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Relationship Between Endogenous Opioid Function and Opioid Analgesic Side Effects

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Abstract

Background and Objectives—Our recent work indicates that endogenous opioid activity influences analgesic responses to opioid medications. This secondary analysis evaluated whether endogenous opioid activity is associated with degree of opioid analgesic side effects, and whether chronic pain status and sex affect these side effects.

Methods—Using a double-blind, randomized, placebo-controlled, crossover design, 51 subjects with chronic low back pain and 38 healthy controls participated in 3 separate sessions, undergoing 2 laboratory evoked pain tasks (ischemic, thermal) after receiving placebo, naloxone, or morphine. Endogenous opioid system function was indexed by the difference in pain responses between the placebo and naloxone conditions. These measures were examined for associations with morphine-related side effects.

Results—Chronic pain subjects reported significantly greater Itching and Unpleasant Bodily Sensations with morphine than controls ($P < 0.05$). Across groups, only 6 out of 112 possible associations between side effects and blockade effects were significant. For the ischemic task, higher endogenous opioid function was associated with greater Itching (VAS; $P < 0.05$), Numbness (Tolerance; $P < 0.001$), Dry Mouth (Tolerance; $P < 0.05$), and Unpleasant Bodily Sensations (VAS; $P < 0.05$). For the thermal task, higher endogenous opioid function was associated with greater Numbness (VAS; $P < 0.05$) and Feeling Carefree (VAS; $P < 0.05$). There were no significant main or interaction effects of chronic pain status or sex on these findings.

Conclusions—No consistent relationships were observed between endogenous opioid function and morphine-related side effects. This is in stark contrast to our previous observation of strong

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relationships between elevated endogenous opioid function and smaller morphine analgesic effects.

INTRODUCTION

With the increased interest in personalized medicine, in which medications and their dosages can be optimized for maximal effect and minimal side effects according to individual genotypic and phenotypic patient variation, understanding sources of these variations is critical.[1,2] Factors contributing to differential responses to opioid analgesic medications across individuals are not fully understood. Most of the limited literature examining variations in opioid analgesic responses as they relate to differences in endogenous opioid activity is restricted to animals, with these studies focused entirely on analgesic effects and not side effects.[3–10] Recent work in our lab demonstrated for the first time in human volunteers that lower endogenous opioid function was associated with heightened analgesic responsiveness to morphine.[11] Results suggested that opioid analgesic medications may, in effect, supplement inadequate endogenous opioid analgesia, with little analgesic effect in those with higher pre-existing endogenous opioid function.[11] Opioid-related side effects are an important component of patients' inability to tolerate opioid medications and are a significant contributor to medication-related morbidity. We are unaware of any previous studies that have examined the impact of endogenous opioid function on opioid analgesic side effects in animals or humans.

Factors other than endogenous opioid function may also affect responses to opioid analgesics, such as sex and possibly chronic pain itself. A meta-analysis, for example, concluded that females exhibit significantly greater analgesic responsiveness to morphine, although THE magnitude of differences was small.[12] Few controlled studies have examined sex-related variations in opioid-induced side effect profiles,[13] with evidence suggesting that females may report higher levels of drug-related side effects, such as "coasting (spaced out)," "heavy or sluggish feeling," and "dry mouth."[14] However, these side-effect studies have not previously examined variations in endogenous opioid activity as a potential contributor to these sex differences. In addition, although evidence suggests that chronic pain itself may be associated with altered endogenous opioid system function,[15] surprisingly, no previous studies have examined the impact of chronic pain on opioid side-effect profiles in a controlled laboratory model.

Although our previous work demonstrated that greater endogenous opioid activity is associated with reduced analgesic responsiveness to opioids,[11] it was unclear whether a similar relationship might exist between endogenous opioid activity and opioid analgesic side effects, especially given the paucity of information regarding side effect mechanisms. We therefore performed a secondary analysis of our original data set to determine whether opioid-induced side effects following administration of a prototypic exogenous opioid analgesic, morphine, displayed consistent relationships with endogenous opioid function. We also sought to determine whether sex directly influenced morphine side effects or whether it affected associations between endogenous opioid function and side effects. Lastly, we aimed to evaluate the influence of chronic pain on opioid side effect profiles, and possible interactions with endogenous opioid function, in a controlled laboratory model.

