Effect of Sedation on Pain Perception

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ABSTRACT

Background: Sedation or anesthesia is used to facilitate many cases of an estimated 45 million diagnostic and therapeutic medical procedures in the United States. Preclinical studies have called attention to the possibility that sedative–hypnotic drugs can increase pain perception, but whether this observation holds true in humans and whether pain-modulating effects are agent-specific or characteristic of IV sedation in general remain unclear.

Methods: To study this important clinical question, the authors recruited 86 healthy volunteers and randomly assigned them to receive one of three sedative drugs: midazolam, propofol, or dexmedetomidine. The authors asked participants to rate their pain in response to four experimental pain tasks (*i.e.*, cold, heat, ischemic, or electrical pain) before and during moderate sedation.

Results: Midazolam increased cold, heat, and electrical pain perception significantly (10-point pain rating scale change, 0.82 ± 0.29, mean ± SEM). Propofol reduced ischemic pain and dexmedetomidine reduced both cold and ischemic pain significantly (−1.58 ± 0.28, mean ± SEM). The authors observed a gender-by-race interaction for dexmedetomidine. In addition to these drug-specific effects, the authors observed gender effects on pain perception; female subjects rated identical experimental pain stimuli higher than male subjects. The authors also noted race–drug interaction effects for dexmedetomidine, with higher doses of drug needed to sedate Caucasians compared with African Americans.

Conclusions: The results of the authors' study call attention to the fact that IV sedatives may increase pain perception. The effect of sedation on pain perception is agent- and pain type-specific. Knowledge of these effects provides a rational basis for analgesia and sedation to facilitate medical procedures.

What We Already Know about This Topic

- Sedative–hypnotic drugs are in general not analgesic; however, some studies suggest that some sedative drugs may increase pain perception

What This Article Tells Us That Is New

- The intensity of pain described by patients undergoing sedation for medical procedures depends on the sedative drug administered
- Gender and race also may influence the effect of sedation on pain

PROCEDURAL sedation is used widely for a variety of painful medical procedures. In October 2010, the Centers for Disease Control and Prevention published the latest data from the National Hospital Discharge Survey, the longest continuously running nationally representative survey of hospital use.[1] For the year 2007, the rate of procedures that include a wide range of healthcare services ranging from obstetric procedures to major cardiovascular surgery was estimated to be 1.5 per 10,000 population. Sedation or anesthesia is used to facilitate many of these estimated 45 million diagnostic and therapeutic medical procedures. The most common IV sedatives are benzodiazepines, the sedative–hypnotic propofol and, less frequently, the α_2-adrenergic receptor agonist dexmedetomidine.[2–4] Examples for short but painful procedures that are facilitated by sedation are cardioversion, anoscopy, fracture reduction, abscess incision, and cervical dilatation and curettage.[5,6] In the intensive care unit, sedation is used extensively for intubated patients.[7,8] Other examples include various nonsurgical diagnostic procedures that require sedation, such as gastrointestinal endoscopy and bronchoscopy.[9] Despite the ubiquitous use of sedative anesthetic drugs, the neurophysiologic mechanism of their action is poorly understood, and sedation and anesthetic depth can be determined only by relatively unreliable physiologic data.[10]

Contrary to the belief of many clinicians that sedative drugs will reduce pain sensation, preclinical studies have called attention to the possibility that those sedative–hypnotic drugs can increase pain perception[11–13] and found that

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propofol has analgesic as well as antihyperalgesic effects,[14] or increases pain intensity and unpleasantness in a dose-dependent fashion using pain self-report.[15,16] This finding calls attention to the need for adequate analgesia in sedated patients and stimulates the ongoing discussion about the pharmacologic profile of anesthetic drugs and their mechanism of action. Although the γ-aminobutyric acid (GABA) receptor agonists midazolam and propofol have been shown to enhance pain, the α_2 agonist dexmedetomidine reportedly has no effect on pain perception[17] or enhances the effects of coadministered analgesic drugs.[18] Thus, dexmedetomidine is described by some as the ideal drug for sedation.[19]

The importance of understanding how sedation might affect pain perception has been recognized in the clinical setting; critically ill patients with a depressed level of consciousness report a high number of unpleasant events that they believe took place before they regained consciousness.[20] This is frequently interpreted as a need for better assessment and treatment of sedation (often accomplished by means of a propofol infusion) in the critically ill patient. Thus, the need for adequate analgesia in the sedated patient may be of equal or even greater importance when considering the possible hyperalgesic effect of the sedative medication. This suggestion is accentuated by the observation that more than half of sedated patients in the intensive care unit actively recall pain,[21] and underscores the importance of adequate analgesia in patients who are being sedated. Similar considerations apply for many endoscopic procedures, procedures in interventional radiology and the emergency room, and some office-based surgical procedures performed under local anesthesia with sedation. With inappropriate analgesia, nociception can cause unfavorable responses of the autonomic nervous system and involuntary movements in the patient and potentially untoward psychological sequelae.

To address these clinically important concerns, we designed a prospective randomized study in healthy volunteers. In this study, we recruited 90 volunteers to rate their pain sensation in response to several experimental pain tasks at baseline and while being sedated with either propofol or midazolam (two GABA-related sedative drugs) or dexmedetomidine, an α_2-adrenergic agent (primary study aim). A secondary study aim was to determine whether study variables were affected by gender or race.

