Subgroup 3 (breast biopsies, excision of lesions, and plastic surgical procedures). All but two patients in the placebo group received rescue midazolam and both underwent cataract surgery.

The mean total dose of rescue midazolam was significantly lower for the dexmedetomidine 0.5- and 1- μ g/kg groups than for the placebo group (1.4 and 0.9 mg vs 4.1 mg, respectively; *P* < 0.001 for each comparison; Fig. 3). Results for the pooled surgery subtypes also significantly favored both dexmedetomidine groups over placebo. The median length of time from the start of study drug until a rescue dose of midazolam was administered was significantly longer for both the 0.5- and 1- μ g/kg groups than for the

placebo group (40.0 and 114.0 min vs 20.0 min, respectively; *P* < 0.001 for each comparison). Significantly fewer patients in both dexmedetomidine groups required additional drugs besides midazolam for sedation than the placebo group. Two patients (1.6%) in the 1- μ g/kg group, four (3.0%) in the 0.5- μ g/kg group, and seven (11.1%) in the placebo group could not be sedated with protocol-specified amounts of study drug or rescue midazolam (0.2 mg/kg) and required additional sedation with propofol or general anesthesia to complete their surgical procedure (*P* < 0.02 for each comparison).

Significantly fewer patients required rescue fentanyl for pain during the infusion period for all surgeries in both the 0.5- and 1- μ g/kg groups compared with the placebo group (59.0% [79/134] and 42.6% [55/129] vs 88.9% [56/63], respectively; *P* < 0.001 for both comparisons; Table 2). Additionally, significantly higher doses of fentanyl were required for the placebo group during the infusion period compared with both dexmedetomidine 0.5- and 1- μ g/kg treatment groups (144.4 μ g vs 84.8 and 83.6 μ g, respectively; *P* < 0.001 for both comparisons; Table 2). More fentanyl was required in all surgical subgroups, except ophthalmic surgery, in the placebo arm than both dexmedetomidine treatment groups.

Median time to recovery and readiness for discharge from the PACU was 29.0 min for patients in the dexmedetomidine 0.5- μ g/kg group, 25.0 min for patients in the dexmedetomidine 1- μ g/kg group, and 14.0 min in the placebo group (*P* = 0.068). Significantly more patients in the placebo group required additional pain medication in the PACU than the dexmedetomidine 1- μ g/kg group (*P* ≤ 0.048). The incidence of postoperative nausea and vomiting was not significantly different among treatment groups.

Results from the anesthesiologists' assessment showed significant differences favoring both dexmedetomidine groups compared with the placebo group for ease of maintenance of sedation (visual analog scale 2.8 and 2.2 cm vs 4.4 cm, respectively; *P* < 0.001 for each comparison). There were no significant differences in anesthesiologists' assessment of hemodynamic stability, respiratory stability, or patient cooperation. After surgery in the PACU, patients' mean anxiety scores were significantly lower in the 1- μ g/kg group than in the placebo group (1.0 vs 1.9; *P* = 0.007). The Iowa Satisfaction with Anesthesia Scale results showed that patients were significantly more satisfied in both dexmedetomidine groups versus placebo (*P* ≤ 0.001 ; Table 3).

Safety

The most common adverse events during the infusion period were protocol-defined changes in arterial blood pressure, HR, and respiratory rate. The majority of adverse events were mild or moderate in severity. A small group of patients received drug interventions for changes in HR and/or arterial blood pressure (Table 4). There was no difference in the incidence of

