Research Paper

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Conditioned open-label placebo for opioid reduction after spine surgery: a randomized controlled trial

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Abstract

Placebo effects have traditionally involved concealment or deception. However, recent evidence suggests that placebo effects can also be elicited when prescribed transparently as "open-label placebos" (OLPs), and that the pairing of an unconditioned stimulus (eg, opioid analgesic) with a conditioned stimulus (eg, placebo pill) can lead to the conditioned stimulus *alone* reducing pain. In this randomized control trial, we investigated whether combining conditioning with an OLP (COLP) in the immediate postoperative period could reduce daily opioid use and postsurgical pain among patients recovering from spine surgery. Patients were randomized to COLP or treatment as usual, with both groups receiving unrestricted access to a typical opioid-based postoperative analgesic regimen. The generalized estimating equations method was used to assess the treatment effect of COLP on daily opioid consumption and pain during postoperative period from postoperative day (POD) 1 to POD 17. Patients in the COLP group consumed approximately 30% less daily morphine milligram equivalents compared with patients in the treatment as usual group during POD 1 to 17 (−14.5 daily morphine milligram equivalents; 95% CI: [−26.8, −2.2]). Daily worst pain scores were also lower in the COLP group (−1.0 point on the 10-point scale; 95% CI: [−2.0, −0.1]), although a significant difference was not detected in average daily pain between the groups (−0.8 point; 95% CI: [−1.7, 0.2]). These findings suggest that COLP may serve as a potential adjuvant analgesic therapy to decrease opioid consumption in the early postoperative period, without increasing pain.

Keywords: Placebo, Open-label, Conditioning, Postsurgical pain, Opioid

1. Introduction

Placebo treatments evoke clinically meaningful benefits beyond spontaneous remission and regression to the mean.[52] Investigations of placebo effects in both randomized controlled trials (RCTs) and experimental pain settings are abundant,[30,80,89,90] with placebo treatments generally eliciting moderate effect sizes.[50,59,75,96] For example, in one meta-analysis (215 RCTs, 41,392 patients) placebo responses were equivalent to 75% the effect of diverse analgesic interventions.[101] Traditionally, studying placebo effects has involved concealment (in RCTs) or deception (in laboratory experiments), which are impractical and ethically problematic for clinical practice. However, open-label placebos (OLPs), which meet the ethical standards of informed consent and transparency,[13] have recently demonstrated efficacy in treating a wide variety of symptoms[22] and conditions, including cancer-related fatigue,[38] irritable bowel syndrome,[49] migraines,[47] chronic knee osteoarthritis,[64] and allergic rhinitis.[78] Open-label placebo treatments have also reduced chronic low back pain and disability in 2 RCTs using pills[20,58] and one using honest sham injections.[4]

Another potentially transparent use of placebos is conditioning of placebos, which use the stimulus substitution principle of classical conditioning. The unconditioned stimulus (US: drug) is repeatedly paired with a conditioned stimulus (CS: placebo), resulting in a new learned response where the CS *alone* can elicit similar responses. Conditioning has a long history in animal research[33,36,68,100] and has been applied to laboratory-based human placebo research,[79] demonstrating reduced need for analgesia when opioids (US) are paired with placebos (CS).[3] Conditioned placebos have shown clinical benefits while allowing a reduction of medication, without increase in morbidity or symptoms, including in psoriasis,[2] insomnia,[69] allergic rhinitis,[31] attention deficit or hyperactivity disorder,[77] and immune suppression in renal transplant patients.[56] To date, however, there has been less research using conditioning as a "dose-extension" or "partial reinforcement" strategy for pain management.[23,50,62]

Although traditional deceptive placebos have shown efficacy in reducing postsurgical pain,[9] the effects of transparent applications of placebos (eg, OLP and conditioned placebos) have not previously been examined in postsurgical pain management. Surgery is a potent noxious stimulus, posing an important challenge to pain management.[54] In particular, spine surgery is

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associated with significant postoperative pain,[55] traditionally, involving management with opioid analgesics, as well as frequent dosing and self-titration of analgesics. However, extensive perioperative and postoperative opioid use has come under increased scrutiny during the opioid epidemic because of its association with an increased risk of persistent use[46] and new opioid dependence,[16] highlighting the need for adjuvant analgesic therapies to facilitate opioid dose reduction and more rapid postoperative tapering. The frequent dosing of opioid analgesics early after spine surgery provides an ideal opportunity to pair opioids with placebos, thus adding the benefit of a transparent conditioning paradigm to OLP, which we called conditioned OLP (COLP).

Open-label placebo, although showing promise for chronic symptoms in patients with low back pain, has not previously been investigated for management of acute moderate-to-severe pain, and in the context of postsurgical pain management. Our aim was to determine whether COLP would reduce opioid consumption and pain after spine surgery. We hypothesized that patients receiving COLP would exhibit lower opioid consumption and a reduction in pain postoperatively. Given the substantial heterogeneity in the magnitude of placebo responses,[72,84,91] another exploratory aim was to examine characteristics associated with greater COLP efficacy. We hypothesized that COLP benefits would vary substantially across patients, potentially interacting with known biopsychosocial modulators of pain.

2. Methods

2.1. Subject recruitment and enrollment

This prospective RCT was approved by the Partners Institutional Review Board and was registered on ClinicalTrials.gov under the study name "Evaluation of Open-Label Conditioned Placebo Analgesia for Postoperative Opioid Reduction Following Spinal Fusion (COLP)" (NCT04574388). Patients scheduled for surgery for degenerative conditions of the spine with a single surgeon were recruited from Brigham and Women's Hospital preoperative clinic in Boston, MA, between November 2018 and February 2020. Patients aged 18 to 75 years, who were without cognitive impairment or English improficiency that would impair completion of study questionnaires or comprehension of procedures, were eligible for participation.

Patients were approached at their preoperative visit to receive information regarding the study, and if interested in participating, provided informed consent. Key study points discussed with patients during recruitment included (1) definition and explanation of placebo effects, (2) evidence highlighting placebos' ability to reduce pain in double-blind RCTs, (3) explanation of "open-label" concept (eg, patient knowingly receiving a placebo), (4) introduction of several previous successful OLP studies, noting the absence of any evidence for postsurgical patients specifically, (5) explanation of conditioning paradigm (pairing the OLP pills with their other analgesics), (6) suggestion that COLP treatment may or may not work to reduce their pain or opioid consumption, (7) emphasis that placebo effectiveness was not contingent on belief, and (8) repeated assurances that taking a COLP would in no way restrict their access to other analgesics, including opioids, after surgery (Appendix A, available at http://links.lww.com/PAIN/B257). Patients underwent baseline quantitative sensory testing (QST) in person during their preoperative visit, and demographic, baseline pain, and psychosocial questionnaires were completed through an email link to a secure database (REDCap) preoperatively.

