Preoperative and Postoperative Hyperalgesia in Dental Patients on Chronic Opioid Therapy: A Pilot Study

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Objective: Opioid-induced hyperalgesia, a paradoxical increase in pain sensitivity associated with ongoing opioid use, may worsen the postoperative pain experience. This pilot study examined the effect of chronic opioid use on pain responses in patients undergoing a standardized dental surgery.
Methods: Experimental and subjective pain responses were compared prior to and immediately following planned multiple tooth extractions between patients with chronic pain on opioid therapy (≥30 mg morphine equivalents/d) and opioid-naïve patients without chronic pain matched on sex, race, age, and degree of surgical trauma.
Results: Preoperatively, chronic opioid users rated experimental pain as more severe and appreciated less central modulation of that pain than did opioid-naïve participants. Postoperatively, chronic opioid-using patients rated their pain as more severe during the first 48 hours and used almost twice as many postoperative analgesic doses during the first 72 hours as the opioid-naïve controls.
Conclusion: These data suggest that patients with chronic pain taking opioids approach surgical interventions with heightened pain sensitivity and have a more severe postoperative pain experience, providing evidence that their complaints of postoperative pain should be taken seriously and managed appropriately.

Key Words: Opioids; Hyperalgesia; Preoperative pain; Postoperative pain; Cold-pressor test; Quantitative sensory testing; Conditioned pain modulation.

In well-intended and industry-driven efforts to provide relief to chronic pain sufferers, the prescription of opioids has dramatically increased since the turn of the century, such that it is currently estimated that over 5 million Americans use opioids on a daily basis.[1] Yet prescription opioid therapy for chronic pain is not an evidence-based intervention; as evaluation data accumulate, it is increasingly clear that health outcomes, including surgical outcomes, are poorer for patients on opioid therapy.[2] A theorized explanation for poorer surgical outcomes in patients on opioid therapy is the phenomenon of opioid-induced hyperalgesia (OIH),[3] where ongoing opioid use results in increased sensitivity to pain.

To evaluate the effects of OIH in a surgical patient population, pain responses and analgesic need of patients on opioid therapy vs those not on opioid therapy undergoing a similar surgical procedure were compared. It was hypothesized that relative to opioid-naïve patients, patients on opioid therapy for the management of chronic pain would have increased pain sensitivity prior to and experience more severe postoperative pain following a planned dental surgical procedure. Evidence that prescribed opioids worsen the perioperative pain experience for patients with chronic pain provides support for the opioid-sparing approaches promulgated by the Centers for Disease Control and Prevention (CDC).[4]

METHODS

Study Design

Utilizing a prospective, observational approach, the effects of chronic opioid therapy on preoperative and

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postoperative pain responses were evaluated. A total of 22 patients were enrolled: 10 regularly taking opioids for the treatment of chronic pain and 12 matched opioid-naïve individuals without chronic pain. Each underwent a standardized dental surgical procedure (multiple tooth extractions) performed by 1 of 2 board certified oral surgeons providing uniform local anesthesia (2% lidocaine with 1:100 000 epinephrine and/or 3% mepivacaine plain) and a nonopioid postoperative analgesic regimen (ibuprofen 400 mg + acetaminophen 500 mg as needed).[5] Prior to the procedure, pain perception was assessed using valid and reliable experimental pain induction techniques. Postoperatively, subjects were asked to rate the severity of their pain every 6 hours using a standard visual analog scale (VAS) and to document all nonopioid analgesic consumption for the first 72 hours. Study nurses collecting preoperative and postoperative study data were blind to group membership, as were the study investigators.

Study Participants

Eligible participants were between the ages of 21 and 75 years and were undergoing multiple tooth extractions. Preoperative trauma rating scores were calculated to ensure that all patients were undergoing a comparable and at least a moderate amount of surgical trauma. Each tooth extracted received a 1 rating for a simple extraction, a 2 rating for a routine surgical extraction, or a 3 rating for a complex surgical extraction. For patients to be included in the study, a total trauma rating score of 5 or higher was required.[5] The preoperative trauma score was confirmed intraoperatively, and the intraoperative score was used for matching and data analyses. Opioid patients were on a daily dose of 30 mg or more morphine milligram equivalents (MMEs) for at least 3 months, and opioid-naïve patients reported no opioid use within the last 3 months and were without chronic pain. Potential participants were excluded from participation if they had an active substance use disorder (except nicotine) or a neurological or psychiatric illness known to affect pain responses as confirmed by the electronic health record. To ensure tolerance to the experimental pain assay and the postoperative analgesics, patients with untreated hypertension, a history of gastrointestinal ulcers, NSAID-induced asthma or allergy, or poor liver or kidney function were also excluded. The study was approved by the University of Pennsylvania Institutional Review Board (protocol 829880); participants provided informed consent and were compensated for their participation.