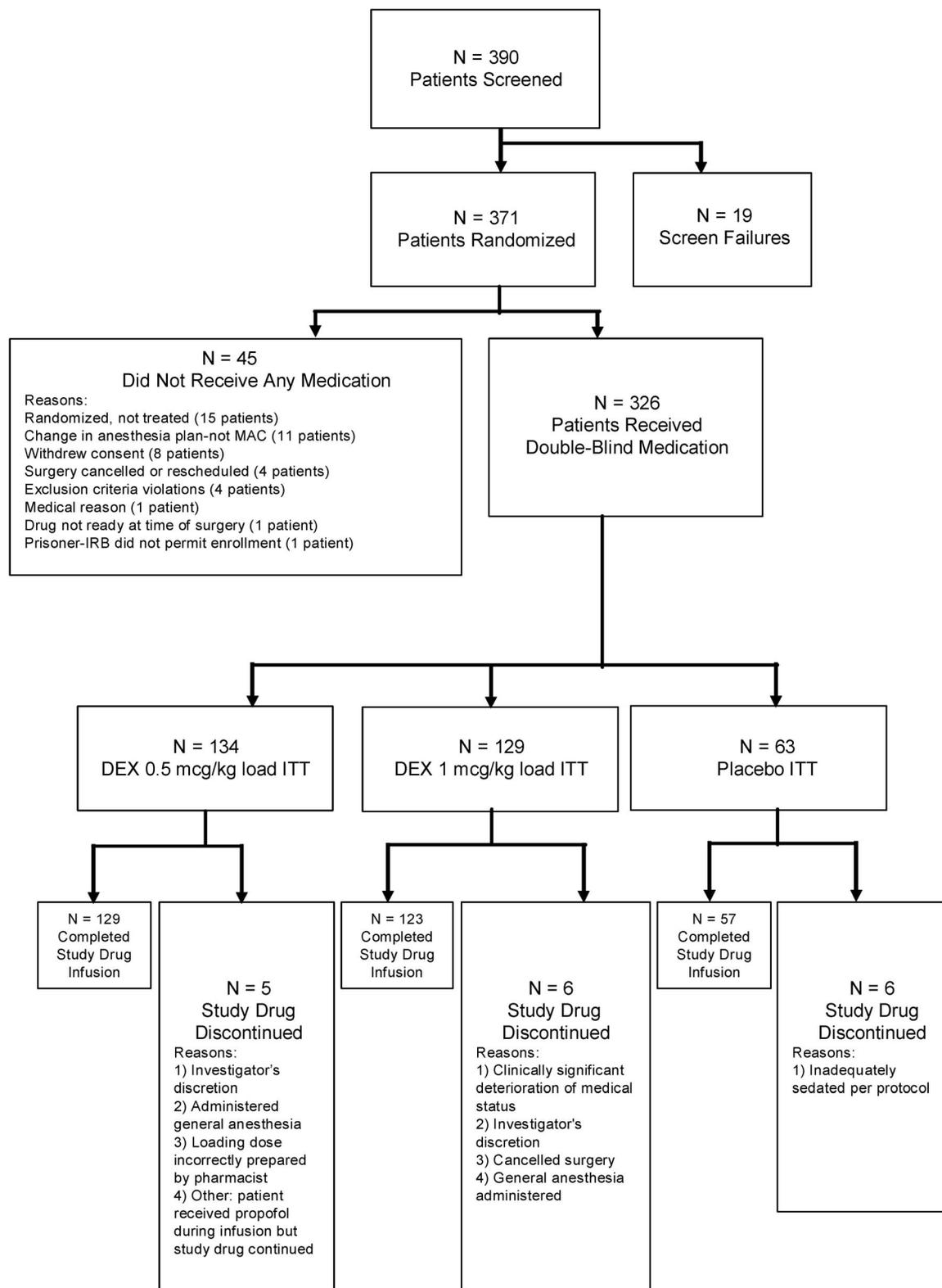


Figure 2. Patient disposition. ITT = intent-to-treat.

adverse events among treatment groups either intraoperatively or in the PACU. Three patients reported serious adverse events during the follow-up period and all were determined by the investigator to be unrelated to study drug. One placebo patient who was converted to general anesthesia experienced laryngospasm and pulmonary edema with placement of a

laryngeal mask airway. Seventeen patients (five patients in the 0.5- $\mu\text{g}/\text{kg}$ group, six in the 1- $\mu\text{g}/\text{kg}$ group, and six in the placebo group) prematurely discontinued study drug infusion (Fig. 2). There were no deaths during the study or follow-up period.