2.2. Assessment of baseline patient pain characteristics

Baseline pain before surgery was assessed using the Brief Pain Inventory (BPI). The BPI contains questions inquiring about current pain, and worst, least, and self-reported average pain within the past 24 hours. The BPI mean is an average of these 4 pain scores. The BPI also contains 7 questions evaluating the impact of pain on general functioning, which are summed to give a functional impact score and then averaged together as BPI interference.[88]

2.3. Psychosocial assessments

Psychosocial assessment tools were selected based on strong psychometric properties and brevity. The Pain Catastrophizing Scale was used to measure pain-associated with catastrophic thinking (range: 0-52).[85] Depressive symptoms (range: 9-40), anxiety (range: 7-35), and sleep disturbance (range: 4-20) were assessed using the Patient Reported Outcome Measurement Information System Short Form (PROMIS-SF).[21] The 6 items related to somatization from the Brief Symptom Index 18-Somatization Scale were used to measure somatization (range: 5-30).[25] The fibromyalgianess scale (range 0-31), adapted from the clinical criteria for fibromyalgia,[15,97] was used to characterize widespread pain (indication of number of body areas with pain) and related symptom severity of generalized symptoms (fatigue, etc). The Positive Affect Negative Affect Scale was used to assess positive (range: 0-40) and negative (range: 0-40) affect,[94] and preferences for coping strategies were measured using the Coping Strategies Questionnaire (range: 0-84).[45,73] The Screener and Opioid Assessment for Patients with Pain (SOAPP-R-8) (range: 0-32) was used to evaluate the risk for developing problems with long-term opioid use.[17]

2.4. Bedside quantitative sensory testing

After providing informed consent at their preoperative visit, patients underwent brief bedside QST in nonsurgical areas (hands, extensor forearm, and trapezius).

2.4.1. Temporal summation of pain

Using methods from our previous studies[81,82] similar to those described by Rolke et al.,[76] mechanical pinprick pain was assessed using standardized weighted pinprick applicators. First, a single stimulation of the lowest force (128 mN) pinprick was applied to the dorsal aspect of the index finger between the first and second interphalangeal joints of the left hand while resting the palm facing downward on a flat surface. The subject rated the pain intensity from the mechanical stimulus on a scale of 0 to 10. If pain was rated as 0 to 1, the next highest force probe was tested as a single application. One of 3 designated force (128, 256, and 512 mN) probes was selected: specifically, the lowest force probe to result in a mildly painful sensation (pain score 1-3) with a single application. After a break of at least 10 seconds, a train of 10 stimuli was applied at the same location at a rate of 1 stimulation/second. The subject rated their pain on a scale of 0 to 10 after the first, fifth, and 10th stimuli. This was then repeated on the right index finger, followed by the third finger of each hand, alternating sides of testing. Temporal summation of pain (TSP) was calculated as Δ (10th-first stimulus) pain rating. This was calculated for each of the 4 finger sites and then averaged.

2.4.2. Pressure pain threshold and tolerance

As in our previous studies,[81,82] pressure pain threshold and tolerance were measured using a digital pressure algometer (Wagner FDX, Greenwich, CT) with a flat round transducer, probe area 0.785 cm^2. Testing was performed bilaterally on the dorsal aspect of the proximal forearm approximately 3 to 4 cm distal to the elbow crease (extremity site) and over the trapezius muscle at the upper back approximately 2 to 3 cm above the scapular spine, midway between C7 prominence and humeral head (truncal site). To determine pressure pain threshold, pressure was increased at a steady rate of approximately 1 lb/s (0.45 kg/second), with the subject indicating when this pressure first became painful. To determine tolerance, the pressure was further increased, with the subject indicating when the pain from the stimulus was no longer tolerable. Testing was performed bilaterally, alternating between sides and extremity or truncal sites.

2.5. Randomization and blinding

Randomization was performed using the randomization function in REDCap. Once initial QST and baseline questionnaires were completed, patients were automatically randomized to either the COLP or treatment as usual (TAU) group (**Fig. 1**). Given the transparency inherent in the treatment being tested, neither patients nor research staff were blind to grouping, and group assignment was revealed to patients on the morning of their surgery. Anesthesiologists and surgical teams were not aware of the patient's group assignment, and any intraoperative medications were administered at the discretion of the anesthesia team. Postoperative analgesic medications were prescribed by the surgical team per typical clinical practice, consisting of oxycodone (5-10 mg) or hydromorphone (1-2 mg), primarily through oral route every 4 to 6 hours as needed, as well as acetaminophen 500 to 1000 mg every 6 to 8 hours.

2.6. Conditioned open-label placebo group and treatment as usual group

After surgery, once patients were out of the recovery phase and admitted as inpatients on postoperative day 0 (POD 0), study staff visited to assess pain, further explain study procedures and answer any potential questions. It was re-emphasized that being in the study would not limit their access to opioid or other analgesics, which followed the standard as needed dosing schedule prescribed to all patients undergoing this procedure under this single surgical provider. Nursing staff was provided information regarding the research study and was instructed that patient participation should not impact their administration of other medications. Patients in the COLP group were provided with placebo pills, which were small white capsules containing microcrystalline cellulose, in a large, easy open prescription bottle prepared by the BWH Investigational Pharmacy. Patients were instructed to self-administer one COLP pill with all analgesics (whether administered intravenously or orally) and record the pairing in a bedside diary. Conditioning with an open-label placebo initiation took place on either POD 0 or early POD 1, depending on the acute postoperative state and time of transfer to inpatient unit. Beginning on POD 2, participants were further instructed to take 3 scheduled placebo pills every day, at 3 convenient times of their choosing, in addition to pairing placebos with all analgesics. In an attempt to continually link the US (analgesics) to the CS (placebos) and prevent habituation, patients in the COLP group were instructed to continue taking *both* paired and scheduled OLP pills until their follow-up appointment.

A concerted effort was made to ensure that an equivalent quantity and quality of attention and time was paid to both the TAU and COLP patients. Patients in both groups were visited twice daily (10-15 minutes visits) by both physician and non-physician study staff during their inpatient hospital stay, and patients in both groups were contacted once daily through phone, text, or email (whatever their preferred contact method) after discharge to collect recorded diary information from the day before. In both groups, topics of conversation with patients during in hospital visits and follow-up visits included pain, use of different analgesics, the recording of pain and analgesic consumption in the daily diary, sleep quality, and recovery, including drain output, physical therapy, plans for discharge, family visits, and overall experience. Specific discussion topics in the COLP group included guidance on taking placebos and re-explanation of the COLP rationale: (1) placebos may induce a physiological response in the brain to decrease pain even without deception (OLP concept), (2) pairing placebos with other pain-reducing medications may strengthen this effect (conditioning concept), and (3) it might not be necessary to believe in the effect for it to work (automatic response concept) (Appendix A, available at http://links.lww.com/PAIN/B257).