Materials and Methods

Subjects and Design

The Institutional Review Board of the University of Alabama at Birmingham (Birmingham, Alabama) approved this study. Recruitment was performed by public advertisement around the university campus. Interested individuals were scheduled for a screening visit, during which we determined eligibility by obtaining a medical history, performing a focused physical examination, and obtaining written informed consent. Enrollment started in April 2009 and finished on January 2012. Inclusion criteria were healthy adults, aged 19–40 yr, who were able to understand all study instructions. Exclusion criteria were any existing and active medical conditions that could affect somatosensation or cognitive function such as diabetes mellitus, neurologic diseases, chronic pain, psychiatric disorders, treatment with any scheduled medication, and a history of drug or substance abuse. If it was determined that interested volunteers were eligible, they were scheduled for a study visit at least 48 h after the screening visit.

We screened 90 participants that met the inclusion criteria. Subjects were randomized to one of three sedation treatment groups (*i.e.*, midazolam, propofol, or dexmedetomidine) on the day before the study. Randomization was achieved with a schedule with SAS, version 9.2 software (SAS Institute, Cary, NC) using the PLAN procedure and was balanced to blocks of 15 participants. Four participants were excluded on the day of the study because of the presence of a previously undisclosed drug or medical history. We did not design a placebo control because this study was a repeated measures trial where participants acted as their own control. We also felt that participants would easily be able to identify whether they did not receive an active intravenous sedative drug. On the study day, we performed a urine pregnancy test on female participants to exclude those with an unknown pregnancy. On the day of the study, participants were exposed to a sequence of measures that are described in detail below. The order of tests was fixed as follows: heat pain threshold and tolerance, heat pain suprathreshold measures, electrical pain, cold pain, and ischemic pain. We started with pain procedures that are known to have a short recovery rate of a few seconds (*i.e.*, heat pain and electrical pain) followed by cold and ischemic pain that, based on the more sustained stimulus exposure, may require 1 or 2 min for full recovery. These recovery characteristics have been well studied.[22–24] The rest periods in-between pain modalities were 3 to 5 min and the rest period from baseline to sedation testing was at least 30 min. This experimental design was constructed such that both habituation and sensitization were avoided. Figure 1 shows the group assignment and gender and race subcategories. We were able to collect all study data (without loss) in subjects included in this study.

Experimental Pain Measures and Assessment

We recorded pain ratings for electrical, cold, heat, and ischemic pain stimuli with participants at an awake, nonsedated state. After the completion of these baseline pain ratings, we started the intravenous sedation as outlined below. Once participants were moderately sedated, we repeated pain ratings.

Heat Pain. We used the TSA-II Neuro Sensory Analyzer (Medoc, Ltd., Ramat-Yishai, Israel) for the administration of heat stimuli. Subjects received nine thermal pain stimuli and were asked to rate the pain intensity with a mechanical slide algometer whose end points were "no pain sensation" and "most intense pain sensation imaginable."[25] Stimulus

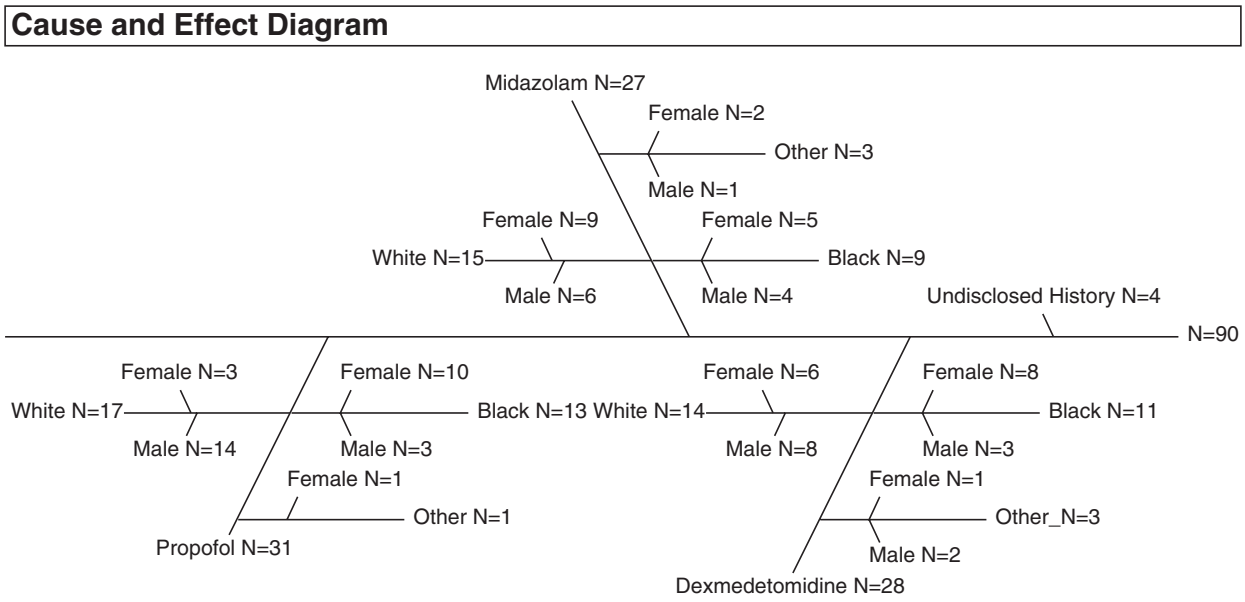

Fig. 1. Diagram showing the race and gender categorization within drug groups. The main categories are midazolam, propofol, dexmedetomidine, and "undisclosed history." Subcategories are organized by race and gender.