The mean decrease in SBP ($P \leq 0.043$) and diastolic blood pressure ($P < 0.001$) from baseline in both

Table 1. Baseline Characteristics by Treatment Group

Variable	DEX 0.5 $\mu\text{g}/\text{kg}$ ($n = 134$)	DEX 1 $\mu\text{g}/\text{kg}$ ($n = 129$)	Placebo ($n = 63$)	<i>P</i>
Age, yr				≥ 0.541
Mean (SD)	56.8 (16.51)	53.8 (16.47)	55.3 (16.69)	
Range	18–93	19–88	20–80	
Gender, <i>n</i> (%)				≥ 0.379
Male	68 (50.7)	65 (50.4)	36 (57.1)	
Female	66 (49.3)	64 (49.6)	27 (42.9)	
Ethnic origin, <i>n</i> (%)				≥ 0.807
Caucasian	91 (67.9)	74 (57.4)	39 (61.9)	
African American	23 (17.2)	30 (23.3)	14 (22.2)	
Asian	1 (0.7)	3 (2.3)	1 (1.6)	
Hispanic	18 (13.4)	22 (17.1)	9 (14.3)	
Other	1 (0.7)	0	0	
ASA classification, <i>n</i> (%)				≥ 0.492
I	13 (9.7)	22 (17.1)	6 (9.5)	
II	63 (47.0)	57 (44.2)	32 (50.8)	
III	51 (38.1)	40 (31.0)	20 (31.7)	
IV	7 (5.2)	10 (7.8)	5 (7.9)	
Baseline OAA/S scores ^a , <i>n</i> (%)				≥ 0.331
5	132 (98.5)	129 (100.0)	63 (100.0)	
4	2 (1.5)	0	0	
3	0	0	0	
2	0	0	0	
1	0	0	0	

DEX = dexmedetomidine; ASA = American Society of Anesthesiologists; OAA/S = Observer's Assessment of Alertness/Sedation Scale.

^a Baseline OAA/S scores: 5 = responds readily to name spoken in normal tone; 4 = responds only after mild prodding or shaking; 3 = responds only after name is called loudly and/or repeatedly; 2 = lethargic response to name spoken in normal tone; 1 = does not respond to mild prodding or shaking.

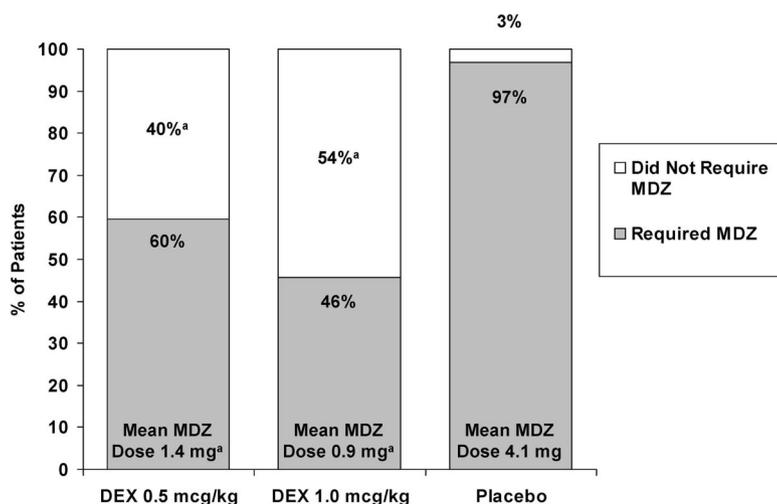


Figure 3. Percentage of patients who did not require rescue midazolam and mean midazolam dosage used in patients requiring rescue midazolam. ^a $P < 0.001$ versus placebo. *P* values for percentage of patients not requiring rescue MDZ based on Cochran-Mantel-Haenszel test, adjusting for surgery/procedure type; *P* values for mean dose of rescue midazolam based on one-way analysis of variance, adjusting for surgery/procedure type. DEX = dexmedetomidine; MDZ = midazolam.