Measures

Preoperative Pain Sensitivity. Pain sensitivity was measured preoperatively using 2 validated methods of pain induction: the cold-pressor test (CPT) and quantitative sensory testing (QST), providing 3 distinct measures of pain response and using procedures consistent with those described in the literature.[6,7] During a single study session, all participants underwent 3 experimental thermal pain tests: (1) cold pain delivered via the CPT, (2) heat pain delivered via QST, and (3) conditioned pain modulation delivered via QST. Objective CPT and QST responses were operationalized as tolerance of the thermal stimulus, whereas conditioned modulation was measured as response to repeated heat stimuli, both with and without a concurrent modulating stimulus (ice bath). Immediately following each pain stimulus, patients rated its subjective severity.

Postoperative Pain Severity. Severity of postoperative pain was recorded every 6 hours until 72 hours postoperatively from subjects' responses on the VAS pain scale, which ranged from 0 (no pain) to 10 (worst pain imaginable). Additionally, the total number of analgesic doses taken during the 72-hour postoperative period was obtained via patient self-report.

Preoperative Opioid Use. For those subjects on opioid therapy, estimated daily opioid dose was obtained via self-report and confirmed with the electronic medical record. Morphine equivalent daily opioid dose was calculated using the CDC opioid conversion table (https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf) and treated as MME.

Procedures

Preoperative Pain Responses. *Cold Pain*. To measure cold pain tolerance, the CPT consisted of a circulating ice water bath maintained at 1.5°C ± 0.5°C into which subjects immersed their dominant hand and forearm to elicit a nociceptive response. The time from arm immersion to when the pain became subjectively intolerable (pain tolerance) or the subjects spontaneously removed their hand from the ice bath was measured in seconds. Immediately following hand withdrawal, subjects were asked to rate maximal pain intensity using the VAS.

Heat Pain. To measure heat pain sensitivity, a thermal testing analyzer (TSA) (TSA-2001; Medoc) with a 30 × 30-mm Peltier thermode was used. Specifically, noxious heat stimulation was applied to the volar surface of the patient's dominant hand using a ramp-and-hold method; baseline temperature was set to 32.0°C, increased at

Table 1. Participant Characteristics: Similarities in Sex, Race, Age, and Degree of Surgical Trauma Between Opioid-Using and Opioid-Naïve Patients

	On opioid therapy (n = 10)	*Opioid naïve (n = 12)*	*P value*
Sex, No. (%)			.793†
Female	3 (30)	3 (25)	
Male	7 (70)	9 (75)	
Race, No. (%)			1.000†
White	5 (50)	6 (50)	
Black	5 (50)	6 (50)	
Age, mean (SD), y	55.6 (9.80)	58.3 (13.88)	.544‡
Surgical trauma score, mean (SD)	6.8 (1.64)	6.9 (2.13)	.880‡
Daily opioid dose, mean (SD), MME	130.4 (140.50)		

* MME = morphine milligram equivalents.
† χ^2 test.
‡ *t* test.

a rate of 1°C/s to a destination temperature of 46.5°C, and then remained constant for 120 seconds. Pain tolerance was also calculated as the number of seconds exposed to the heat stimulus before the subject requested to end the test. Following the heat stimulus, subjects rated the magnitude of their perceived pain using the VAS.

Conditioned Pain Modulation. Using QST apparatus, the TSA thermode was applied to the thenar eminence of the dominant hand, and subjects were asked to verbally rate the pain severity (0–100) of 4 consecutive heat pain stimuli of 47°C (starting from 37°C at an increasing and decreasing rate of 10°C/s), each lasting 3 seconds with an interval of 12 seconds. For the second stimulus, the nondominant hand was concurrently immersed in an ice water bath (1.5 ± 0.5°C) to provide counterstimulation. Comparison of perceived heat pain severity with and without counterstimulation provided evidence of dynamic central pain modulation.

