Study protocol: randomised controlled trial of conditioned open-label placebo (COLP) for perioperative pain management in patients with head and neck cancer

Danielle R Trakimas, Luana Colloca, Carole Fakhry, Marietta Tan, Zubair Khan, Peter S Vosler

ABSTRACT

Introduction Patients with head and neck cancer have a substantial risk of chronic opioid dependence following surgery due to pain and psychosocial consequences from both the disease process and its treatments. Conditioned open-label placebos (COLPs) have been effective for reducing the dose of active medication required for a clinical response across a wide range of medical conditions. We hypothesise that the addition of COLPs to standard multimodal analgesia will be associated with reduced baseline opioid consumption by 5 days after surgery in comparison to standard multimodal analgesia alone in patients with head and neck cancer.

Methods and analysis This randomised controlled trial will evaluate the use of COLP for adjunctive pain management in patients with head and neck cancer. Participants will be randomised with 1:1 allocation to either the treatment as usual or COLP group. All participants will receive standard multimodal analgesia, including opioids. The COLP group will additionally receive conditioning (ie, exposure to a clove oil scent) paired with active and placebo opioids for 5 days. Participants will complete surveys on pain, opioid consumption and depression symptoms through 6 months after surgery. Average change in baseline opioid consumption by postoperative day 5 and average pain levels and opioid consumption through 6 months will be compared between groups.

Ethics and dissemination There remains a demand for more effective and safer strategies for postoperative pain management in patients with head and neck cancer as chronic opioid dependence has been associated with decreased survival in this patient population. Results from this study may lay the groundwork for further investigation of COLPs as a strategy for adjunctive pain management in patients with head and neck cancer. This clinical trial has been approved by the Johns Hopkins University Institutional Review Board (IRB00276225) and is registered on the National Institutes of Health Clinical Trials Database.

Trial registration number NCT04973748.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial to evaluate conditioned open-label placebo (COLP) for adjunctive pain management in patients with head and neck cancer following surgery.

⇒ The open-label design of this study eliminates concerns about deception and safety of patients, but inherently introduces reporting bias.

⇒ Our study design incorporates surveys about patients’ perceptions of pain, opioids, and placebo prior to surgery and after completion of COLP to address this potential source of implicit bias.

⇒ To accurately determine the efficacy of COLPs we have limited the patient population to those without chronic opioid use or substance use disorders. However, this limits the external validity of our study and may require future studies to investigate the efficacy in this patient population that would likely benefit from COLPs.

INTRODUCTION

The opioid epidemic continues to be a considerable problem in the United States, with more than 5 million Americans currently affected by opioid-related substance use disorders. While prescription medications may be thought of as safe and controlled, many opioid-naïve patients report continued prescription opioid consumption over 1 year after surgery, and the majority of heroin users report starting with abuse of prescription opioids. At the same time, prescription opioids have more than doubled from 2001 to 2013 and studies suggest that surgical patients receive opioids in excess of their perioperative pain needs. Patients with head and neck cancer are at a particularly high risk of chronic opioid dependence after surgery given pain and psychosocial consequences of both the disease itself as well as surgical treatment.
Pharmacological conditioning aims to elicit a classically conditioned, or Pavlovian, response through consistent pairing of a medication with a neutral stimulus. Treatment involves repetitive reinforcement, which prior studies have accomplished with simultaneous presentation of a characteristic cue (eg, odour) with each dose of an active and inactive medication. These studies have shown efficacy of pharmacological conditioning paired with placebo to decrease the total dose of active medications required for a clinical response, including opioids for pain following spinal cord injury, stimulants for attention deficit hyperactivity disorder, corticosteroids for psoriasis, zolpidem for insomnia, desloratadine for allergic rhinitis and immune suppressive drugs after renal transplant. Many of these successful studies have also been performed as ‘open-label placebo (OLP)’ trials, wherein patients were aware of their group assignment and were informed of each placebo treatment, eliminating the ethical dilemma of using deception in clinical settings. OLP induced short-term outcome improvements in pain disorders such as adult and paediatric irritable bowel syndrome and other chronic pain disorders (eg, back pain, knee pain). Overall, these results suggest that non-deceptive conditioned open-label placebos (COLP) may also be beneficial for head and neck cancer perioperative symptom management.