dexmedetomidine groups was greater than the placebo group during the infusion and PACU periods, except for the difference between the 1- $\mu\text{g}/\text{kg}$ group and placebo group during the infusion period. The mean HR in both dexmedetomidine groups decreased significantly from baseline versus placebo during the infusion and PACU periods ($P < 0.001$). During study drug infusion, there was no difference in protocol-defined hemodynamic stability among the treatment groups. Fourteen patients (10.9%) in the 1- $\mu\text{g}/\text{kg}$ group and 16 patients (11.9%) in the 0.5- $\mu\text{g}/\text{kg}$ group received an intervention (titration of study drug, IV fluid bolus, or pharmacologic treatment) for treatment-related arterial blood pressure or HR adverse events during the infusion period, compared with two patients (3.2%) in the placebo group. The

coadministration of midazolam or fentanyl with dexmedetomidine was not associated with an increase in hypotension or bradycardia. There was no significant increase in the incidence of hypotension or bradycardia when dexmedetomidine was administered to patients taking chronic antihypertensive therapy, including β -blockers. Differences between the dexmedetomidine groups and the placebo group in cardiac monitoring, 12-lead electrocardiogram results, and laboratory profiles were unremarkable.

The incidence of absolute respiratory depression (defined as a respiratory rate of < 8 or an oxygen saturation of $< 90\%$) was significantly lower in both the 0.5- and 1- $\mu\text{g}/\text{kg}$ dexmedetomidine groups compared with placebo during the infusion period (3.7% and 2.3% vs 12.7%, respectively; $P = 0.018$). The

Table 2. Fentanyl Requirements During Surgery According to the Surgical Subgroups

Total dose of fentanyl (μg)	DEX 0.5 $\mu\text{g}/\text{kg}$ load	P^*	DEX 1 $\mu\text{g}/\text{kg}$ load	P^*	Placebo
All surgeries					
<i>n</i>	79		55		56
Mean	84.8	<0.001	83.6	<0.001	144.4
SD	52.9		52.7		100.1
Pooled Type 1 (orthopedics)					
<i>n</i>	38		39		20
Mean	50.1	0.0001	37.2	<0.0001	128.8
SD	56.42		49.29		90.06
Pooled Type 2 (ophthalmic)					
<i>n</i>	34		35		18
Mean	19.1	0.0048	8.6	0.0002	57.6
SD	29.55		25.68		64.64
Pooled Type 3 (breast biopsies, excision of lesions, and plastic surgical procedures)					
<i>n</i>	38		34		15
Mean	67.8	<.0001	56.6	0.0001	151.7
SD	55.11		66.09		85.81
Pooled Type 4 (arteriovenous fistulas, vascular stents, and other)					
<i>n</i>	24		21		10
Mean	65.5	0.0002	44.0	<0.0001	220.0
SD	78.81		59.11		137.84

Fentanyl was administered for pain score >3 during study drug infusion. Significantly less fentanyl was administered in both dexmedetomidine groups.

DEX = dexmedetomidine.

* P value from analysis of variance model comparing each DEX arm versus the placebo arm.