METHODS

Design

We performed a secondary analysis of the data from our original study of associations between endogenous opioid activity and analgesic responses to opioid medications[11] in order to evaluate the extent of any relationships between endogenous opioid function and opioid analgesic side effects. The study was a double-blind, placebo-controlled crossover design with administration of an opioid antagonist (naloxone) and an opioid analgesic (morphine) to determine endogenous opioid function (indexed by opioid blockade effects as described below) and morphine-related side effects. The order of drug administration was randomized and counterbalanced, with the 3 study sessions conducted on separate days approximately 1 week apart to reduce possible carryover effects. The study was a multisite study, with identical data collection procedures and equipment employed in a closely coordinated fashion at 2 sites (Vanderbilt University Medical Center and Rush University Medical Center). All procedures were conducted at the Vanderbilt General Clinical Research Center or a dedicated research room at the Rush University Pain Center. All procedures were approved by the Institutional Review Boards at the respective institutions.

Subjects

Subjects included 38 healthy controls and 51 individuals with chronic low back pain. All subjects were recruited either through on-line advertisements on the Vanderbilt e-mail recruitment system, the Rush Pain Clinic, advertisements in local print media, or posted flyers. General criteria for participation included age 18 to 55 years; no self-reported history of cardiovascular disease, hypertension, liver or kidney disorders, posttraumatic stress disorder, bipolar disorder, psychotic disorder, diabetes, seizure disorder, or alcohol or drug dependence; no use of anti-hypertensive medications; and no daily use of opioid analgesics (absence of recent use was verified via urine opiate screen before each laboratory study session).

As in our past opioid blockade studies, additional inclusion criteria for the chronic pain group were chronic daily low back pain of at least 3 months' duration with an average past month severity of at least 3 on a 0 to 10 verbal numeric pain intensity scale.[11] Individuals with chronic pain related to malignancy, autoimmune disorders, or fibromyalgia (based on self-report) were excluded. Potential subjects who were pregnant (determined by urine pregnancy screens) were excluded to avoid unknown effects of naloxone on the fetus. No subjects in the healthy group were taking antidepressants, neuroleptics, or as-needed opioid analgesics. No subjects in the chronic low back pain group were taking neuroleptic adjuvant therapy for pain control, and only 2 (3.7%) were taking antidepressants. In addition, no subjects in either group reported use of any opioid analgesics in the 3 days before each study session (confirmed by opioid urine screen).

Procedures

After providing informed consent, subjects completed a packet of questionnaires, including information regarding demographics and chronic pain. Individuals then participated in 3 identical experimental sessions (placebo, naloxone, morphine) that were scheduled

approximately 1 week apart; sessions were scheduled at the same time of day to control for variance due to circadian rhythms.

Subjects remained seated upright in a comfortable chair throughout all laboratory procedures. During each session, subjects initially completed a 10-minute seated rest period, after which an indwelling venous cannula was inserted into the dominant arm by a trained research nurse under physician supervision. After a 30-minute resting adaptation period, subjects received (via the cannula) either saline placebo, naloxone, or morphine, with order of drug administration across the 3 sessions randomly determined and counterbalanced. The investigational pharmacy at each institution prepared and provided the study drugs in blinded fashion to the study nurses.

After a 15-minute rest period to allow peak drug activity to be achieved, subjects engaged in the ischemic pain task and thermal pain tasks, as detailed in our previous work.[11] For the ischemic task, subjects first engaged in 2 minutes of dominant forearm muscle exercise using a hand dynamometer at 50% of his or her maximal grip strength, as determined before beginning the laboratory procedures. Then they were asked to raise their dominant forearm over their head for 15 seconds. A manual blood pressure cuff was then inflated on the subject's dominant biceps to 200mmHg systolic blood pressure, the arm was lowered, and the cuff remained inflated until tolerance was reached, to a maximum of 8 minutes. Subjects were instructed to indicate when they first experienced pain after the cuff was inflated, with this ischemic pain threshold defined as the time elapsed from task onset to when the sensation was first described as "painful."