temperatures were 45, 47, and 49°C and were presented using a 3 × 3 Greco-Latin squares design to achieve balance to temperature level and order. Each stimulus was maintained for 3 s and alternated with a neutral temperature (32°C). The ramp-up temperature increase was 10°C/s. Each successive stimulus was initiated once the participant had competed the pain rating. The heat probe was moved by 3 cm within the upper section of the ventral forearm after each stimulus to avoid redness of the skin and stimulus habituation. The temperatures were selected because they have been shown to activate A-δ and C fibers.[26]

Cold Pain. To induce sustained but tolerable cold pain, we alternated immersion of the volunteer's right hand into a plastic cup filled with either ice water (2–3°C) for 20 s alternating with immersion of the hand into a plastic cup filled with tepid water (30°C). This cycle (cold–tepid) was repeated two times. After each cold immersion, participants were asked to rate their cold pain using a mechanical slide algometry as described above.

Electrical Pain. We used a Digitimer (model DS7A; Digitimer Ltd., Letchworth, Garden City, United Kingdom), a high-voltage, constant-current stimulator, to deliver electrical stimuli. Electrodes were attached to the palmar surface of the skin over the proximal and distal phalanges of the right middle finger. We delivered stimuli of 2-ms duration that were manually adjusted to 6, 8, and 10 mA presented using a 3 × 3 Greco-Latin squares design to achieve balance to stimulus intensity level and order. Subjects were asked to rate the pain intensity with a mechanical slide algometer whose endpoints were "no pain sensation" and "most intense pain sensation imaginable."[25] Successive stimuli were initiated once the participant had completed the pain rating. The intensities were selected because they have been shown to activate A-δ and C fibers.[27]

Ischemic Pain. Ischemic pain was assessed using the modified submaximal tourniquet procedure.[28,29] During this procedure, the right arm was exsanguinated by elevating it above heart level for 30 s, after which the arm was occluded with a standard blood pressure cuff positioned proximal to the elbow and inflated to 240 mmHg using an E20 Rapid Cuff Inflator (D.E. Hokanson, Bellevue, WA). Subjects then performed 20 handgrip exercises of 2-s duration at 4-s intervals at 50% of their maximum grip strength. Subjects were instructed to rate pain intensity every 30 s using the mechanical slide algometer described above for a total of 5 min.

Administration of Intravenous Sedation

On the day of the study, a 20-gauge intravenous catheter was placed on the left forearm. IV sedative drugs were infused with a Graseby 3400 infusion pump (Smiths Medical, St. Paul, MN) controlled by a personal computer using the STANPUMP software.§ This software uses a three-compartment pharmacokinetic model adjusted by height, weight, age, and sex to predict plasma concentrations of certain IV drugs. This computer-assisted infusion was approved by the United States Food and Drug Administration (investigational device exemption no. G060183) for research use. Pharmacokinetics for propofol were published by Marsh *et al.*,[30] and pharmacokinetic parameters for the administration of dexmedetomidine and midazolam were published by Dyck *et al.*[31] and Greenblatt *et al.*,[32] respectively. Unlike traditional drug infusions, with this method, the infusion rate varies constantly to rapidly attain

§ Shafer R: STANPUMP. Available at: http://www.opentci.org, 1998. Accessed November 3, 2012.

and maintain a desired drug plasma concentration. The method has great utility in a situation where the investigator needs to rapidly achieve a new drug plasma concentration, as was the case in our study.

The dose of the IV sedation was based on the person's individual sedation rating, a sedation biomarker that correlates well with IV drug concentrations and observer assessment of sedation.[33,34] Subjects received escalating doses of their assigned IV sedative. They were asked to rate their own sedation after having received 10 min of IV sedation at each level by making a mark on a 5-inch horizontal line bounded by "fully awake" to "completely sedated" (sedation self-assessment scale). We also obtained the Observer Assessment Sedation Scale, which produces a composite sedation assessment ranging from 1 (deep sleep) to 5 (alert). These biomarkers of sedation were chosen because these methods have proven to be sensitive and reliable measures of sedation.[35,36]

Doses were increased until participants were considered moderately sedated by either making their sedation mark in the midsection of the sedation self-assessment line (approximately between 4 and 6 cm on a 10-cm line) or receiving an Observer Assessment Sedation Scale composite score of less than 3. At that point, the (sedation) pain assessment sequence was carried out. We stepped the infusion up or down by one step if, during the pain assessment, participants appeared too sedated or too alert. At the end of the pain assessment, we repeated the participants' self-evaluation of sedation (final sedation rating) and recorded the infusion dose (final dose). Drug dose steps were based on previously published data.[30–33] Dexmedetomidine plasma concentrations were 0.1, 0.2, 0.4, 0.6, and 0.8 ng/ml; predicted midazolam concentrations were 10, 20, 40, 60, and 80 ng/ml; and predicted propofol concentrations were 0.4, 0.8,1.2, and 1.6 μg/ml.

All subjects were monitored according to the standards of the American Society of Anesthesiologists using pulse oximetry, electrocardiography, and noninvasive blood pressure in addition to inspection of the subject's breathing and circulation during the sedation component of the study.