Study staff reinforced instructions about study procedures, including recording pain and analgesic data in the study diary towards the end of the inpatient stay. In this way, before discharge, all patients in both groups were trained to use the study diary to record daily mini-BPI data, including pain scores and analgesic use (COLP and TAU groups), and placebo pills taken (COLP group alone) after hospital discharge. Patients were instructed to complete diary entries until postsurgical follow-up appointment or POD 17, and study staff contacted all patients daily through phone, text, or secure email to collect mini-BPI and analgesic utilization data.

2.7. Postsurgical daily pain assessment

A brief version of the BPI (mini-BPI) was used to assess daily pain severity during the postoperative course of the study. The mini-BPI included questions about current pain, worst pain, self-averaged pain, and least pain during the preceding 24 hours, which was collected verbally from participants during PM visits while inpatient. After hospital discharge, the mini-BPI was filled out by the patient in their daily diary and was conveyed to study staff during a daily text, phone call, or secure email link.

2.8. Analgesic consumption

Patients took opioids and other analgesics on an as needed basis. Patients in both groups recorded daily opioid analgesic consumption and pain scores, beginning while inpatient, at which time this was cross-referenced with the medication administration record, and at home in a daily diary until their follow-up appointment. Patients reported the number, type, and dose of opioid analgesics consumed each day. All opioids were converted to daily morphine milligram equivalents (MMEs) (Appendix B, available at http://links.lww.com/PAIN/B257).

2.9. Follow-up appointment

Study staff met all patients to repeat QST at the surgical follow-up appointment, which occurred at a median of 20 days after surgery

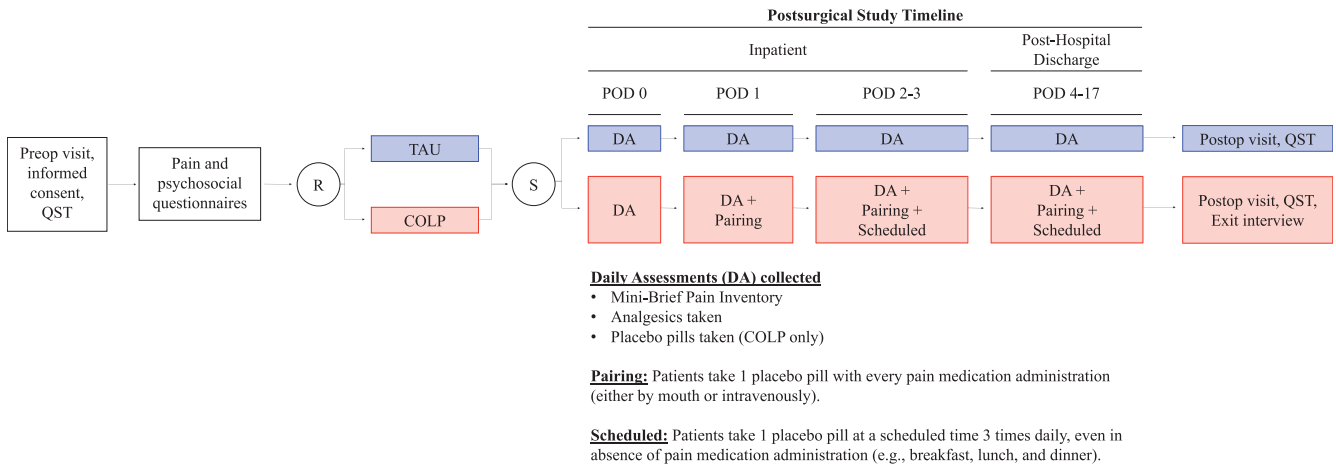

Figure 1. Patients consenting to participation completed baseline questionnaires and were randomized to either the treatment as usual (TAU) or conditioned open-label placebo (COLP) group. Study staff visited patients in both groups twice daily while inpatient and contacted once daily after hospital discharge to collect daily reports on their analgesics taken and pain scores. Patients in the COLP group also reported how many placebo pills were taken each day. On POD 1, COLP patients began the "pairing" regime by taking one open-label placebo pill each time they took an opioid analgesic. On POD 2, COLP patients were instructed to begin taking 3 daily scheduled placebo pills in addition to the placebo pills paired with each opioid analgesic ("pairing + scheduled"). All patients were asked to continue recording daily analgesic consumption and pain scores, with COLP patients also continuing the "pairing + scheduled" regime, until their postoperative follow-up appointment (approximately 17 days after surgery). DA, daily assessments; POD, postoperative day; QST, quantitative sensory testing; R, randomization; S, surgery.

(range: 11-33 days). At this time, patients in the COLP group, after finishing psychophysical testing, also underwent a semistructured qualitative interview regarding their experience on taking a COLP. The results of these qualitative assessments will be reported in a separate manuscript.

2.10. Statistical analyses

Continuous variables are reported as means with SDs, and categorical variables are reported as counts and percentages. All opioid analgesics were converted to MMEs (Appendix B, available at http://links.lww.com/PAIN/B257). Differences in postoperative opioid consumption and pain scores between COLP and TAU treatment groups were assessed using the general estimating equation (GEE) method with an autoregressive correlation structure, which takes into account the correlation between repeated measurements on the same patient and can accommodate missing data across timepoints (POD 1-17), if this missingness is random. Effect sizes are reported as differences in means through the GEE model beta coefficients (B) and confidence intervals (CIs).

To address the second exploratory aim of identifying variation in COLP effectiveness among individuals, we assessed for interactions between COLP and baseline patient characteristics known to significantly impact pain and opioid consumption. Potential moderators were each tested in separate regression models, with independent variables being the treatment group (COLP vs TAU), the potential moderator, and an interaction term. For continuous moderators, the groups in the interaction terms were defined by values corresponding to the 16th percentile, the median, and the 84th percentile of the distribution of that variable.[35]

Based on postoperative opioid consumption from a previous cohort of orthopedic postsurgical patients,[1] we estimated a mean ± SD postoperative cumulative MME dose over the study period of 200 ± 70 in the TAU group. Using this estimated mean and SD, an a priori power analysis determined that a sample size of 18 patients per group would provide 80% power to detect a 30% difference in opioid use at a two-sided alpha level of 0.05. Statistical analyses were conducted using R version 3.6.2. and IBM- SPSS v26, with the PROCESS macro[35] used to assess moderation between treatment groups and outcomes.

3. Results

3.1. Study participants

Of the 144 patients assessed for eligibility, 51 provided informed consent, underwent psychophysical testing, completed electronic baseline questionnaires, and were randomized to receive COLP (n = 26) or TAU (n = 25) before surgery (**Fig. 2**). Before beginning treatment, 2 participants in the COLP group withdrew consent because of anxiety about surgery and recovery, and one participant became ineligible because of prolonged admission to the intensive care unit. After treatment initiation, 4 patients in the COLP group and 3 in the TAU group discontinued study participation in the early postoperative period because of delirium or being overwhelmed by demands of recovery. Ultimately, the final analysis included 19 COLP and 22 TAU patients who provided postoperative data regarding opioid consumption and pain. Assessment of missing pain and opioid data from participants revealed an average of 8.3% missing data on any given assessment day, with data missing from 0 to 6 of 41 participants on any given day, with consistency of missingness over time. There were relatively similar amounts of missingness between treatment groups (COLP: 7.1%; TAU: 9.3%), suggesting a random pattern of missingness that would allow for use of the GEE analysis.