Ischemic pain tolerance was defined as the time elapsed between onset of the pain task and subjects' expressed desire to terminate the task (set at a maximum of 8 minutes). Given the extended duration of the ischemic task, verbal numeric rating scale (NRS) pain intensity ratings were obtained every 30 seconds (0= no pain, 100 = worst pain possible); mean NRS ratings for the task were used in analyses below. Immediately following the ischemic task, subjects used a 100 mm visual analog pain intensity scale (VAS; anchored with "no pain" and "worst possible pain") to rate the pain experienced during the task.

The second laboratory pain task was a heat pain task using a Medoc TSAII NeuroSensory Analyzer (Medoc US, Minneapolis, Minneapolis). Four trials each were conducted for heat pain threshold and tolerance, with each trial conducted sequentially at 1 of 4 different non-overlapping sites on the nondominant ventral forearm. An interval of 30 seconds between successive stimuli was used. For pain threshold trials, the probe started at an adaptation temperature of 32°C, with the temperature increasing at a ramp rate of 0.5°C/s until the subject indicated that the stimulus had begun to feel "painful" by depressing a button on a computer mouse. For each tolerance trial, the probe started at an adaptation temperature of 40°C, with the temperature increasing at a ramp rate of 0.5°C/s until the subject indicated maximum tolerance had been reached. The means of the 4 thermal pain threshold and tolerance trials were separately derived for use in analyses. Immediately following the last thermal tolerance trial, subjects again used the VAS intensity scale to rate the pain experienced during the task. Maximum possible tolerance temperature was 51°C due to an automatic hardware cutoff in the TSAII device to ensure subject safety. Before beginning

the first laboratory session, all subjects underwent standardized training to familiarize them with the thermal stimulus device and the concepts of pain threshold and tolerance.

After the pain tasks were completed, the subjects were asked to describe the opioid side effects they experienced using the Opioid Adjective Rating Scale (OARS) and the VAS Opioid Effects Questionnaire (only morphine condition side effects were examined in the analysis given the focus of this study). All subjects remained in the lab under observation for 2 hours after peak drug activity had been achieved to allow drug effects to remit, after which they were released to a responsible adult.

Study Drugs

Blockade of endogenous opioid activity was achieved by administration of naloxone, an opioid antagonist with a brief half-life (1.1 hours).[16] As in past work,[17–19] an 8 mg dose in 20 mL normal saline was infused intravenously over a 10-minute period through an intravenous cannula placed in the nondominant arm. At this dosage, naloxone provides effective blockade of all three major opioid receptor subtypes.[20] Peak naloxone activity is achieved within approximately 15 minutes.[21]

The opioid analgesic medication examined in this study was morphine sulfate, the prototypic mu opioid receptor agonist. As in similar laboratory evoked pain studies with morphine,[13] the current study employed a dosage of 0.08 mg/kg (in 20mL normal saline), which was infused in the same manner as naloxone. This dosage (approximately 7 mg for an average sized male) was selected because it was judged to be sufficient to produce analgesia, but low enough to avoid ceiling effects that might obscure key individual differences in morphine responding. Peak morphine activity is achieved within approximately 15 minutes.[21]

Measures

Before conducting analyses, blockade effects to index endogenous opioid function were derived for each of the 7 evoked pain measures (Ischemic Tolerance, Ischemic Threshold, Ischemic NRS, Thermal Tolerance, Thermal Threshold, Thermal NRS, and Thermal VAS Intensity). These blockade effects reflected the difference between placebo and naloxone condition pain values, calculated so that higher scores reflected greater endogenous opioid function (i.e., greater pain sensitivity under opioid blockade compared to placebo). For example, if the Ischemic NRS score was 30/100 in the placebo condition, but increased to 65/100 after naloxone administration, the blockade effect value would be 35, indicating substantial endogenous opioid analgesia in the intact state.