Statistical Analysis

Statistical analysis was performed using SAS statistical software, version 9.2.

Sample Size Calculation. Our sample size estimation was based on the previously published variability of pain ratings, where we found pain ratings to have a standard deviation of 1.7 on a scale from 0 to 10.[16] A clinically significant difference in pain ratings would be an average change in one unit on the 10-point pain rating scale. Using these numbers, we calculated that we needed 25 participants per treatment group to achieve 80% power to detect an average change in one unit in pain ratings.

Descriptive Statistics. Table 1 shows the descriptive statistics for the study population. The drug-by-race association was estimated with the Fisher exact test based on an algorithm described by Patefield because of the small number of participants in some cells.[37] The drug-by-gender association was tested with a chi-square test of independence. Age differences between drug groups were tested with a one-way ANOVA.

Effect of Sedation on Pain Rating. We performed separate analyses for each pain type (*i.e.*, electrical pain, ischemic pain, heat pain, and cold pain). Each analysis was performed with a mixed linear model using the restricted maximum likelihood estimation and was based on a two-tailed hypothesis. Several models include interaction terms. If the parameter estimate for the interaction was not to be significant, we reported our results on the main effect of the corresponding model without interaction. In the model specifications below, bold-faced characters represent vectors, which denote categorical variables that had more than two levels. In the first analysis, subject (si) was treated as a random effect and drug ($\boldsymbol{D}$) as a fixed effect, and the change in pain rating, comparing baseline to while sedated, was the outcome variable (Yi). Our first analysis was designed to answer the

Table 1. Descriptive Statistics of Study Population

	Dexmedetomidine	Midazolam	Propofol
Race			
African American	11	9	13
Asian	1	3	0
Hispanic	2	0	0
Pacific Islander	0	0	1
Caucasian	14	15	17
Gender			
Female	15	16	14
Male	13	11	17
Age, yr	24.74 ± 4.47	24.46 ± 4.64	25.83 ± 5.41

No difference among drug groups was noted for race (Fisher exact test, $P = 0.2949$), gender (χ^2 test statistic, 0.7466; $P = 0.6885$), or age (F ratio, 0.6435; $P = 0.5281$). Age is described as mean ± SD.

question of whether, on average, midazolam, propofol, and dexmedetomidine had different effects on pain perception. In this model (model 1), participants (subjects) were added as random effect to attribute to the fact that pain perception varies from person to person:

$$Y_i = \alpha + s_i + \boldsymbol{D}\beta_{1,2} + \varepsilon_i \qquad \text{(model 1)}$$

The subscript i, ranging from 1–86, denotes the i^{th} participant in the study. To consider the notion that race and gender may have an effect on pain perception, we added these variables (fixed effects) and their interaction to the model. In doing so, model 2 allowed us to control for the race and gender effects when considering differences of drug effects and to determine whether drug ($\boldsymbol{D}$) effects differed by gender ($\boldsymbol{G}$) and race ($\boldsymbol{R}$) and whether there was a race-by-gender interaction ($\boldsymbol{R} * G$):

$$Y_{ik} = \alpha_k + s_{i,k} + \boldsymbol{D}\beta_{1-2,\mathrm{k}} + \boldsymbol{R}\beta_{3-4,\mathrm{k}} + G\beta_{5,\mathrm{k}} + \boldsymbol{R} * G\beta_{6-7,\mathrm{k}} + \varepsilon_{ik} \qquad \text{(model 2)}$$

We performed the analysis of model 2 separately for each pain type. The subscript k = 1–4 denotes the pain types. Because there were only seven participants in the Hispanic, Asian, and Pacific Islander race categories, we did not include these participants in subsequent analyses. The subscript i denotes the i^{th} participant in the study and ranges from 1–79. Because we performed four separate analyses (by pain type), we adjusted the significance level to $\alpha = 0.0125$ (0.05/4) according to the Bonferroni correction.

Effect of Gender on Baseline Pain Rating. Next, we focused on the question of whether there was a gender effect on baseline pain ratings. We designate Yi as an outcome variable, which—for models 3 and 4—represents baseline pain rating. Gender (G), pain type ($\boldsymbol{T}$), and the gender-by–pain type interaction ($G * \boldsymbol{T}$) were treated as (fixed effect) explanatory variables, subject (si) was treated as a random effect:

$$Y_i = \alpha + s_i + G\beta_1 + \boldsymbol{T}\beta_{2-4} + G * T\beta_{5-7} + \varepsilon_i \qquad \text{(model 3)}$$

Effect of Race on Baseline Pain Rating. Next, we focused on the question of whether there was a race effect on baseline pain ratings. We again use Yi to denote baseline pain. Race (R) pain type ($\boldsymbol{T}$) and the race-by-pain-type interaction ($R * T$) were treated as (fixed effect) explanatory variables, subject si was treated as a random effect:

$$Y_i = \alpha + s_i + R\beta_1 + \boldsymbol{T}\beta_{2-4} + R * \boldsymbol{T}\beta_{5-7} + \varepsilon_i \qquad \text{(model 4)}$$

Race and Gender Differences of Sedation Requirement. As an additional, exploratory analysis, we investigated whether there was a race or gender difference in sedation requirements. This analysis was not planned a priori, and results may not replicate as well as previously described analyses. Because the dose of the sedative drug was titrated to effect (midrange of the sedation scale as described above), we considered the final drug concentration a measure of sedation requirements. In models 5 and 6, we denote this outcome measure as Yi. Because of the differences in the dosage ranges of drugs, we performed separate analyses by drug as follows:

$$Y_{ik} = \alpha_k + R\beta_k + \varepsilon_{ik} \qquad \text{(model 5)}$$

$$Y_{ik} = \alpha_k + G\beta_k + \varepsilon_{ik} \qquad \text{(model 6)}$$

The explanatory variables in these general linear models (model 5 and 6) were race (R) and gender (G). Because there were only seven participants in the "other" race category, we did not include those in the model 5 and 6 analyses. The subscript i = 1,2,..,79 denotes the i^{th} participant in the study as before and the subscript k = 1–3 denotes the k^{th} drug (midazolam, propofol, or dexmedetomidine).