3.2. Baseline patient characteristics

Patient demographic, psychosocial, and psychophysical baseline characteristics were similar between groups (**Table 1**). Importantly, both baseline pain severity (COLP: 5.3 ± 2.6; TAU:

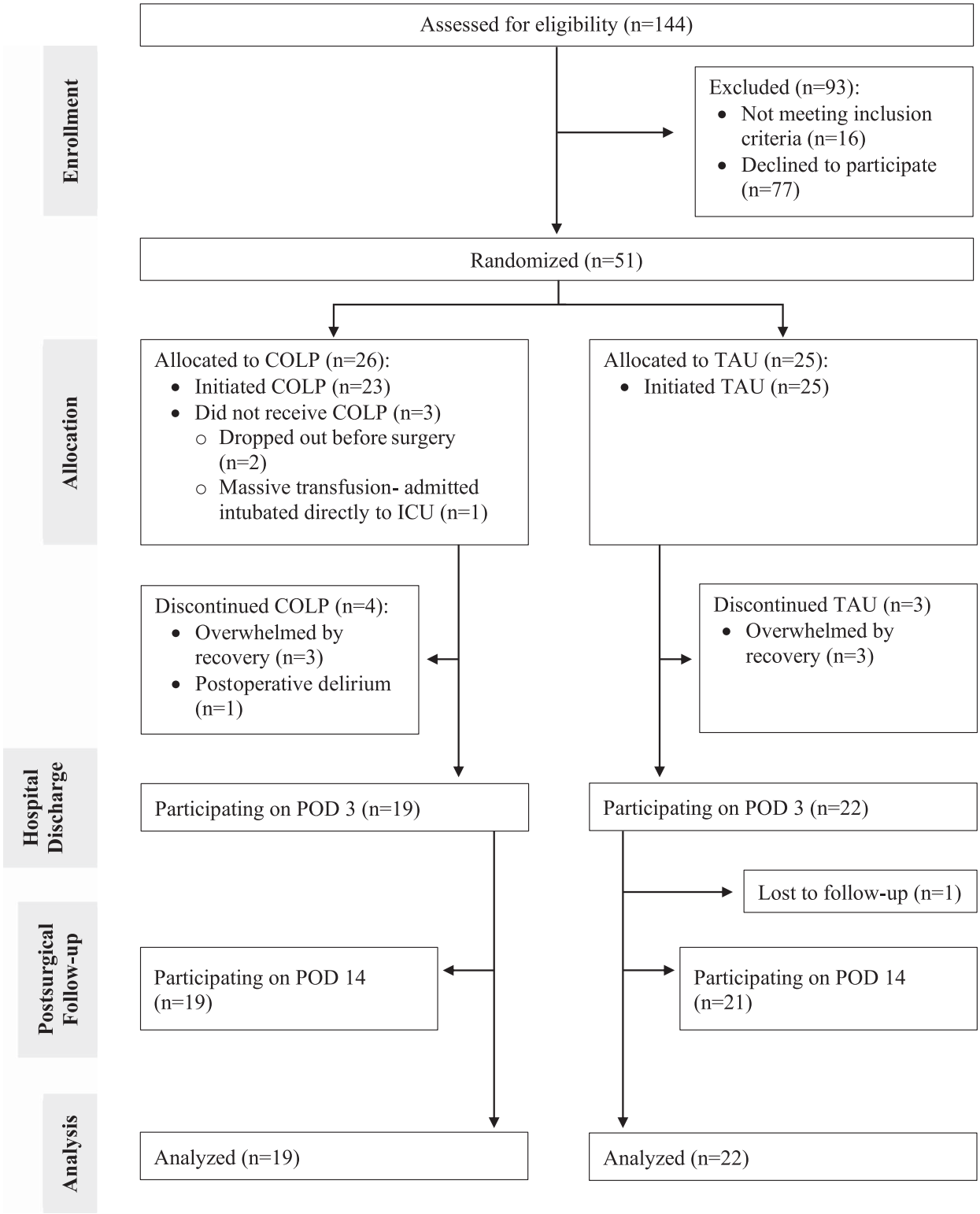

Figure 2. CONSORT study flow diagram. Patients were approached and recruited from the anesthesia preoperative clinic. Of the 144 patients assessed for eligibility, 51 patients were enrolled and randomized to either the TAU (n = 25) or COLP (n = 26) group. Before beginning COLP treatment, 2 participants withdrew because of anxiety about the upcoming surgery, and one participant became ineligible because of postoperative complications necessitating intensive care unit admission postoperatively. After beginning allocated treatment, 4 patients in the COLP group and 3 in the TAU group withdrew. There were 41 patients included in the final analysis (TAU: n = 22 and COLP: n = 19). COLP, conditioned open-label placebo; POD, postoperative day; TAU, treatment as usual.

5.4 ±1.4) and preoperative opioid use (COLP:11%; TAU:18%) were similar between groups, with all holding only minimal prescriptions for as needed oxycodone of the 5 mg denomination.

3.3. Surgical and anesthetic treatment

Patient surgical variables are reported in **Table 2**. Pain was the most frequently reported symptom present at the time of surgery

Table 1

Patient baseline characteristics for the TAU and COLP groups.

Baseline characteristics	TAU (n = 22)	COLP (n = 19)
Demographics		
Age	61.2 ± 13.0	59.1 ± 13.1
Female	13 (59%)	7 (37%)
Non-Hispanic White	22 (100%)	18 (95%)
BMI	31.6 ± 7.8	31.5 ± 8.0
Education level		
High school	1 (5%)	1 (5%)
Technical school	0 (0%)	1 (5%)
Some college	4 (18%)	5 (26%)
Associate degree	3 (14%)	2 (11%)
Bachelor's degree	9 (41%)	3 (16%)
Master's degree	3 (14%)	6 (32%)
Doctoral degree	2 (9%)	1 (5%)
Psychosocial measures		
Catastrophizing	15.1 ± 10.0	16.4 ± 14.0
Depression	14.2 ± 6.3	13.3 ± 6.1
Sleep disturbance	27.9 ± 7.3	26.1 ± 7.7
Anxiety	14.9 ± 6.3	16.3 ± 6.1
Somatization	11.1 ± 3.6	11.2 ± 3.4
Positive affect	31.1 ± 7.8	31.2 ± 7.8
Negative affect	18.5 ± 5.6	19.4 ± 7.2
Pain and opioid use		
BPI mean	5.4 ± 1.4	5.3 ± 2.6
BPI interference	5.6 ± 2.0	4.6 ± 2.5
Fibromyalgianess	11.8 ± 5.0	9.4 ± 4.3
Opioid misuse risk (SOAPP)	3.5 ± 2.4	2.9 ± 2.3
Taking opioid medications	4 (18%)	2 (11%)
Quantitative sensory testing (QST)		
Temporal summation of pain (TSP)	2.9 ± 1.6	2.2 ± 1.8
Forearm threshold	8.0 ± 3.0	9.23 ± 4.7
Forearm tolerance	12.7 ± 4.7	13.5 ± 5.6
Trapezius threshold	10.9 ± 4.6	12.9 ± 4.4
Trapezius tolerance	15.4 ± 5.0	16.3 ± 4.6