This trial is designed as a randomised, controlled, open-label, superiority trial with two parallel groups with 1:1 allocation. We hypothesise that the addition of COLP and conditioning to standard multimodal analgesia will be associated with reduced baseline opioid consumption by 5 days after surgery in comparison to standard multimodal analgesia alone in patients with head and neck cancer. This may provide an innovative intervention to decrease the risk of long-term opioid dependence in this patient population.

METHODS AND ANALYSIS
This study will be a randomised, controlled, open-label, superiority trial of 62 individuals, age 18 years and older. Patients undergoing surgical resection of a head and neck tumour in the Otolaryngology – Head & Neck Surgery (OHNS) department of the Johns Hopkins Hospital (JHH) that meet inclusion and exclusion criteria will be recruited for participation. This clinical trial has been approved and is sponsored by the Johns Hopkins University Institutional Review Board (IRB00276225) and is registered on the National Institutes of Health Clinical Trials Database. Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used for this protocol.

Patient and public involvement
No patient involved.

Participant population and recruitment
Potential participants will be identified by Head and Neck Cancer surgeons at JHH that are also coinvestigators on the study, during preoperative clinic visits. A member of the research team will provide potential participants with information about the study. Potential participants that are interested in the study will then contact the research team to review the study eligibility and details as well as the Institutional Review Board (IRB) approved study consent form. Potential participants will be asked to paraphrase the study purpose and procedures, including the fact that all participants will receive standard multimodal analgesia and will not have pain medication withheld for study purposes. A video about the placebo effect and patients’ experiences with placebo, from a previously published study, will also be shown (https://www.youtube.com/watch?v=41mvPEn5zQo). Potential participants that agree to participate in the trial will complete a checklist to document comprehension of the study and the participant and research team member will sign and date the informed consent form (online supplemental file 1). Eligibility will then be re-confirmed after surgery. Participants may withdraw from the study at any time by verbal or written communication.

Eligibility
Inclusion criteria
All patients undergoing preoperative evaluation of head and neck cancer in the OHNS department at JHH will initially be screened. Those meeting the following criteria will be eligible: (a) planned surgery for resection of and/or reconstruction after prior resection of a head and neck tumour at JHH from 15 November 2022 to 15 May 2024, (b) expected duration of inpatient admission of at least 5 days, (c) age 18 years or older, (d) ability to provide informed consent and willingness to participate regardless of group assignment and (e) willingness to participate from 1 week prior to surgery through 6 months following surgery.

Exclusion criteria
Patients with any of the following criteria will not be eligible for the study: (a) inability to understand the procedures and the potential risks as determined by study staff, (b) inability to participate in study procedures due to psychiatric comorbidity, cognitive impairment or delirium, (c) contraindication to receiving standard multimodal analgesia with acetaminophen, ibuprofen, oxycodone and hydromorphone, (d) new prescription for a gabapentinoid within 2 weeks of surgery, (e) chronic opioid use (>3 months), (f) chronic pain or (g) substance use disorder.

Randomisation and blinding
Randomisation and allocation
Participants will be randomised into one of two study arms with 1:1 allocation once consent has been obtained and eligibility has been reconfirmed after surgery (figure 1). Randomisation will be performed using a 1:1-balanced randomisation list that is generated and uploaded into the randomisation function in Research Electronic Data
Capture (REDCap) software\textsuperscript{21,22} by a research assistant. REDCap is a secure, web-based software platform designed to support data capture for research studies. Allocation will be concealed until the time of group assignment.