Subjects were asked to describe opioid-related side effects with the Opioid Adjective Rating Scale (OARS) and the 26-item VAS Opioid Effects Questionnaire developed by Zacny.[22] The OARS is a 12-item checklist of somatic and sensory effects of opiates that are rated on a scale from 0 (“not at all”) to 4 (“extremely”). These items are: “flushing,” “skin itchy,” “sweating,” “turning of stomach,” “numb,” “dry mouth,” “drive (motivated),” “carefree,” “good mood,” “headache,” “nodding,” and “vomiting.”[23] The Zacny 26-item VAS Opioid Effects Questionnaire consists of 26 known opioid side effects each rated on a 100mm VAS scale (anchored with “not at all” and “extremely”).[23]

Because of the large number of side effects on the VAS Opioid Effects Questionnaire, we used a principal components analysis (PCA) approach to reduce the number of variables examined and substantially reduce the number of analyses performed. PCA (with varimax rotation) indicated that 5 components, each with eigenvalues > 1.5, accounted for 62% of the total variance in side effects. VAS Opioid Effects Questionnaire items loading at least 0.50 on a given factor were summed (and rescaled to a 0–100 scale for each), resulting in 5 VAS side effect subscales (2 items, “tingling” and “drunk,” did not meet the criterion for inclusion in any of the subscales). Based on item content, the 5 subscales were labeled as follows: Sedation Subscale (sluggish, sedated, lightheaded, confused, dreamy, coasting, floating, sleepy, reduced ability to concentrate; Cronbach’s alpha = 0.92), Unpleasantness Subscale (irritated, down, unpleasant thoughts, feeling bad; Cronbach’s alpha = 0.77), Euphoria Subscale (stimulated, elated, pleasant thoughts, pleasant bodily sensations, feeling good; Cronbach’s alpha = 0.81), Negative Body Sensations Subscale (nauseated, dizzy, anxious, unpleasant bodily sensations; Cronbach’s alpha = 0.63), and Control Subscale (ability to control thoughts and ability to control body; Intraclass Correlation Coefficient= 0.93).

Baseline chronic back pain intensity for the chronic pain subjects was evaluated using the well-validated McGill Pain Questionnaire-Short form (MPQ), which includes separate standardized subscales assessing sensory (MPQ-Sensory) and affective (MPQ-Affective) pain qualities.[24] Subjects were asked to rate their overall chronic pain over the preceding month.

Statistical Analysis

All analyses were conducted using IBM SPSS for Windows Version 20 (IBM Corp, Armonk, New York). Primary analyses used independent samples *t* tests for comparisons by chronic pain status and sex, and Pearson correlation coefficients to examine linear associations between morphine side effects and both endogenous opioid function indices (blockade effects) and chronic pain intensity. Nonlinear effects were not examined.

RESULTS

Subject Characteristics

Subject characteristics are summarized in Table 1. Both subsamples were predominately female and nonHispanic Caucasian. Comparison of the chronic pain group (n=51) and healthy controls (n=38) revealed no significant differences between the 2 study groups by age, gender, race, or ethnicity ($P > 0.10$).

Relationship of Side Effects to Chronic Pain Status or Sex

Comparisons (via *t* tests) of mean reported side effects by chronic pain status (Table 2) revealed significantly greater scores for OARS-Itchy (t =-2.64, df=88, $P = 0.01$) and the VAS Unpleasantness Subscale (t =-2.09, df = 88, $P = 0.04$) in chronic pain patients compared to controls. A similar analysis performed regarding sex differences in opioid side effects did not reach significance for any measure. Since there were only 2 side effects that reached significance out of 32 comparisons when differentiating the sample by chronic pain

status or sex, all subjects were combined into one group for analyses of blockade effects. To ensure that combining groups would not confound results, we repeated the endogenous opioid blockade effect analyses below using a series of hierarchical linear regressions separately for chronic pain status and sex, examining main and interaction effects with blockade effects as they influenced side effect outcomes. Results indicated that neither chronic pain status nor sex, nor their interactions with blockade effects, contributed significantly to the observed variance in side effects.