Data are given in either mean ± SD or n(percent). Treatment groups were balanced across all variables.
BMI, body mass index; BPI, Brief Pain Inventory; COLP, conditioned open-label placebo; SOAPP, Screener and Opioid Assessment for Patients with Pain; TAU, treatment as usual

Table 2

Patient surgical variables for the TAU and COLP groups.

Surgical variables	TAU (n= 22)	COLP (n= 19)
No. of levels	3.1 ± 1.3	3.5 ± 1.4
Duration of surgery (min)	161 ± 49	168 ± 53
Blood loss during surgery (mL)	710 ± 632	622 ± 629
Re-operation	4 (19%)	4 (21%)
Spinal segments involved		
Cervical	5 (23%)	6 (32%)
Thoracic	1 (5%)	1 (5%)
Lumbar	17 (77%)	13 (68%)
Sacral	1 (5%)	3 (16%)
Surgical aspects involved		
Discectomy	3 (14%)	5 (26%)
Laminectomy	20 (91%)	17 (90%)
Fusion	21 (96%)	16 (84%)
Other	2 (9%)	3 (16%)
Indication(s) for surgery		
Spinal stenosis	19 (86%)	14 (74%)
Spondylolisthesis	13 (59%)	10 (53%)
Herniated disk	1 (5%)	2 (11%)
Fracture	3 (14%)	1 (5%)
Other	9 (41%)	9 (47%)
Symptoms present at time of surgery		
Pain	21 (96%)	18 (95%)
Weakness	3 (14%)	6 (32%)
Numbness	3 (14%)	5 (26%)
Other	3 (14%)	1 (5%)

Data are given in either mean ± SD or n(percent). Treatment groups were balanced across all surgical variables.
COLP, conditioned open-label placebo; TAU, treatment as usual.

(COLP = 95%; TAU = 96%), with additional symptoms including weakness (COLP = 32%; TAU = 14%), numbness (COLP = 26%; TAU = 14%), and other symptoms (COLP = 5%; TAU = 14%). Eight patients had previous spine surgery (COLP = 21%; TAU = 19%). Surgical procedures involved cervical, thoracic, lumbar, and/or sacral spine, with nearly all involving spinal fusion (COLP = 84%; TAU = 96%). All patients received general anesthesia, including both volatile and IV-based anesthetics for maintenance, with 46% of cases involving intraoperative remifentanil and sufentanil infusions. The average amount of opioids (MME/hr) consumed on the evening of surgery, both while admitted to the post-anesthesia care unit (COLP: 13.3 ± 9.2; TAU: 13.6 ± 11.0) and once transferred to the inpatient floor (COLP: 3.6 ± 2.31; TAU: 4.1 ± 2.7), was similar between groups.

3.4. Postoperative opioid consumption

There was a significant difference in overall opioid consumption between groups on POD 1 to 17, with lower average daily MMEs consumed by patients receiving COLP (B = −15.90, 95% CI: −28.69, −3.10; Wald χ^2: 5.93, P = 0.015) (**Fig. 3A**). This represents an overall average 30% reduction in opioid use in the COLP group, although substantial intragroup variability was also observed (**Figs. 3B and C**). The percentage of patients still taking some opioids on POD 7 was 94% for the TAU group and 68% for the COLP group, and on POD 14 was 75% for the TAU group and 52.6% for the COLP group.

3.5. Postoperative pain

Postoperative daily worst pain and average pain scores are shown in **Figure 4**. The GEE analysis revealed a significant between-group difference in overall worst pain for POD 1 to 17, with significantly lower values reported among patients receiving COLP (B=−1.03, 95% CI: −1.99, −0.08, Wald χ^2: 4.50, P = 0.034). There was no significant difference in average pain (BPI mean) between groups (B = −0.70, 95% CI: −1.59, 0.188; Wald χ^2: 2.39, P = 0.122).

3.6. Exploratory analysis of differential response to conditioning with an open-label placebo among patients

We found a significant moderating effect of baseline pain on treatment, suggesting that the COLP was more effective at lowering postoperative worst daily pain in patients who reported greater baseline pain before surgery (baseline pain 3/10: −0.20 [−0.78, 0.38] vs baseline pain 5.75/10: −1.33 [−1.69, −0.97] vs baseline pain 7.25/10: −1.94 [−2.46, −1.43]) (**Fig. 5A**, Appendix C, available at http://links.lww.com/PAIN/B257). We also observed a significant interaction between sex and treatment group, with the effects of COLP on postoperative opioid consumption being more pronounced in females compared with males (males: −4.89 [−11.47, 1.70] vs females: −26.0 [−33.22, −18.73]) (**Fig.**