Postoperative Pain Responses. Patients were provided a paper-and-pencil pain diary to record the severity of pain experienced every 6 hours and the time and date of analgesic doses consumed during the first 72 hours postoperatively. Completed diaries were returned to the study coordinator via text or mail with prepaid envelopes.

Data Analyses

All study data were entered and managed using REDCap electronic data capture tools. Preliminary analyses included generating descriptive statistics to characterize the sample and evaluate the efficacy of the matching procedures. Correlations were inspected between MME and cold and heat pain responses, conditioned pain modulation, self-reported postoperative pain severity, and number of postoperative analgesic doses used. Because of the small sample sizes, group difference analyses remained at the level of description, with χ^2 statistics calculated for categorical variables and *t* test statistics calculated for continuous variables; statistically significant differences were set at $P < .05$ a priori. The 72-hour trajectory of self-reported postoperative pain severity was visually inspected, and the number of analgesic doses used was compared between groups. All data analyses were conducted using SPSS 27 statistical software.

RESULTS

Patients on opioids were taking relatively large doses, with an average dose higher than 100 MME/d (Table 1). These patients suffered from various chronic pain conditions; the majority (70%) suffered from more than one painful condition, and the most commonly reported pain syndromes were low back pain (50%) and arthritis (40%). Matching was successful between opioid-using and opioid-naïve participants on sex, age, race, and degree of surgical trauma (calculated trauma score). No adverse events were experienced during either the preoperative or postoperative data collection time periods.

Across all experimental pain measures, women were consistently more sensitive to noxious stimuli and had more severe pain ratings. No clear patterns emerged with respect to race, with Black participants reporting slightly less pain sensitivity for cold pain severity and heat pain tolerance, and slightly more sensitivity on cold-pressor tolerance and heat pain severity. Women (–2.22 points, SD = 7.794) displayed a greater analgesic effect from the counterstimulus than did men (–4.58 points, SD = 11.979), as did Black (–3.03 points, SD = 13.618) in comparison with White participants (–4.85 points, SD = 7.797).

Table 2. Preoperative Experimental Pain Responses: Decreased Pain Tolerance, Increased Perceived Pain Severity, and Decreased Conditioned Pain Modulation in Opioid-Using Patients with Chronic Pain vs Opioid-Naïve Patients without Chronic Pain Across Pain Assays

	On opioid therapy (n = 10)	*Opioid naïve (n = 12)*	*P value*
Cold-pressor test			
Pain tolerance, mean (SD), s	61.1 (89.53)	77.1 (106.95)	.711†
Maximal pain VAS severity rating, mean (SD)	72.5 (16.87)	56.6 (24.98)	.075†
QST heat stimulus			
Pain tolerance, mean (SD), s	93.7 (43.00)	120 (0.00)	.050†
Maximal pain VAS severity rating, mean (SD)	45.0 (15.81)	23.3 (21.46)	.106†
QST conditioned pain modulation, mean (SD)‡	−9.0 (10.89)	0.3 (9.26)	.043†

* VAS = visual analog scale (0 = no pain, 100 = severe pain); QST = quantitative sensory testing.
† *t* test.
‡ For each of the pain assays, the value provided is the average value for each group: opioid-using patients with chronic pain ["On opioid therapy (n = 10)"] and opioid-naïve patients without chronic pain ["Opioid naïve (n = 12)"].

The number of MMEs used by the patients taking opioids correlated significantly with cold pain responses, such that those on higher doses had lower pain tolerance ($r = -0.876$, $P = .001$) and rated their pain as more severe ($r = 0.759$, $P = .011$). However, MME was associated neither with preoperative heat pain tolerance or severity nor with degree of pain modulation. Similarly, MME was associated neither with postoperative pain severity ratings at any time point nor with the number of postoperative analgesic doses used.

Group differences were noted between opioid-using and opioid-naïve patients, such that the former were likely to rate the cold and heat pain as more severe, although not to a statistically significant degree (Table 2; Figure 1a and b). Similarly, this trend was reflected in cold-pressor and heat pain tolerance, with opioid users tolerating each for a shorter period than the opioid naïve; notably, all opioid-naive subjects tolerated the full 120 seconds of the heat stimulus, whereas 3 of the opioid-using subjects tolerated it for less than half as long, although neither response achieved statistical significance. With respect to conditioned pain modulation, clearer group differences emerged, such that opioid-naïve patients appreciated a slight, significant analgesic effect from the counterstimulus (+0.28 points, SD = 9.261), whereas patients using opioids rated the heat stimulus as more painful during counterstimulation (–9.00 points, SD = 10.892; $P = .043$).