Does The Intensity of Chronic Pain Relate to Morphine Side Effects?

Higher MPQ-Sensory chronic pain ratings correlated with significantly higher side effect scores on OARS-Itchy (r = 0.29, $P = 0.04$), OARS-Dry Mouth (r = 0.34, $P = 0.01$), OARS-Headache (r = 0.31, $P = 0.03$), and the VAS Unpleasantness Subscale (r = 0.53, $P < 0.001$). Higher MPQ-Affective ratings were associated with greater side effects on OARS-Headache (r = 0.36, $P = 0.01$) and the VAS Unpleasantness Subscale (r =0.47, $P = 0.001$), but lower scores on OARS-Good Mood (r =-0.35, $P = 0.01$). Only the associations between the VAS Unpleasantness subscale and MPQ-Sensory and MPQ-Affective chronic pain ratings remained significant after Bonferroni correction for multiple comparisons.

Association Between Endogenous Opioid Activity and Side Effects

Pearson correlations between reported morphine side effects and blockade effects (Table 3) revealed only 6 significant associations out of 112 examined. Higher ratings of Itchiness (r = 0.23, $P = 0.03$) on the OARS and the VAS Unpleasantness Subscale (r = 0.23, $P = 0.04$) were related to greater Ischemic VAS blockade effects. Higher ratings of Numb feelings on the OARS were associated with greater endogenous opioid analgesia (ie, larger blockade effects) derived for Ischemic Tolerance (r = 0.33, $P = 0.001$) and Thermal VAS measures (r = 0.25, $P = 0.02$). Dry Mouth also displayed a positive correlation with the Ischemic Tolerance blockade effect measure (r = 0.22, $P = 0.04$). Finally, greater feelings of being Carefree were observed on the Thermal VAS blockade effect measure (r = 0.23, $P = 0.03$). However, none of these associations remained significant after the Bonferroni adjustment for multiple comparisons was made (adjusted $P < 0.0004$), which would require a correlation of r = 0.37 to be significant.

DISCUSSION

Our previous work revealed a strong relationship between lower endogenous opioid activity (as indexed by blockade effects) and elevated analgesic responses to morphine. In the current study, we performed a secondary analysis of this dataset to determine whether there were parallel relationships between endogenous opioid activity and morphine-induced side effects. Analyses revealed only 6 significant, albeit modest (r = 0.22 – 0.33), associations between endogenous opioid function measures (blockade effects) and morphine side effects out of 112 correlations examined. Few of these remained significant after adjustment for multiple comparisons. Therefore, in contrast to our previous publication, which revealed strong and consistent inverse relationships between endogenous opioid function and analgesic responses to morphine across both evoked pain measures, we observed virtually no significant associations between the same blockade effects and opioid-related side effects

in this study. A post-hoc power analysis revealed that this study had a power of 0.80 to detect a small to medium effect size of r = 0.25 at a 2-tailed alpha level of $P < 0.05$. It was believed that an effect size at least this large was necessary for any hypothesized effects to be clinically meaningful. Although ratings of "numbness" following morphine reached this criterion for 2 blockade effect measures, the general absence of significant effects in the context of adequate statistical power in this study suggests that the pattern of findings can be interpreted as indicating little meaningful influence of endogenous opioid activity on morphine side effects.

Neither chronic pain status nor subject sex exerted a consistent influence on morphine side effects, with 2 significant observed correlations for the former, and none for the latter. The absence of side effect differences by gender is in contrast to previous publications.[13,14] Neither chronic pain status nor gender accounted for the few significant associations observed between endogenous opioid function and side effects.