Results

Effect of Sedation on Pain Perception

We observed an overall statistically significant effect of sedation (drug effect) on pain perception (model 1, F ratio = 13.43, $P < 0.001$). Pain type and drug effects on pain change are evaluated using model 2 and illustrated in figure 2. The clinically and statistically most significant finding is that the GABA agonist midazolam increased cold, heat, and electrical pain perception. Midazolam increased pain cold pain ratings by 0.82 unit (95% CI, 0.26–1.39; $P = 0.005$), ischemic pain by 0.56 unit (95% CI, −0.02 to 1.13; $P = 0.057$), heat pain ratings by 1.30 units (95% CI, 0.72–1.87; $P < 0.001$), and electrical pain ratings by 0.78 unit (95% CI, 0.29–1.27; $P = 0.002$). The GABA agonist propofol increased heat pain by 0.40 unit (95% CI, −0.15 to 0.95; $P = 0.153$) but reduced ischemic pain (cold by 0.35 unit [95% CI, −0.89 to 0.19; $P = 0.195$], ischemic by 1.58 units [95% CI, −2.12 to −1.03; $P < 0.001$], and electrical by 0.30 unit [95% CI, −0.70 to 0.24; $P = 0.329$]). The α_2-receptor agonist dexmedetomidine reduced cold pain by 1.56 units (95% CI, −1.72 to −0.60; $P < 0.001$) and ischemic pain by 0.60 unit (95% CI, −1.17 to −0.04; $P = 0.036$) but increased heat by 0.42 unit (95% CI, −0.14 to 0.99; $P = 0.140$) and electrical pain by 0.05 unit (95% CI, −0.43 to 0.53; $P = 0.832$). All parameter estimates for the control variables (gender, race, and their interaction) were nonsignificant except for the gender-by-race interaction in participants having received dexmedetomidine. In that treatment group, gender changed a race effect; in African Americans, both genders showed a pain reduction (least-squares means of pain rating chance for African American men = −0.63 [95% CI, −1.50 to 0.24; $P = 0.151$], for African American women = −0.26 [95% CI, −0.84 to 0.32; $P = 0.370$]). In Caucasians, only women showed a significant pain reduction (least-squares mean of pain rating chance for Caucasian men = 0.24 [95% CI, −0.29 to 0.77; $P = 0.368$], least-squares

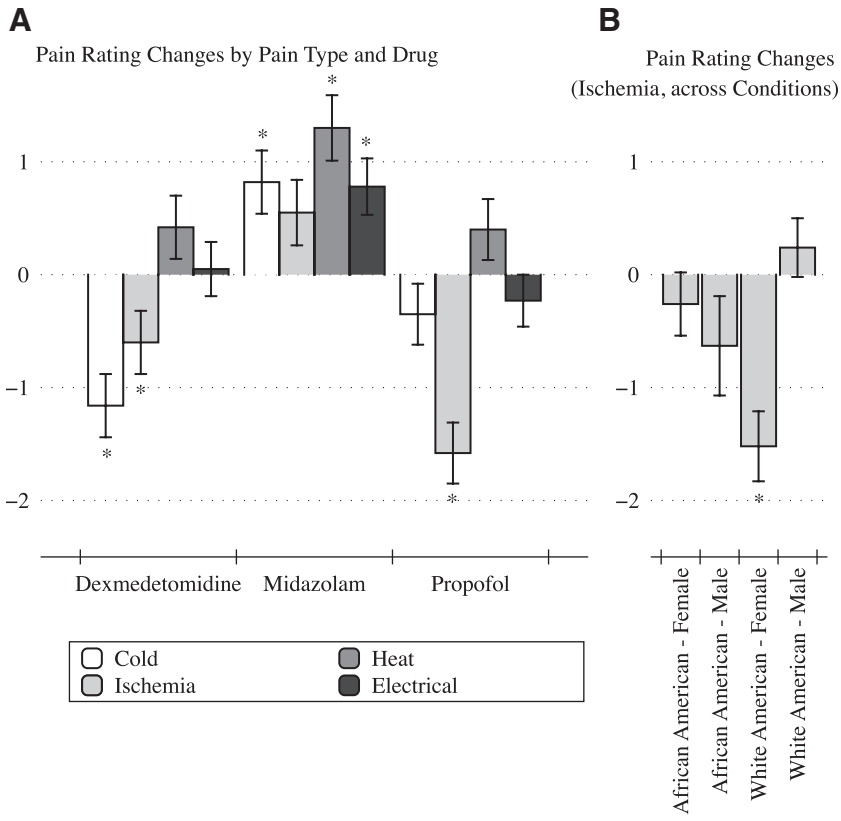

Fig. 2. The *y* axis represents least-squares means of change in pain rating. *Error bars* represent the corresponding standard error. The scale of pain ratings ranged from 0 to 10. (*A*) Bar graphs that represent least-squares means of pain rating changes by drug (*x* axis category) and pain type (*gray scale*). (*B*) Least-squares means of pain rating changes (*y* axis) for dexmedetomidine by race and gender (*x* axis category) to illustrate the interaction effect observed only within the ischemic pain task. Significant pain rating changes (95% CI does not include 0) are marked with an *asterisk*.