With respect to postoperative pain outcomes, opioid-using patients reported more severe pain for the first 42 to 48 hours following surgery than the opioid naïve (Table 3; Figure 2); this difference was significant only at hour 6 (respective pain scores 7.4, SD = 2.46, vs 3.6, SD = 3.17; $P = .007$). Consistent with a more severe postoperative pain experience, opioid users took nearly twice as many analgesic doses (8.5 doses, SD = 5.30) as opioid-naïve patients (4.8 doses, SD = 4.20) during the first 72 hours (Figure 3). This was in addition to the opioids they continued to take on a regular basis for their chronic pain condition.

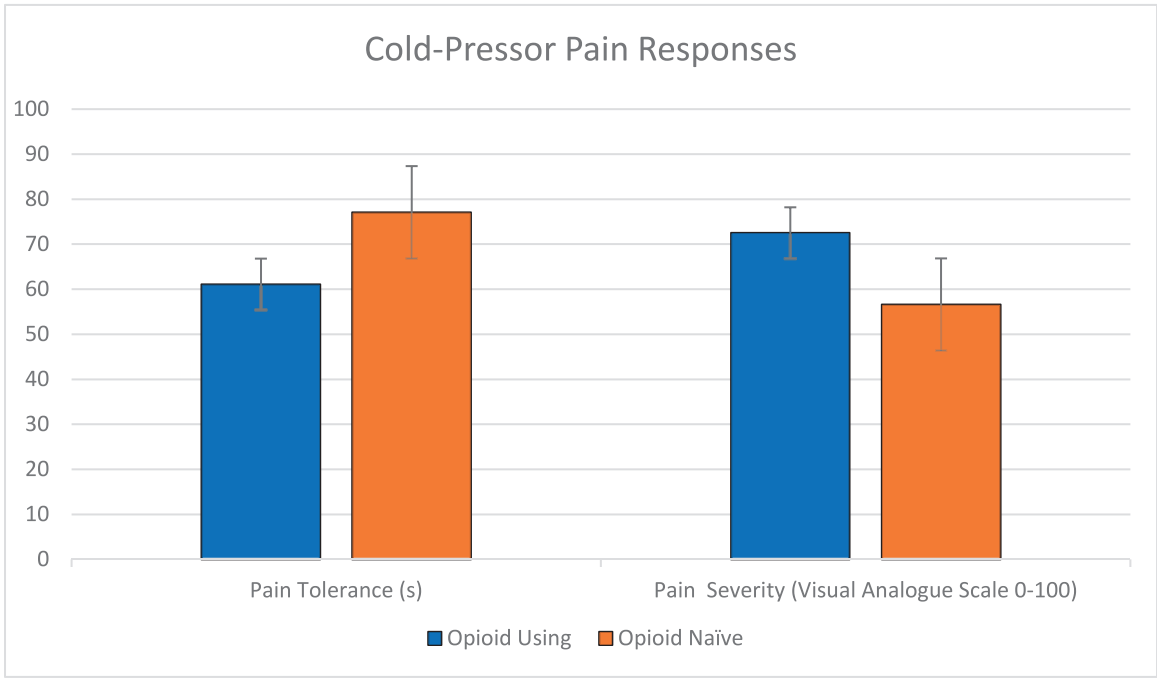
DISCUSSION

There is preclinical and clinical evidence to suggest that the analgesia provided by opioids is countered by an opposing hyperalgesic effect, which becomes the dominant allostatic response over time. The findings from this pilot study indicate that patients with chronic pain on opioid therapy demonstrate OIH on multiple experimental pain assays and that OIH concomitantly appears to worsen their postoperative pain experience. To the degree that these postoperative pain responses are related to preoperative opioid use, opioid-sparing and opioid-tapering approaches are supported prior to surgery.[8]