Although having chronic pain did not consistently influence side effects, there was weak evidence that baseline intensity of chronic pain might impact side effects. Specifically, greater pain intensity was linked to more intense morphine side effects, including increased skin itchiness, dry mouth, headache, and unpleasant subscales in addition to decreased good mood. Reasons for these associations are unknown, but do not appear likely to involve endogenous opioid mechanisms. It is possible that greater chronic pain intensity is associated with elevated somatic awareness, which might also make individuals more aware of drug side effects. Because somatic awareness was not assessed in the current study, this possibility remains to be explored. An alternative possibility is that these significant correlations were spurious, resulting from Type I error, given that most were no longer significant after Bonferroni correction.

The source of differing patterns of relationships between endogenous opioid function and morphine analgesic effects in our previous work[11] versus morphine side effects in the current study is unclear. Morphine, in addition to its mu agonist activity, may also have weak agonist effects at kappa opioid receptors, which are known to be linked to many common opioid side effects similar to those observed in the current study.[25] Given that beta-endorphin, the primary endogenous opioid agonist, appears more selective to mu receptors,[25] this receptor subtype affinity difference might in principle have contributed to the differing pattern of associations between endogenous opioid function and analgesic versus side effects observed across studies.[11]

Our previous work showing a clear inverse relationship between endogenous opioid function and analgesia[11] and the current work showing minimal relationship between endogenous opioid function and opioid-related side effects when taken together may have importance for risk/benefit considerations in opioid medication management. For example, if a patient has known high endogenous opioid activity (perhaps indexed by low baseline evoked pain responsiveness[11]), we now know that morphine is less likely to provide significant analgesia, but would be associated with the same degree of side effects expected in a person with low endogenous opioid function. In this situation, alternative pain treatment strategies may be preferable, including multimodal non-opioid medications, regional anesthesia, and

non-pharmacological approaches (eg, cognitive behavioral pain management). While opioid medications are often the default choice for initial treatment of pain, more time consuming and occasionally more expensive modalities may prove optimal for selected patients. Improved ability to identify these patients in advance, whether based on endogenous opioid-related biomarkers or other factors, could enhance both pain management efficiency and efficacy.

Several study limitations are noted. Additional studies are required to determine whether the current side effect findings extend to other opioids beyond morphine. Also, confirmation of these laboratory results would be needed in a clinical environment before any clinical application would be possible. The chronic pain patients in this study only included patients who were not regularly taking opioid medications at the time of the laboratory experiments; however, many chronic pain patients in clinical practice are taking daily high dose opioids for extended periods. Whether and how the current findings might have been influenced by the unique nature of this sample is unclear. Opioid-related side effects were not assessed pre-drug, and we, therefore, could not assess changes in side effects as they related to endogenous opioid function. While this is a potential limitation, it seemed reasonable to assume that subjects were not experiencing opioid-related side effects prior to drug infusion. Additionally, to verify that very small to negligible correlations exist between endogenous opioid activity and opioid-related side effects, a dose response study would be required to ensure that the dose of opioid that we delivered was not so high as to obscure any subtle differences in relationship to endogenous opioid function, or rather, too low to elicit such differences.

In summary, contrary to our previous observations documenting a strong inverse relationship between endogenous opioid function and morphine-induced analgesia, endogenous opioid activity did not appear to be significantly associated with opioid-related side effects. Sex differences and chronic pain status also did not appear to significantly influence the likelihood of developing side effects with morphine in a controlled laboratory environment.

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Table 1

Subject characteristics.

Characteristic	Control (n=38)	Chronic Pain (n=51)
Age	34.2±9.5	37.1±10.7
Female	19 (50.0%)	35 (68.6%)
Race:		
Black/African American	15 (39.5%)	17 (33.3%)
White	19 (50.0%)	30 (58.8%)
Other race	4 (10.5%)	4 (7.9%)
Non-Hispanic or Latino	35 (92.1%)	49 (96.1%)
VAS Baseline Past Month Pain Intensity		56.2±23.6
Median Pain Duration (IQR)		89.7 (103.7)

Note: All demographic comparisons across groups were nonsignificant. Summary statistics are presented as percentages or means (± SD) except where otherwise indicated. IQR = interquartile range.