mean of pain rating chance for Caucasian women = −1.52 [95% CI, −2.18 to −0.86; $P < 0.001$]). These findings are illustrated in the right panel of figure 2. Detailed statistical data are presented in tables 2–10.‖

Effect of Gender and Race on Baseline Pain Ratings

The results of our analysis of baseline pain ratings by gender and race indicated that women had significantly higher baseline pain ratings (F = 7.02, $P = 0.010$, model 3). Baseline pain rating (least-squares mean) for women was 3.4 as opposed to 2.4 for men. These results are illustrated in figures 3 and 4. We did not observe a statistically significant race effect (F = 2.6714, $P = 0.106$, model 4) with respect to baseline pain ratings. However, African American participants showed higher baseline pain ratings (least-squares mean): 3.3 for African American participants and 2.7 for Caucasian participants.

Effect of Gender and Race on Sedation Dose Requirement

Model 5 investigated the effect of gender on final drug dose. We did not observe a significant gender effect on final drug dose in any of the three drugs (dexmedetomidine group, F ratio = 0.864, $P = 0.364$; midazolam group, F ratio = 0.701, $P = 0.415$; propofol group, F ratio = 1.674, $P = 0.209$). Model 6 investigated the effect of race on final drug dose. A significant race effect was observed in the dexmedetomidine group (F ratio = 7.357, $P = 0.014$) but none in the other drug groups (midazolam group, F ratio = 0.206, $P = 0.655$; propofol group, F ratio = 1.162, $P = 0.692$): The final drug dose was higher in Caucasian Americans (0.730 ± 0.164 ng/ml) compared with African Americans (0.436 ± 0.156 ng/ml).

‖ These tables show the statistical results corresponding to analyses 1–6. The fixed effects tests are presented with test statistic and probability value. Least-squares estimates for selected explanatory variables are also provided. Because of the heterogeneous nature of the "other" race category and the resulting very small counts, patients who fell into the "other" race category were not included in analyses that used race as an explanatory variable.

Discussion

The most important finding of the present study was that it demonstrated that effects of sedative drugs on pain perception are both drug-dependent and pain modality–dependent. Notably, the drug midazolam increased most pain perceptions evoked by experimental stimuli, whereas the drugs propofol and dexmedetomidine produced analgesia in many of the same pain modalities. For many decades, scientists have debated the possible effects of intravenous sedatives on pain perception. Discussions initially were limited to barbiturates, which were used widely as sedative–hypnotic drugs both in research and in clinical practice. Although Keats and Beecher[38] in 1950 suggested that small doses of pentobarbitone were analgesic in clinical pain, subsequent work using experimental pain techniques in humans suggested that barbiturates may actually cause an increased sensitivity to pain.[13,39–41] Despite isolated scientific

Table 2. Model 1: Fixed Effect Tests and Least-Squares Means

Source	df	Denominator	F ratio	*P* Value
Drug	2	83.2	13.432	<0.001

reports, the question about the effect of IV sedation on pain remained obscure.

In the 1980s, the IV sedative–hypnotic propofol was introduced into clinical practice. Quite naturally, investigators studied its effects on pain perception and, just like early reports on barbiturates, noted hyperalgesic action associated with propofol both in preclinical, experimental studies and in clinical studies.[12,14,16,42,43] However, despite these reports, the use of propofol as an analgesic drug remained a topic of discussion. The notion that propofol was used to treat inadequate analgesia in a scientific report in 1999[44] prompted the following commentary: "Too often, in our opinion, patients receive propofol, at a time when an analgesic would serve them better. Many times, our surgical colleagues insist that propofol, or "that white stuff, works much better. They seem to think propofol can replace adequate analgesia obtained by infiltration with local anesthesia."[45] Despite this debate, many clinicians remain convinced that propofol could be effectively used as an analgesic drug as recent reports about the use of propofol to treat pain indicate.[46–49]

More recently, the α_2-adrenergic receptor agonist dexmedetomidine has been introduced into clinical practice. It is used for procedural sedation, as an adjuvant hypnotic during surgery, and in mechanically ventilated patients in an intensive care setting. There are some preclinical reports[50] suggesting that dexmedetomidine has analgesic effects and some clinical evidence regarding its inhibition of pain conditioning[51] and as an adjuvant analgesic for intractable cancer pain,[52] but its direct effects on pain remain unclear.