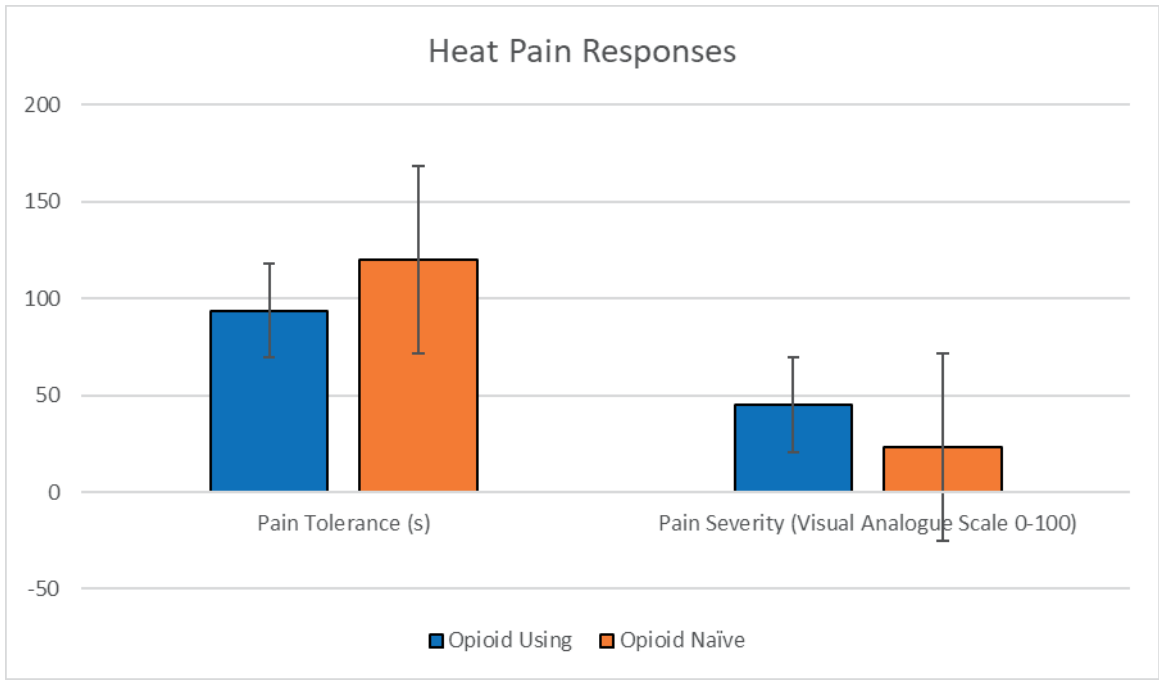
Known sex differences in experimental pain tolerance and severity were confirmed in the current study: regardless of opioid use, women were found to be less tolerant of thermal pain and rated it more severely than men. Contrary to a limited literature,[9,10] women in the current study appreciated greater conditioned pain modulation than men; however, inconsistent reliability of this task across sexes[11] may explain this finding. Mixed findings with respect to race are likewise at odds, with the literature showing poorer experimental pain tolerance in Black compared with White participants[12]; however, the greater degree of conditioned pain modulation among Black participants is aligned with existing research.[13] In the opioid-using patients, daily opioid dose was inconsistently associated with experimental preoperative pain responses, which is similarly reflected in the literature.[11,14] More work is needed to determine if specific patient or drug (individual opioid agonists) characteristics can explain the inconsistent association between opioid dose and experimental pain responses in patients with chronic pain.

Figure 1. (a) Cold-Pressor and (b) Heat Pain Tolerance and Severity in Opioid-Using and Ppioid-Naïve Patients.

a. Cold-Pressor Pain Responses



b. Heat Pain Responses



Decreased pain tolerance and increased perceived pain severity (mean, SD) in patients with chronic pain on opioid therapy vs opioid-naïve patients without chronic pain across cold-pressor and heat pain assays.

Table 3. Postoperative Pain Severity Ratings up to 72 Hours.

Postoperative hour	*Opioid using, Mean (SD)*	*Opioid naïve, Mean (SD)*	*P value**
6	7.6 (2.55)	3.6 (2.97)	.007
12	5.0 (3.57)	2.3 (2.44)	.050
18	5.5 (3.60)	2.6 (2.59)	.052
24	4.8 (3.05)	2.8 (1.93)	.076
30	4.2 (3.08)	2.2 (2.45)	.105
36	3.7 (3.24)	2.7 (1.86)	.375
42	4.2 (3.54)	2.8 (2.35)	.280
48	3.3 (2.93)	2.8 (2.55)	.673
54	2.7 (2.74)	2.7 (1.99)	1.000
60	2.8 (3.28)	3.1 (2.50)	.810
66	2.8 (2.87)	1.9 (1.99)	.397
72	2.1 (2.67)	2.2 (2.30)	.926

Seventy-two–hour postoperative pain severity ratings on increased postoperative visual analog scale (0 = no pain, 10 = severe pain) in opioid-using patients with chronic pain vs opioid-naïve patients without chronic pain.