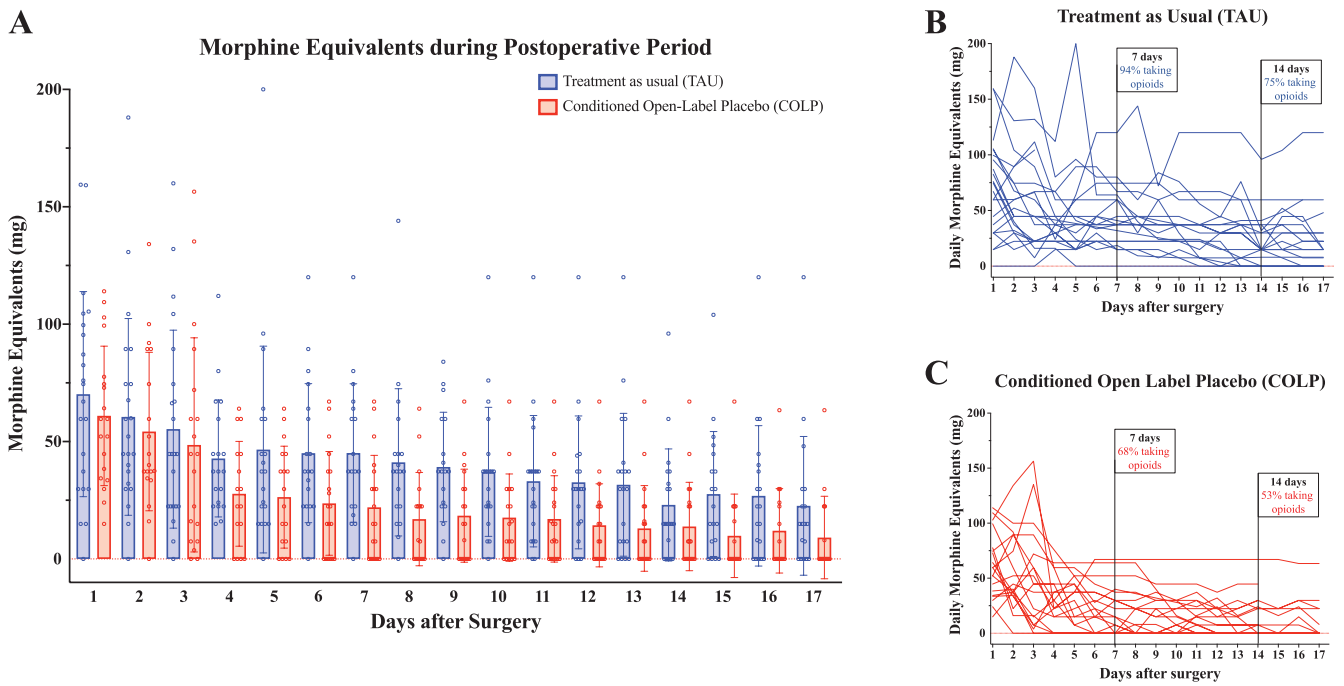

Figure 3. Daily opioid analgesic consumption in the postoperative period. Daily opioid consumption during the postoperative period was calculated by converting all opioids to morphine milligram equivalents (MMEs) for both inpatient (approximately POD 1-3) and outpatient (approximately POD 4-17) periods. (A) Daily opioid consumption was compared between groups over time. Overall, patients randomized to COLP consumed significantly less opioids daily from POD 1 to POD 17 compared with patients in the TAU group (Wald χ^2: 5.93, $P = 0.015$). (B) Timelines of daily opioid consumption for individual patients in the TAU group (EMM: 43.1, 95% CI: [33.4, 52.9]). On POD 7, 94% of patients in the TAU group were taking opioids, with 75% of TAU patients still taking opioids on POD 14. (C) Timelines of daily opioid consumption for individual patients in the COLP group (EMM: 28.6, 95% CI: [21.1, 36.2]). On POD 7, 68% of patients in the COLP group were taking opioids, with 53% of COLP patients still taking opioids on POD 14; CI, confidence interval; COLP, conditioned open-label placebo; EMM, Estimated Marginal Mean; POD, postoperative day; TAU, treatment as usual.

5B, Appendix D, available at http://links.lww.com/PAIN/B257). Similarly, age moderated the treatment effect on both opioid use and worst pain, with younger patients receiving COLP having lower opioid utilization (age 48: −28.64 [−35.24, −22.04] vs age 63: −13.31 [−18.25, −8.38] vs age 72: −4.12 [−10.67, 2.43]) and lower worst pain (age 47: −1.93 [−2.43, −1.43] vs age 63: −0.96 [−1.33, −0.59] vs age 72: −0.41 [−0.90, 0.08]) than patients receiving TAU (**Fig. 5C**, Appendix D and 5D, Appendix C, available at http://links.lww.com/PAIN/B257). Baseline TSP, which tests pain amplification after a repeated stimulus, also moderated COLP efficacy, such that between-group differences in worst pain were more pronounced among patients with higher

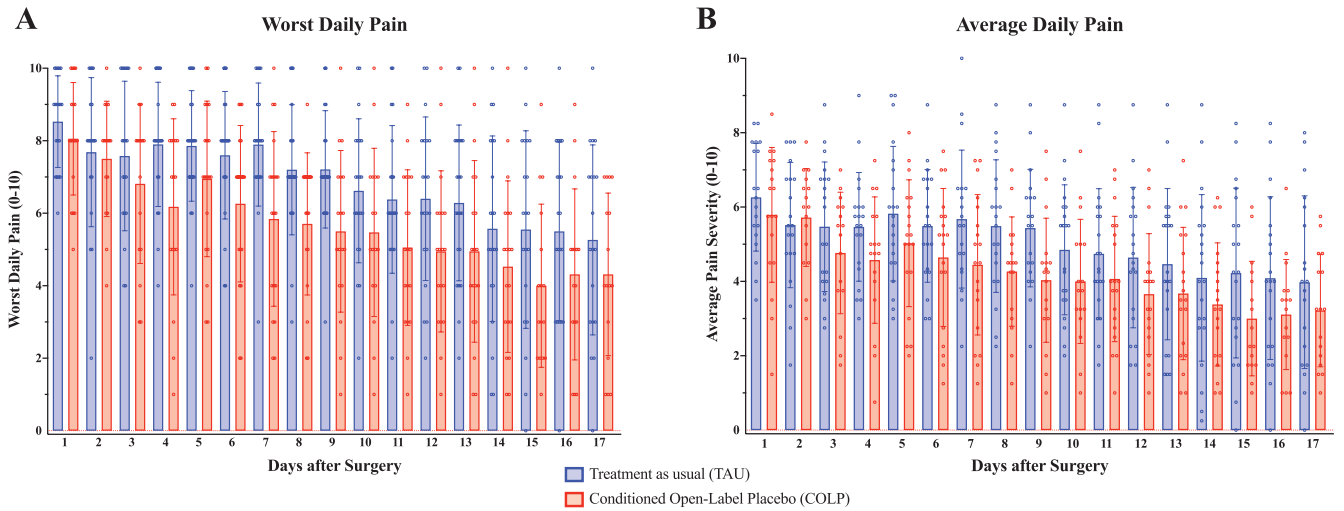

Figure 4. Daily pain scores in the postoperative period. Patients provided daily reports of their worst pain and average pain experienced in the previous 24 hours. (A) Patients in the COLP group reported significantly lower worst daily pain scores in the postoperative period compared with patients in the TAU group (COLP EMM: 5.9, 95% CI: [5.2, 6.6] vs TAU EMM: 6.9, 95% CI: [6.3, 7.6]; Wald χ^2: 4.50, $P = 0.034$). (B) Patients' average daily pain (BPI mean) experienced in the previous 24 hours was not significantly different between groups (COLP EMM: 4.4, 95% CI: [3.8, 5.0] vs TAU EMM: 5.1, 95% CI: [4.4, 5.7]; Wald χ^2: 2.39, $P = 0.122$). BPI, Brief Pain Inventory; CI, confidence interval; COLP, conditioned open-label placebo; EMM, Estimated Marginal Mean; POD, postoperative day; TAU, treatment as usual.