Blinding
As an open-label study, in accordance with prior studies,\textsuperscript{8,14,19} all research study members, clinical staff and participants will be aware of each participant’s study group assignment and will know when a placebo medication is administered. Participants will enter their survey responses, including pain levels, directly into REDCap to limit clinician biases towards certain outcomes. A study team member will be available to assist participants with this task while in the hospital and will be trained to use a pre-written script with participants to further limit potential bias.

Study design
Participants included in this open-label, randomised controlled trial will have a length of hospital stay of at least 5 days, with an average length of stay of 7–10 days. An outline of the study design is shown in table 1.

Treatment as usual and standard multimodal analgesia regimen
The treatment as usual (TAU) arm will receive standard postoperative care with multimodal analgesia, including opioids. This group was chosen as the comparator given historical data showing that TAU results in persistent opioid consumption through the first week after surgery. The COLP arm will also receive standard multimodal analgesia, including opioids, as well as pharmacological conditioning, as described later. The standard multimodal analgesia regimen for postoperative care of patients with head and neck cancer is outlined below:

1. Scheduled, enteral acetaminophen (1000 mg every 8 hours (Q8h)) and ibuprofen (400 mg Q6h).
2. Enteral oxycodone as needed (PRN) based on Likert scale pain severity. Opioid naïve participants: starting dose of 5 mg Q4h PRN for pain 4–6 or 10 mg Q4h PRN for pain 7–10. Participants prescribed opioids prior to surgery: starting doses for oxycodone will be comparable to preoperative opioid doses and titrated during postoperative day (POD) 1.
3. Intravenous (IV) hydromorphone as needed (0.5 mg Q3h PRN) for breakthrough pain.

Figure 1 Overall study design. Participants enrolled in the randomised controlled trial (RCT) are randomised with 1:1 allocation to either the treatment as usual (TAU) or conditioned open-label placebo (COLP) group. All participants are started on a standard pain regimen on postoperative day (POD) 0. The COLP group additionally receives conditioning with active oxycodone from POD 1–5 and with placebo oxycodone from POD 2–5. Follow-up (f/u) continues through POD 180 with surveys on opioid consumption, pain and depression symptoms. FPS, Functional Pain Scale; N, number of participants; NOSE, Numerical Opioid Side Effects; PHQ-9, Patient Health Questionnaire-9; PRN, as needed; QXh, every X hours; TID, three times per day; VAS, visual analogue scale.

![Figure 1](image-url)

Table 1 Timeline for study protocol

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<td>Q4h (daily after DC)</td>
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COLP, conditioned open-label placebo; DC, discharge; FPS, functional pain scale; MME, morphine milligram equivalents; NOSE, Numerical Opioid Side Effects survey; PHQ-9, Patient Health Questionnaire-9; POD, postoperative day; PPP, survey on perceptions of pain, opioids and placebo; Q4hr, every 4 hours; ST, standard multimodal analgesia; ST+C, ST with C; TAU, treatment as usual; PL+C TID, placebo with conditioning (C) three times per day; VAS, visual analogue scale.
4. Oxycodeone dosing will be adjusted in 2.5–5 mg equivalents if a participant requires more than 1 intravenous breakthrough dose in 24 hours or as clinically indicated.

5. The acute pain service will be consulted for participants with significant pain not able to be controlled on the above standard multimodal analgesia regimen.

**Intervention with COLP**

Participants in the COLP group start conditioning (ie, exposure to clove oil scent) with all active doses of oxycodone on POD 1, continuing through POD 5. From POD 2 through POD 5, participants also receive placebo oxycodone paired with conditioning three times per day, scheduled approximately 8 hours apart. To strengthen the acquisition phase of the conditioning, the conditioning stimulus is paired with the active oxycodone dose alone for the first day. Depending on the severity of the participant’s pain over POD 1, participants will receive up to 6 pairings of the conditioning stimulus with active oxycodone before treatment with the COLP begins on POD 2. Continued pairing of the conditioning stimulus with active oxycodone on POD 2–5 further strengthens acquisition throughout treatment with the COLP. Nursing staff will provide the participant with the ‘Sniffin’ Stick’ (MediSense, Groningen, Netherlands), which are used clinically to assess olfactory performance and for smell retraining. 