We previously studied the effects of propofol in a small group of volunteers using the heat pain model and found that propofol increased pain perception in a dose-dependent fashion.[16] Because this was only a small study limited to one experimental pain modality, it remained unclear whether this hyperalgesic effect would be characteristic of just the GABA-acting drug propofol or could be observed in other experimental pain modalities and with other types of sedative–hypnotic drugs. In the present study, we found that the GABA-acting drug midazolam increases pain perception across all modalities, an observation that has not been reported before but that has important implications for clinical practice because midazolam is frequently used as premedication in patients who may undergo a painful procedure. We also confirmed our previous observation that propofol increased heat pain perception. However, we also gained new information, as we observed that propofol significantly decreased cold and ischemic pain. Very similar effects were noted in volunteers who received dexmedetomidine. In that drug group, a significant reduction of pain ratings was noted for cold and ischemic pain, but heat pain ratings increased. It appears that the presumed receptor kinetics, the action on the GABA receptor or the α_2-adrenergic receptor, had limited bearing on their analgesic property.

Because the observed effect of dexmedetomidine and propofol on pain rating depended on the pain task used, it is appropriate to discuss how the experimental pain conditions that were applied relate to clinical pain. Several scientists demonstrated that, among a variety of experimental pain conditions, sustained tasks such as the ischemic pain task and the cold pain task are thought to represent clinical pain better because of their psychophysical qualities[22,53,54] and because they are predictive of clinically relevant doses of analgesics[23,29,54] as well as acute and chronic pain-related clinical outcomes.[55,56] Others showed that heat pain is valid because the combined use of a mechanical slide algometer to quantify pain perception in combination with the heat pain modality has been shown to provide ratio scale measures of pain and internally consistent measures of experimental and clinical pain when both forms of pain are rated by pain patients.[24,25,57] The latter method is also predictive of changes in clinical pain intensity because conventional analgesic treatments such as opioid administration have been shown to produce similar magnitudes of pain reduction in both

Table 3. Outcome: Pain Rating Change (Sedation – Baseline) for Model 1*

Drug Level	Least-Squares Means	SEM
Dexmedetomidine	–0.253	0.168
Midazolam	0.762	0.171
Propofol	–0.346	0.159

*Fixed effect tests and least-squares means.

Table 4. Model 2: Fixed Effect Tests

Source	*df*	Denominator *df*	F Ratio	*P* Value
Drug	2	73	12.573	0.001
Race	2	73	1.498	0.225
Gender	1	73	0.130	0.719
Race * Gender	1	73	0.019	0.890

Table 5. Model 3: Fixed Effect Tests and Gender Least-Squares Means

Source	*df*	Denominator *df*	F Ratio	*P* Value
Gender	1	78.58	7.021	0.010
Type	3	2283	116.816	0.001
Gender * type	3	2283	2.401	0.066

Table 6. Model 3: Outcome of Baseline Pain Rating Change

Gender Level	Least-Squares Means	SEM
Female	3.375	0.244
Male	2.443	0.253

Table 8. Model 4: Outcome of Baseline Pain Rating Change

Race Level	Least-Squares Means	SEM
African American	3.276	0.280
White	2.677	0.237

clinical and experimental pain testing setup.[57] We should also note that the experimental pain conditions as described in our study were neither repeated nor maintained in a fashion that is known to produce central sensitization, a mechanism that is relevant to certain types of clinical pain conditions such as chronic pancreatitis, rheumatoid arthritis, and osteoarthritis.[58–61] Thus, our findings are most relevant to acute types of clinical pain such as postoperative pain. Our results indicate that both propofol and dexmedetomidine significantly reduce pain types that were sustained beyond a very brief exposure (cold, ischemic), whereas midazolam significantly increased both short, intermittent pain (electrical, heat) and sustained pain types. We would argue that the reduction of the deep tissue type of pain (ischemic, cold) probably reflects the type of pain that one might experience with most visceral or myofascial tissue–related procedures. In that sense, it is reassuring that propofol appears to reduce this type of pain. Superficial (electrical, heat) types of pain, in contrast, appear to be augmented. This underscores the need for robust use of local anesthetic and additional opioid analgesia with procedures such as pacemaker implantation or placement of an arteriovenous dialysis shunt. We should also emphasize that midazolam appears to be hyperalgesic across pain modalities and should always be used in combination with an analgesic drug for painful procedures or analog sedation in the intensive care setting.

At the conclusion of enrollment, we recognized that the gender and race distribution of participants in our study groups were such that they appeared quite suitable for further exploration of race and gender on baseline pain in our study. We noted that the overall effects of gender and race were consistent across pain tasks; women rated their pain higher than men, and African American participants rated their pain higher than Caucasian participants. Reviewing the literature on gender and race effects on pain perception, we recognized that our observations are consistent with the existing literature. In separate studies, Edwards *et al.*[62] and Sheffield *et al.*[63] found that compared with nonHispanic whites, African American individuals rated heat pain stimuli consistently higher. Similar observations have been reported about cold pain ratings.[64,65] Analogous findings of higher pain ratings by African American participants have been observed for electrical[66] and ischemia pain.[67] Several, largely speculative factors have been discussed in an attempt to explain these differences: social and cultural beliefs and expressiveness toward pain, psychological factors such as the race and gender of the tester, and biological factors such as alterations in the endogenous pain control systems. In an effort to minimize known psychological factors, we consistently used an African American female tester and a nonHispanic white male tester in our experiments. Also consistent with the existing literature are the gender differences of pain perception that we observed. Sex-related differences in the experience of both clinical and experimentally induced pain have been widely reported. Specifically, women are at greater risk for developing several chronic pain disorders, and women exhibit greater sensitivity to noxious stimuli in the laboratory compared with men.[68] The magnitude of both gender and race differences have not been well characterized in previous studies. In our study, we noted that, on a 10-point scale, women rate pain 1.0 points higher than men and African Americans rated pain 0.6 points higher than nonHispanic whites. This well-supported finding creates a scientific basis for future investigations to identify ethnic and gender differences in pain perception.