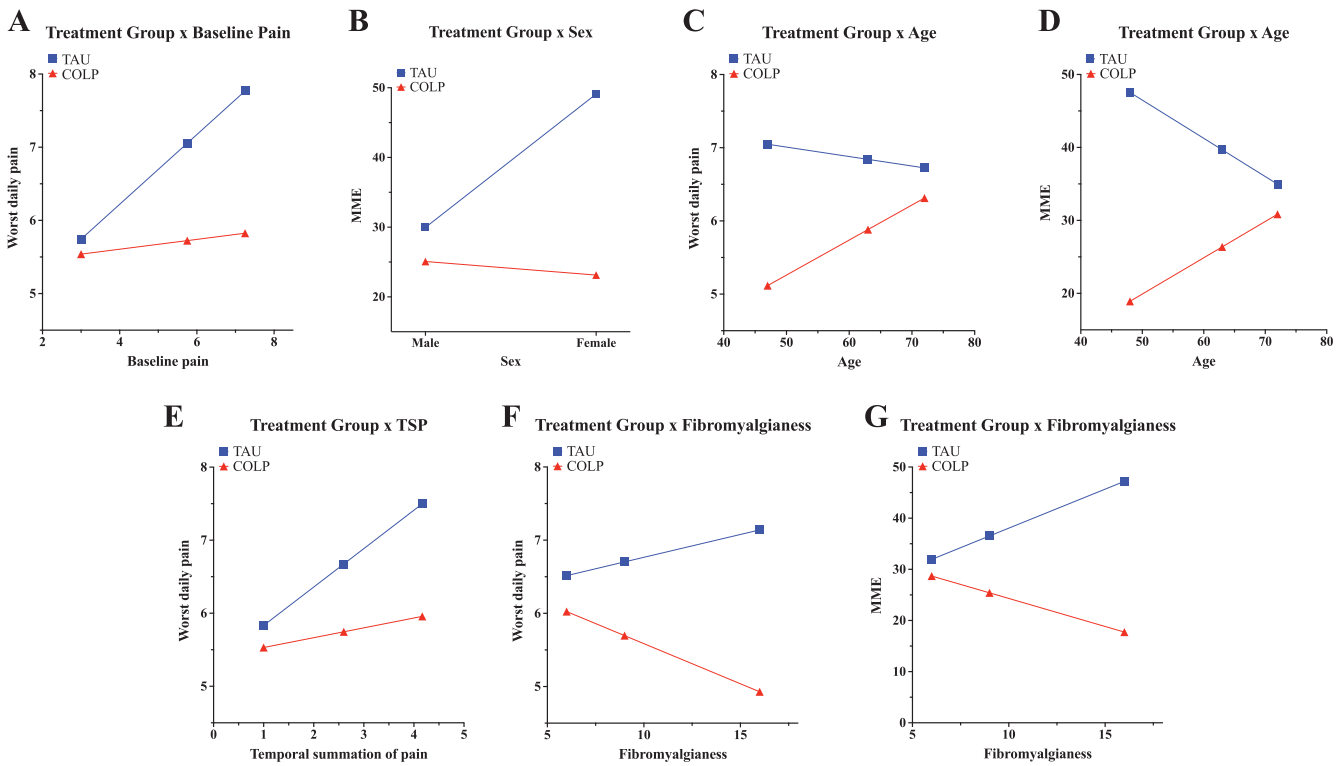

Figure 5. Exploratory analysis of treatment moderation by baseline patient characteristics. Interactions between treatment and baseline characteristics were assessed using the PROCESS macro in SPSS, which assesses for significant moderation of treatment effect by other variables. (A) Significant treatment x baseline pain interaction, suggesting a greater benefit of COLP among patients with higher reported baseline pain. (B) Significant treatment x sex interaction, with COLP associated with lower opioid consumption predominantly among female patients. (C and D) Significant treatment x age interaction, with COLP associated with decreased pain (C) and opioid consumption (D) among younger patients. (E) Significant treatment x TSP interaction, suggesting a greater benefit of COLP among patients higher baseline TSP. (F and G) Significant treatment x fibromyalgianess interaction, with COLP associated with lower pain (F) and daily opioid consumption (D) among patients with higher baseline fibromyalgianess scores. COLP, conditioned open-label placebo; POD, postoperative day; TAU, treatment as usual; TSP, temporal summation of pain.

TSP (TSP 1/10: −0.30 [−0.81, 0.20] vs TSP 2.6/10: −0.93 [−1.29, −0.57] vs TSP 4.17/10: −1.54 [−2.03, −1.05]) (**Fig. 5E**, Appendix C, available at http://links.lww.com/PAIN/B257). Interestingly, baseline fibromyalgianess (FM) moderated treatment effect on both postoperative opioid use (FM 6: −3.25 [−10.06, 3.57] vs FM 9: −11.11 [−16.33, −5.89] vs FM 16: −29.47 [−37.59, −21.35]) and worst pain (FM 6: −0.49 [−0.99, 0.01] vs FM 9: −1.01 [−1.39, −0.62] vs FM 16 −2.21 [−2.81, −1.61]), with COLP efficacy greatest among individuals with higher baseline fibromyalgianess scores (**Fig. 5F**, Appendix D and **Fig. 5G**, Appendix C, available at http://links.lww.com/PAIN/B257).

4. Discussion

This RCT examined the efficacy of COLP in reducing opioid use and postoperative pain among spinal fusion patients. Compared with TAU, COLP treatment was associated with approximately 30% less postoperative daily opioid consumption and lower worst daily pain scores during the postoperative period (POD 1-17). Before initiating treatment, early postoperative opioid consumption and pain scores were comparable between groups (**Figs. 3 and 4**, POD 1 and 2). Beginning around POD 3, we observed reduced consumption of daily opioids and worst pain scores in the COLP group, which seemed to be sustained through follow-up (**Fig. 3**). There also seemed to be an earlier discontinuation from opioids after surgery in the COLP group, which is of interest in light of the current opioid epidemic. Exploratory moderation analyses suggested greater COLP efficacy among younger patients, women, and patients with higher overall baseline pain severity, TSP, and fibromyalgianess scores. This study is, to the best of our knowledge, the first to examine the efficacy of COLP on postoperative opioid reduction and pain.

The use of placebos in an open fashion[48] obviates important ethical concerns about deception,[14] which can limit the clinical application of placebo treatment. Other studies have also demonstrated OLP benefits on a variety of symptoms,[20,49,53,61] including back pain,[20,58] and conditioned-placebo studies have shown successful conditioning of opioid effects in laboratory experiments,[3] exhibiting analgesic efficacy in the form of opioid dose reductions.[23,62] The current findings suggest that a combination of these techniques (COLP) may facilitate decreased opioid requirements and reduced postoperative pain intensity after spine surgery. Of note, large survey[13] and focus group[3] studies indicate that participants are amenable to accepting placebo treatments if they are transparently prescribed, with one study showing that 50% to 84% of patients reported willingness to take OLP under the recommendation of their physician.[40]

Open-label placebo seeks to directly reduce symptoms by introducing a radical paradoxical cognitive and embodied conundrum: physicians transparently prescribe "inert" pills, while suggesting that they might have, in fact, benefits.[8,48] Although OLP has sometimes produced medication dose reductions,[19,20] symptom amelioration has generally been the primary target. On the other hand, classical conditioning in clinical RCTs has primarily targeted dose reduction ("dose-extension") as the

primary outcome.[56] Other successful RCTs have included pairing placebos with corticosteroids in psoriasis,[2] zolpidem in insomnia,[69] and amphetamines in attention deficit or hyperactivity disorder.[77] Such dose-extension methods mitigate extinction processes because active drugs serving as the unconditioned stimuli are interspersed with conditioned stimuli (the placebos). This type of intermittent reinforcement was likely also in play in the current study because the protocol included both pairing and scheduled pills.