Table 3. Overall Patient Assessment of Satisfaction

Patient assessment ^a	DEX 0.5 $\mu\text{g}/\text{kg}$ mean (SD) (<i>n</i> = 134)	P^*	DEX 1 $\mu\text{g}/\text{kg}$ mean (SD) (<i>n</i> = 129)	P^*	Placebo mean (SD) (<i>n</i> = 63)
1—I threw up or felt like throwing up	2.2 (1.67)	0.959	2.2 (1.70)	0.970	2.2 (1.74)
2—I would have the same anesthetic again	2.2 (1.32)	<0.001	1.8 (2.02)	0.054	1.2 (2.35)
3—I itched	2.4 (1.26)	0.064	2.4 (1.34)	0.051	2.0 (1.76)
4—I felt relaxed	1.8 (1.71)	0.009	1.9 (1.64)	0.002	1.0 (2.44)
5—I felt pain	1.6 (1.98)	<0.001	1.3 (2.16)	0.002	0.3 (2.28)
6—I felt safe	2.1 (1.40)	0.409	2.3 (1.33)	0.092	1.9 (1.68)
7—I was too hot or cold	1.9 (1.79)	0.792	2.1 (1.69)	0.264	1.8 (1.83)
8—I was satisfied with the anesthesia care	2.5 (1.06)	0.007	2.6 (0.90)	<0.001	1.9 (1.82)
9—I felt pain during surgery	1.3 (2.11)	0.159	1.8 (1.91)	0.006	0.9 (2.33)
10—I felt good	1.7 (1.72)	0.075	1.8 (1.66)	0.019	1.2 (2.17)
11—I hurt	1.8 (1.89)	0.002	1.9 (1.83)	<0.001	0.8 (2.36)
Overall ISAS score	2.0 (0.97)	<0.001	2.0 (0.97)	<0.001	1.4 (1.39)

DEX = dexmedetomidine; ISAS = Iowa Satisfaction with Anesthesia Scale.

^a For items 1, 3, 5, 7, 9, and 11, the scores are reassigned as follows: +3 = disagree very much; +2 = disagree moderately; +1 = disagree slightly; -1 = agree slightly; -2 = agree moderately; -3 = agree very much. For items 2, 4, 6, 8, and 10, the scores are reassigned as follows: -3 = disagree very much; -2 = disagree moderately; -1 = disagree slightly; +1 = agree slightly; +2 = agree moderately; +3 = agree very much. The Overall ISAS score is the mean of all reassigned item scores. The higher score indicates more favorable outcome.

* P values from analysis of variance model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 4. Patients with Cardiovascular Adverse Events Who Received Interventions During Study Drug Infusion

Reason for intervention ^a	DEX 0.5 $\mu\text{g}/\text{kg}$ <i>n</i> (%) (<i>N</i> = 134)	P^*	DEX 1 $\mu\text{g}/\text{kg}$ <i>n</i> (%) (<i>N</i> = 129)	P^*	Placebo <i>n</i> (%) (<i>N</i> = 63)
Hypertension					
Infusion period	3 (2.2)	0.336	1 (0.8)	0.069	3 (4.8)
Hypotension					
Infusion period	16 (11.9)	0.046	11 (8.5)	0.166	2 (3.2)
Tachycardia					
Infusion period	0	0.144	0	0.151	1 (1.6)
Bradycardia					
Infusion period	1 (0.7)	0.492	6 (4.7)	0.082	0

DEX = dexmedetomidine.

^a Intervention for hypertension, hypotension, tachycardia, and bradycardia had occurred if these adverse events (or equivalent) were recorded, and the action taken was any value other than "None." Interventions were titration of study drug, IV fluid bolus, or pharmacologic.

* P values based on Pearson χ^2 test comparing each DEX arm versus the placebo arm.

coadministration of midazolam or fentanyl in both dexmedetomidine groups was not associated with increased absolute respiratory depression or a need for intervention for respiratory depression. No patient in any of the three groups received a reversal drug for the opioid or midazolam.