Finally, we performed a preliminary evaluation of race and gender on sedation requirement. Because the dose of sedative drugs was titrated to participants' self-rating of sedation (midrange on the sedation scale), we considered the final drug dose as our indicator of sedation requirement. Even though this analysis was limited by the relatively small numbers in the respective race and gender subcategories, we observed a significant difference between African Americans and nonHispanic whites in the dexmedetomidine treatment arm. It is conceivable that genetic variations in the α_2 receptor through which dexmedetomidine

Table 7. Model 4: Fixed Effect Tests and Race Least-Squares Means

Source	*df*	Denominator *df*	F Ratio	*P* Value
Race	1	78.49	2.671	0.106
Type	3	2283	113.757	<0.001
Race * type	3	2283	0.428	0.733

Table 9. Model 5: Effect of Gender on Final Drug Dose by Drug (Outcome: Final Drug Dose)

Drug	*df*	Sum of Squares	F ratio	*P* Value
Dexmedetomidine	1	0.070	0.864	0.364
Midazolam	1	256.6	0.701	0.415
Propofol	1	0.138	1.674	0.209

Table 10. Model 6: Effect of Race on Final Drug Dose by Drug (Outcome: Final Drug by Dose)

Drug	*df*	Sum of Squares	F ratio	p-value
Dexmedetomidine	1	0.452	7.357	0.014
Midazolam	1	77.778	0.206	0.655
Propofol	1	0.014	0.162	0.692

These tables show the statistical results corresponding to analyses 1 – 6. The fixed effects tests are presented with test statistic and probability value. Least squares estimates for selected explanatory variables are also provided.

acts may explain differences in sedation requirements.[69] Further work will be needed to investigate this speculative mechanism.

We conclude by highlighting the significance of our primary study findings on the effect of sedation on pain perception. We noted that effects on pain perception are agent-specific; midazolam increases pain perception across all modalities, a finding that has not been reported in the literature. Propofol and dexmedetomidine show similar effects despite their very different chemical structure and presumed mechanism of action; they decrease sustained pain modalities (ischemic pain and cold pain) and have no (propofol) or an opposing effect on short, intermittent types of pain (electrical and heat pain). These findings help to explain the somewhat contradictory literature on the use of sedation on painful procedures. The degree of analgesia observed for propofol and dexmedetomidine does not justify their use for sedation in painful procedures without supplemental analgesic medication. We also confirm previously reported race and gender effects on pain perception; women rate identical experimental pain stimuli higher than men, and African Americans tend to rate identical pain stimuli higher than white Americans.

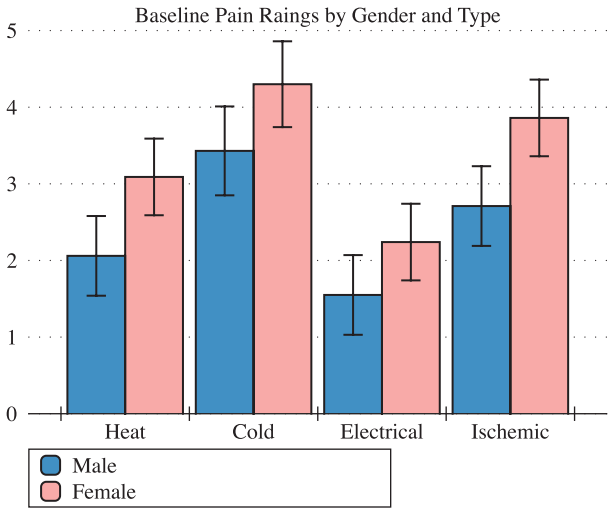

Fig. 3. Pain self-report data by subjects at baseline (without sedation). *Blue columns* represent male data and *pink columns* represent female data. The difference was significant for all pain types (heat, cold, electrical, and ischemic).

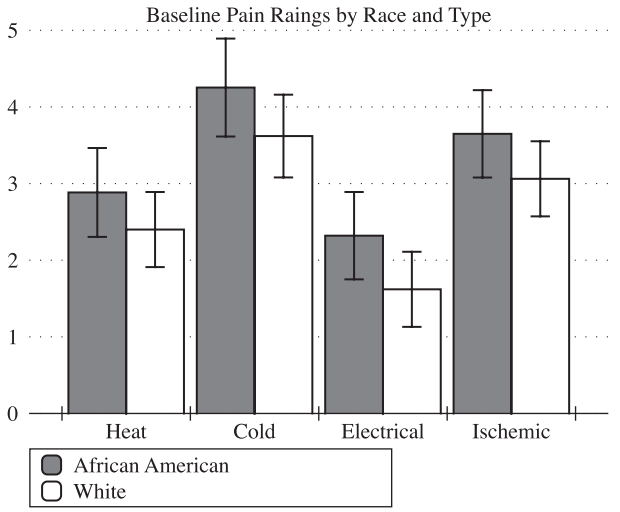

Fig. 4. Pain self-report data by subjects at baseline (without sedation). *Gray columns* represent data from African American participants (n = 33) and *white columns* represent data from Caucasian participants (n = 45). The difference was significant for all pain categories (heat, cold, electrical, and ischemic). Because of the small counts, other race categories were not included in this illustration.

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