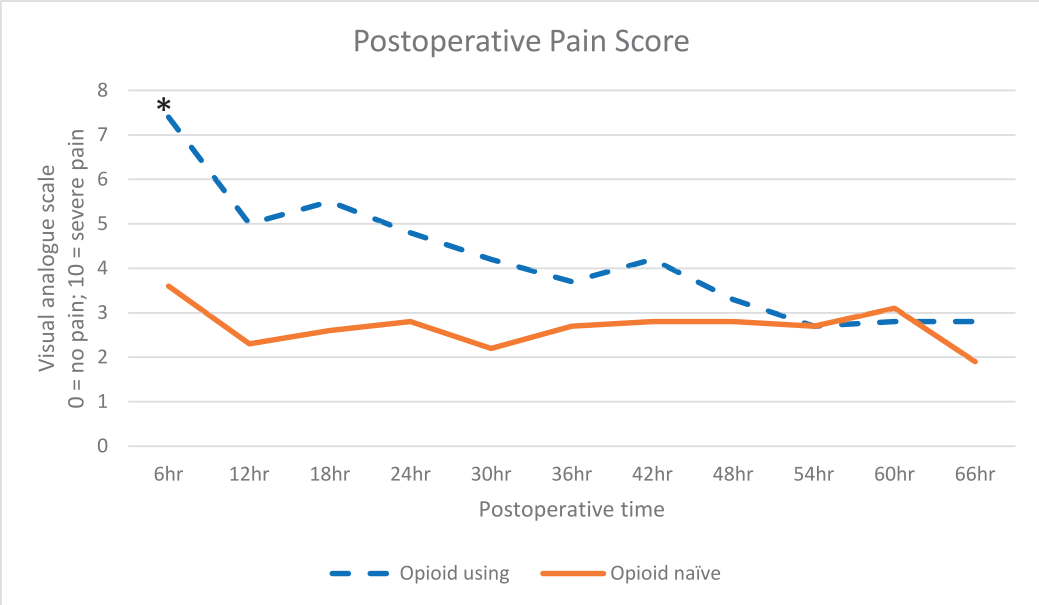
* *t* test.

Consistent with the literature,[14] patients with chronic pain on opioid therapy appeared hyperalgesic to experimental thermal pain in comparison with opioid-naïve patients, rating pain as more severe with decreased tolerance. In both cross-sectional and prospective investigations, significantly decreased tolerance for QST-delivered cold and heat pain at temperatures like those used in the current study has been reported in chronic pain patients using opioids in comparison with pain-free controls as well as to patients with chronic pain not using opioids. As in the current study, in a group of preoperative orthopedic patients, Hina and colleagues[15] found that those consuming opioids had a significantly decreased duration of tolerance to a heat stimulus than patients not taking opioids. Persons taking opioids on a regular basis for the treatment of chronic pain have decreased tolerance for experimental thermal pain and tend to have more severe pain ratings than persons with the same disorder not on opioid therapy.

The current findings that opioid-naïve patients appreciated more robust conditioned pain modulation than those on opioids is further supported by the recent narrative review of Petersen et al.[16] Of note, this is opposite to the effect of acute opioid administration, which appears to enhance descending inhibition activity even among those with chronic pain.[17] In that a theorized explanatory mechanism for OIH is heightened activity in descending pain facilitatory systems,[18] this observed decreased activity in descending inhibitory systems of persons chronically taking opioids may be a potential indicator of OIH.

In addition to evidence of preoperative OIH, this study also describes a more challenging postoperative pain experience for patients with chronic pain using opioids prior to the surgical experience. As recently summarized by Quinlan et al,[8] multiple poor surgical