DISCUSSION

Dexmedetomidine was effective and well tolerated for sedation of patients requiring MAC. Efficacy results showed that significantly fewer patients in both the 0.5- and 1- $\mu\text{g}/\text{kg}$ dexmedetomidine groups required supplemental midazolam or fentanyl for sedation or analgesia. The mean total dose of rescue midazolam used to achieve and/or maintain the targeted sedation level was significantly lower in both dexmedetomidine groups: 0.9 mg for dexmedetomidine 1 $\mu\text{g}/\text{kg}$ and 1.4 mg for dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ compared with 4.1 mg for the placebo group. The percentage of subjects who required rescue fentanyl for analgesia during the infusion period was significantly lower for both dexmedetomidine groups (42.6% of 1 $\mu\text{g}/\text{kg}$ and 59.0% of 0.5 $\mu\text{g}/\text{kg}$ dexmedetomidine subjects) compared with 88.9% of placebo subjects ($P < 0.001$ for both comparisons); and the dose of fentanyl during study drug infusion was significantly lower in both dexmedetomidine groups, 83.6 and 84.8 μg of fentanyl for the dexmedetomidine 1 $\mu\text{g}/\text{kg}$ and 0.5 $\mu\text{g}/\text{kg}$, respectively, compared with 144.4 μg of fentanyl in the placebo group ($P < 0.001$ for each comparison). Significantly fewer subjects required postoperative analgesics in the dexmedetomidine 1- $\mu\text{g}/\text{kg}$ group than in the placebo group ($P = 0.025$). Patients in both dexmedetomidine groups expressed significantly greater satisfaction than the placebo group rescued with midazolam and fentanyl.

An important finding in this trial was the higher incidence of clinically significant respiratory depression in the placebo group as compared with both dexmedetomidine groups. Despite following a protocol with clearly defined variables for administering midazolam or fentanyl, 13.1% and 16.1% of patients in the placebo group who received midazolam with fentanyl, respectively, had an intervention for respiratory depression and 12.7% had a documented oxygen saturation $<90\%$ or respiratory rate <8 . This may be attributed to the significantly higher doses of midazolam and fentanyl that were required for sedation and analgesia in the placebo group versus the dexmedetomidine treatment groups. The doses of midazolam and fentanyl that were used may have been due to the study design although other trials have demonstrated similar findings or have shown no increase in respiratory complications between dexmedetomidine and midazolam with fentanyl.^{12,13} The analgesic-sparing effect of dexmedetomidine demonstrated herein and in other studies could potentially reduce the risk of developing respiratory depression and its related sequelae.^{5,8,12,20,21}

In a study by Alhashemi¹⁴ evaluating the use of dexmedetomidine for cataract surgery and by Zeyneloglu et al.²² in patients undergoing lithotripsy, the time for recovery and discharge from PACU was longer with dexmedetomidine. Although not statistically or clinically significant, the time for recovery and readiness for discharge from the PACU in our study was longer for both dexmedetomidine groups than the placebo group. Readiness for discharge may have been longer in the dexmedetomidine groups due to the fact that to maintain the blind in our study all groups had their infusions continued until the end of the surgery. It is expected that in standard practice an infusion such as dexmedetomidine would have been tapered before the end of surgery. In general, an infusion drug, such as dexmedetomidine, may be more difficult to use compared with bolus drugs in terms of when to stop the infusion, the time required to change dosage, and the need for an initial loading dose given over 10 min.

Both patient and anesthesiologist satisfaction and comfort were better with dexmedetomidine than placebo. Dexmedetomidine-treated patients were significantly more satisfied with their anesthetic than patients in the placebo group, and patients in the 1- $\mu\text{g}/\text{kg}$ group had significantly less postoperative anxiety after their MAC procedure. Higher satisfaction scores for dexmedetomidine compared with midazolam have been reported in other trials as well.¹⁴⁻¹⁶ In addition, anesthesiologists indicated that the ease of achieving and maintaining the targeted sedation level was significantly better in both dexmedetomidine groups compared with the placebo group using midazolam.