Table 2

Side effects by chronic pain status and sex.

Side Effect	Subject Type		Sex	
	Healthy Control	Chronic Pain	Female	Male
OARS:				
Flushing	0.51±0.76	0.49±0.67	0.53±0.75	0.46±0.65
Itchy	0.10±0.31	0.51±0.93**	0.38±0.81	0.27±0.65
Sweating	0.28±0.65	0.10±0.36	0.19±0.59	0.17±0.38
Turn Stomach	0.31±0.61	0.45±0.76	0.38±0.53	0.41±0.90
Numb	0.04±0.68	0.41±0.64	0.38±0.51	0.58±0.80
Dry Mouth	0.79±1.06	0.75±1.00	0.92±1.07	0.54±0.90
Motivated	1.08±1.20	0.76±1.01	0.75±0.96	1.11±1.27
Carefree	1.64±1.27	1.55±1.30	1.55±1.32	1.65±1.23
Good Mood	2.10±1.35	2.00±1.34	2.08±1.43	2.00±1.23
Headache	0.15±0.43	0.43±0.92	0.38±0.79	0.22±0.71
Nodding	0.28±0.87	0.53±0.92	0.53±1.03	0.27±0.65
Opioid VAS Subscales:				
Sedation	23.35±20.00	29.88±21.49	29.57±22.50	23.28±18.16
Unpleasantness	5.12±9.25	11.73±17.97*	9.66±17.61	7.67±10.47
Euphoria	33.00±20.45	36.35±21.86	35.37±22.65	34.30±19.23
Neg. Body Sensations	10.55±15.41	11.06±10.55	10.90±13.28	10.74±12.24
Control	76.08±29.65	67.49±29.21	68.98±30.74	74.56±27.76

Note: Statistics presented as means (± SD).

* $P < 0.05$;

** $P < 0.01$

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Table 3

Pearson correlations (r) between blockade effects and side effects.

	Blockade Effect – Ischemic Tolerance	Blockade Effect – Ischemic Threshold	Blockade Effect – Ischemic NRS	Blockade Effect – Ischemic VAS	Blockade Effect – Thermal Tolerance	Blockade Effect – Thermal Threshold	Blockade Effect – Thermal VAS
OARS:							
Flushing	0.02	0.05	0.01	−0.15	−0.04	0.00	0.07
Itchy	0.15	0.03	0.10	0.23*	0.01	0.05	0.16
Sweating	−0.03	−0.06	0.04	−0.14	0.01	−0.05	−0.01
Turn Stomach	0.02	0.10	0.09	0.14	0.06	0.00	0.13
Numb	0.33***	0.22	−0.01	0.10	0.02	0.01	0.25*
Dry Mouth	0.22*	0.16	0.09	0.11	0.07	−0.01	0.09
Motivated	−0.04	0.00	−0.16	−0.01	−0.21	−0.08	0.04
Carefree	0.28	0.77	0.47	0.97	0.11	−0.03	0.23*
Good Mood	0.02	0.07	−0.01	−0.06	−0.12	0.12	0.07
Headache	0.09	0.04	0.08	−0.01	−0.12	0.03	0.14
Nodding	0.10	0.07	−0.02	0.04	0.10	−0.00	0.12
Opioid VAS Subscales:							
Sedation	0.16	0.10	−0.04	0.07	0.07	−0.05	0.20
Unpleasantness	0.16	0.09	0.13	0.23*	−0.01	0.02	0.17
Euphoria	0.13	0.01	−0.13	−0.02	−0.07	0.15	0.03
Neg. Body Sensations	−0.04	0.01	−0.05	0.00	−0.06	−0.05	−0.04
Control	0.05	−0.01	0.11	0.01	0.04	0.10	−0.02

* $P < 0.05$;

*** $P < 0.001$