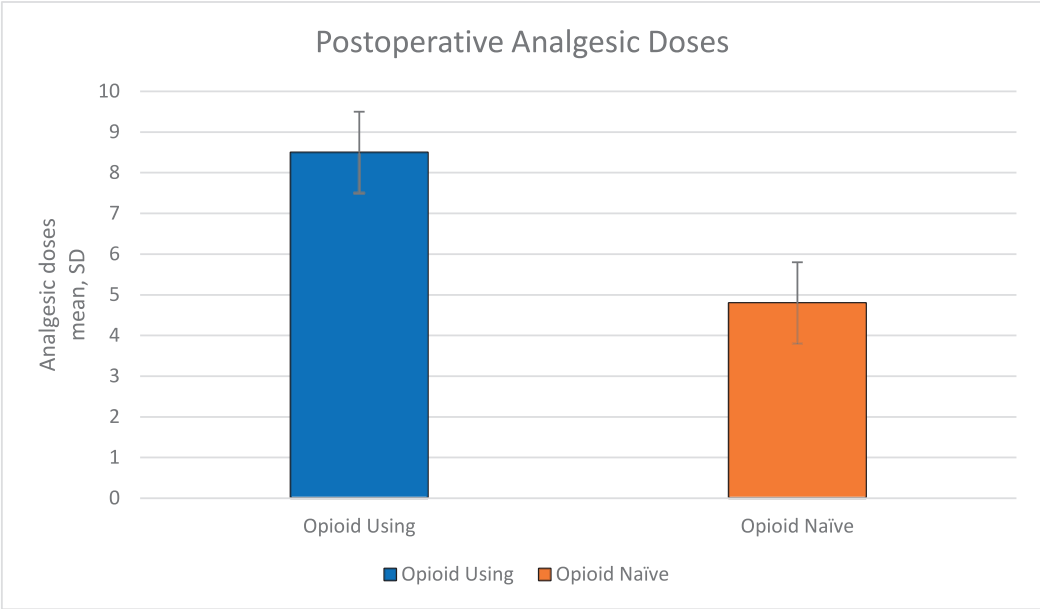
Figure 2. Seventy-Two–Hour Postoperative Pain Severity in Opioid-Using and Opioid-Naïve Patients.



*Statistically significantly difference at 6 hr, *P*=.007

Increased perceived postoperative pain severity as measured with a visual analog scale (0 = no pain and 10 = severe pain; mean, SD) in patients with chronic pain on opioid therapy vs opioid-naïve patients without chronic pain.

Figure 3. Analgesic Doses Taken During the First 72 Hours Postoperatively in Opioid-Using and Opioid-Naïve Patients.



Patients with chronic pain on opioid therapy used more analgesics (mean, SD) during the first 72 hours postoperatively vs opioid-naïve patients without chronic pain.

outcomes are associated with preoperative opioid use, including surgical site infection, prolonged hospital stay, higher readmission rates, and higher health care costs. Surprisingly, relatively unexplored are the effects of preoperative opioid use on postoperative pain outcomes. Although multiple examinations have explored the hyperalgesic effects of opioid administered intraoperatively, description of the potential effects of preoperative OIH on postoperative pain experiences is limited. Similar to the findings of Hina and colleagues,[15] in this small sample of patients undergoing dental surgery, patients with chronic pain on chronic opioid therapy reported more severe pain and consumed more nonopioid analgesics in the first 72 hours following surgery than matched controls without chronic pain and not using opioids. This work further supports that preoperative OIH persists through the surgical experience to result in a more severe postoperative experience.

Limitations

In this observational pilot, the sample size was small and self-selected; thus, generalizability to the broader population of patients with chronic pain on opioid therapy is limited. Further, the data are cross-sectional, thus a causal role for opioids on pain responses (although demonstrated in the work of others[14,19]) cannot be ascribed. In cases where group differences were seemingly apparent but failed to reach statistical significance, this is likely attributed to a lack of power related to the small sample size. If adequately powered, these findings may have, in fact, demonstrated statistically significant group differences. All postoperative data were based upon self-report; although this is the research standard for many analgesic trials, there may be error related to recall or misrepresentation. Finally, and as inferred by Johansen and colleagues,[20] all patients taking opioids concurrently had chronic pain, bringing with it neuroplastic changes to the central and nociceptive nervous system that may be reflected in preoperative and postoperative pain responses.

CONCLUSION

The results of this small proof-of-concept study contribute to the accumulating literature examining the consequences of preoperative opioid use in the context of chronic pain on surgical outcomes. These findings suggest that patients with chronic pain and on opioid therapy arrive preoperatively with a degree of OIH that appears to carry over into increased postoperative pain severity and analgesic need. Pain management for the opioid-using patient with chronic pain may require more individualized oversight by the care provider. Understanding that preoperative opioid use worsens the postoperative pain experience supports

provision of adequate analgesics for these patients, particularly in the current environment of more restrictive opioid use.

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