Dexmedetomidine was well tolerated in a variety of age groups and populations for a broad range of surgical and diagnostic procedures, and the incidence of treatment-emergent adverse events was similar among patients receiving dexmedetomidine or placebo. Overall, dexmedetomidine caused a predictable and manageable decrease in HR and arterial blood pressure. Protocol-defined hypotension was the most common adverse event in dexmedetomidine-treated patients during the infusion period; however, all cases were mild or moderate in severity and responded to intervention, when indicated. Additionally, no significant differences were noted for the rate of treatment of hypotension or bradycardia intraoperatively, however, interventions were increased in the PACU. McCutcheon et al.²⁰ found that dexmedetomidine, when compared with midazolam and fentanyl in carotid surgery patients, was associated with fewer interventions for hypertension and tachycardia. The effect of reducing HR and arterial blood pressure could be beneficial for patients at risk for cardiac morbidity because perioperative tachycardia and hypertension are associated with adverse cardiac outcomes in the postoperative period.^{23,24}

The surgical procedures that were studied in this trial were notably diverse, and it is possible that

dexmedetomidine may prove more suitable for some procedures than others. For example, a previous study of dexmedetomidine sedation during colonoscopy reported more adverse events in this population.²⁵ Although one study reported better patient cooperation during cataract surgery with dexmedetomidine than with midazolam, another reported more hypotension and delayed recovery room discharge.^{11,26} We believe that additional trials delineating the advantages and disadvantages of dexmedetomidine in specific procedures and populations are justified.

In conclusion, dexmedetomidine at the doses studied is a well tolerated, safe, and effective primary sedative alternative to traditional benzodiazepine/opioid combinations in patients undergoing MAC for a variety of surgical procedures. Using dexmedetomidine as the primary sedative permits significantly reduced requirements for both midazolam and fentanyl. Within the confines of the design of our study, dexmedetomidine-treated patients had a lower incidence of clinically relevant respiratory depression and significantly better patient satisfaction. Mean arterial blood pressure and HR were significantly lower in dexmedetomidine-treated patients compared with placebo patients receiving midazolam and fentanyl.

APPENDIX

The members of the MAC Study Group are as follows: Loma Linda University Medical Center, Loma Linda, CA: Martin W. Allard; New York University Medical Center, New York, NY: Alex Y. Bekker; The Ohio State University Medical Center, Columbus, OH: Sergio D. Bergese; University of Miami, Miami, FL: Keith A. Candiotti; Crossroads Research, Inc., Owings Mills, MD: Eric L. Diamond; University of Alabama at Birmingham, Birmingham, AL: Dennis D. Dobljar; VA Medical Center, Milwaukee, WI: Thomas J. Ebert; Cleveland Clinic Foundation, Cleveland, OH: Marc Feldman; University of Missouri Health Care, Columbia, MO: Robert B. Fisher; Duke University Medical System, Durham, NC: Tong J. Gan; University of Miami, Miami, FL: Steven Gayer; Chesapeake Research Group, LLC, Pasadena, MD: Ira J. Gottlieb; William Beaumont Hospital, Royal Oak, MI: Craig T. Hartrick; Medical University of South Carolina, Charleston, SC: Gary R. Haynes; VA North Texas Health Care System, Dallas, TX: Fima Lenkovsky; VA Medical Center, Durham, NC: Terri Monk; University of Pittsburgh, Pittsburgh, PA: Paul A. Moore; University of Virginia, Charlottesville, VA: Thomas N. Pajewski; Brigham and Women's Hospital, Boston, MA: Beverly K. Philip; Baylor University Medical Center, Dallas, TX: Michael A.E. Ramsay; Miami Clinical Trials, South Miami, FL: Ruben Ricardo; The University of Texas M.D. Anderson Cancer Center, Houston, TX: Bernhard J.C.J. Riedel; Scott and White Memorial Hospital, Temple, TX: Charles R. Roberson; Beth Israel Deaconess Medical Center, Boston, MA: Fred E. Shapiro; The Mount Sinai School of Medicine, New York,

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ANNOUNCEMENT

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