With the exception of a recent small feasibility study,[62] our RCT is the first that combines OLP and conditioning methodologies. An important limitation of bundling these approaches is that we cannot determine whether their effects were additive, synergistic, or otherwise. Our study is a "proof-of-concept," and future RCTs comparing COLP vs OLP alone vs conditioning alone would clarify this issue.

Although the underlying mechanisms of COLP have not been fully delineated, neurophysiological studies have produced compelling evidence that placebo effects involve an array of pain-relevant neurotransmitters (eg, endorphins, cannabinoids, and dopamine),[28,30] with placebo-evoked activation of specific, pain-relevant areas of the brain (eg, prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala).[90,102] Emergent research also suggests genetic signatures of likelihood to respond may exist.[34,93] The question of whether similar mechanisms may operate in COLP requires further research.

One potential mechanism often posited for placebo effects is classical conditioning,[5,28] which likely contributed to COLP's benefits here. Generally, however, the placebo literature suggests that expectation is the dominant factor,[57] with expectancies based on previous experiences and verbal suggestions strongly impacting placebo responses.[24,71,72] It is clear that when participants in laboratory experiments involving short-term pain are told the placebo will provide pain relief, they are generally more likely to experience placebo analgesia.[11,12,47] Furthermore, laboratory experiments have shown that conditioning is more powerful than verbal suggestion alone for inducing placebo effects.[5,6,18] Interestingly, the findings of our qualitative research, which will be fully described in a forthcoming paper, largely found that most patients expressed skepticism or uncertainty towards our intervention, making it more likely that any such expectations were nonconscious.[43,44] Another theoretical mechanism underpinning OLP is Bayesian brain/prediction coding. In most clinical situations, there is an inherent hope for and uncertainty of a clinical benefit, even in the paradoxical intervention of "nothing." This uncertainty and hope are thought to have the potential to automatically and nonconsciously shift previous neutrally encoded sensory biases of heightened pain to sensory biases of reduced pain.[50,67] Collectively, the extent to which COLP involves conditioning, expectations, Bayesian brain processes, and/or other processes is still to be determined.

Many conditioning methods have been used in human clinical situations. For instance, one study design using conditioning involved pairing an active drug (US) with a gustatory stimulus (CS) plus placebo pills,[56] using 50% active medication and 50% placebos randomly arranged in blister packs, to create an intermittent reinforcement paradigm.[69] In this study, our goals in finding the best conditioning approach were simplicity and transparency. Thus, the conditioning we used in this study was to simply pair the OLP pill with active analgesic medications taken by the patient. The US was the pain relief provided by these analgesic medications, and the CS was the OLP pill. Once conditioned, subsequent self-administration of this CS on its own (which started with the 3× daily scheduled dosing of OLP on postoperative day 2) might provoke the unconditioned response (ie, analgesia). As ongoing reinforcement, to avoid an extinction of this pairing, patients still also continued to pair OLP with any other analgesics, even after starting to take OLP on a schedule. Another important consideration was the temporal link of pharmacodynamic effect of the opioid compared with the timing of swallowing the OLP pill (which could be considered immediate). When opioids were administered IV, this delay would be insignificant. However, it was more typical for postoperative oxycodone to be administered by mouth, with a delay in full effect of 10 to 20 minutes, which provides a slower, prolonged analgesic profile and less of an euphoric effect. It is unknown what the critical closeness in time is for effective pairing, but it is possible that this relative temporal mismatch may have somewhat decreased the effectiveness of the pairing in this case.

In the era of personalized medicine, it is important to examine which patients benefit most from COLP,[10] considering that the magnitudes of placebo and conditioning responses are quite variable.[51,72,84,91] Variation in a placebo response has been attributed to patient expectation of clinical benefit,[24,84,91,92] extent of conditioning,[3,56] individual psychosocial characteristics,[24,29,63,83] and baseline variability and uncertainty.[7,27,41,87] Previous studies suggest that some patient characteristics are associated with greater placebo efficacy, including female sex[60,65,66,99] and younger age.[37,74,86,99] These results are consistent with our findings suggesting an interaction of COLP treatment with both sex and age.

In addition, patients scoring high on indices of central sensitization, including TSP and fibromyalgianess, benefitted most from COLP. Temporal summation of pain, a measure of central pain-facilitatory processes, predicts greater acute[1,39,82,95] and persistent postsurgical pain.[26,32,70,98] Previous findings have also suggested enhanced benefits of nonpharmacologic treatments, such as high-frequency TENS, in back pain in patients who showed the greatest QST-assessed pain sensitivity.[42] Similarly, higher fibromyalgianess scores,[97] which predict greater persistent postsurgical pain severity and opioid consumption,[15] were related to greater COLP benefit. One possible explanation for the observed moderation effects may be that the neural mechanisms by which COLP provides benefits overlap most closely with the neural mechanisms that are indirectly assessed by central sensitization indices, such as TSP and fibromyalgianess. Future studies are needed to specifically investigate whether "central sensitization" phenotypes may respond more favorably to COLP.

4.1. Limitations

Although this study found both a significant main effect of COLP on opioid consumption and worst pain, the sample size was relatively small, and definitive conclusions regarding the efficacy of COLP require a larger RCT. The observed moderating effects of age, sex, fibromyalgianess, and TSP on COLP treatment are exploratory, although these preliminary findings suggest the utility of careful preoperative patient phenotyping in future trials. In addition, participants were recruited at a tertiary referral hospital from a single surgeon and surgical type (spine surgery), potentially limiting the generalizability to other patients and settings. As with any RCT, a self-selection bias by participants willing to volunteer for a nonpharmacological clinical trial may have also been operative. Furthermore, as the trial centered around acute postoperative pain and opioid use, the findings may not be extrapolated to longer-term COLP effects or COLP effects on nonopioid analgesics. Finally, it is unknown to what extent OLP,

conditioning, or some interaction/combination was this intervention's active ingredient.

4.2. Conclusion

The findings suggest that this innovative treatment approach combining conditioning and open-label placebo has the potential to serve as an analgesic adjuvant, potentially reducing pain, lowering opioid requirements, and facilitating earlier opioid tapering in the postoperative period.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B257.

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