Clove oil (ie, eugenol) has been shown to stimulate both olfactory and trigeminal chemoreceptors. Prior to administration of the active and placebo oxycodone doses, a member of the nursing staff will provide the participant with the ‘Sniffin’ Stick’ and advise the participant to waft the scent for at least 10 s. There is minimal risk associated with this intervention as a new ‘Sniffin’ Stick’ is used for each treatment, limiting the chance for contamination. A member of the research team will also assist with conditioning on a daily basis to ensure adherence to the study protocol. This method will condition participants to a physiologic response to both opioids and placebo.

Placebo will be formulated by the JHH Osler Investigational Drug Services, a research core at our institution. Placebo will contain a suspensory agent and strawberry flavouring (ORA-Blend sugar-free suspension with 4% volume/volume FLAVORx Inc Strawberry flavour) to match ingredients in the brand of oxycodone solution used by inpatient pharmacies at JHH. Placebo will be dispensed by the pharmacy in 5 mL amber oral syringes to match those used for administration of oxycodone solution.

As an open label study, all research study members, clinical staff and participants will be aware of each participant’s study group assignment and will know when a placebo medication is administered.

**Surveys and data collection**

Within 1 week prior to scheduled surgery, enrolled participants will complete online surveys on pain severity measured by visual analogue scale (VAS), functional pain, perceptions of pain and placebo (PPP), and depression symptoms through a Health Insurance Portability and Accountability Act (HIPAA)-compliant REDCap link. The Functional Pain Scale (FPS) evaluates both pain intensity as well as how pain affects a patient’s ability to participate in physical activities. It has been validated for use in hospitalised adults and includes both physical and emotional aspects of pain, suggesting it may be more sensitive to changes in pain than other tools.

The Patient Health Questionnaire -9 (PHQ-9) is a well-validated and succinct tool for evaluating symptoms of depression in hospitalised patients with substantial crossover to diagnostic criteria for depression and excludes many neuro-vegetative symptoms that can be attributed to the disease or surgical treatment itself in patients with head and neck cancer. After discharge from the hospital, any potential adverse effects from opioid medications will be monitored with the Numerical Opioid Side Effect (NOSE) assessment tool. Following surgery, the VAS, FPS, PPP, PHQ-9 and NOSE will be completed by REDCap surveys through POD 180 as outlined in table 1. The research assistant will assist participants with surveys each day while they are inpatient.

While inpatient, nursing staff will document opioid consumption and pain severity by Likert scale every 4 hours in the Electronic Medical Record (EMR), as is standard of care. Following discharge from the hospital, participants will complete REDCap surveys about daily opioid consumption. Responses to surveys after discharge from the hospital will be reviewed by the study team and reminder emails will be sent to participants that do not complete surveys within 24 hours. Demographic information and relevant medical, surgical, medication and social history will be obtained from chart review. Medical records will also be reviewed after discharge from the hospital to determine timing and duration of any adjuvant chemotherapy or radiation therapy. Patients will be followed for a total of 6 months after surgery.

**Study discontinuation**

Participants will be removed from the study if any of the following occur: (a) postoperative complication that requires return to the operating room or other surgical procedure performed within the first 5 days after surgery given confounding from pain caused by an additional procedure, (b) minimal opioid use (<2 doses of oxycodone/day) for the first 2 days after surgery as this limits acquisition of conditioning, (c) change in surgical procedure performed that no longer meets inclusion criteria, (d) delirium or cognitive impairment preventing study participation within the first 5 days after surgery, (e) deviation from standard multimodal analgesia regimen (ie, inability to tolerate a medication or new pain medication added) within the first 5 days after surgery or (f) 

participant in COLP group misses >2 placebo doses in a single day or >1 placebo dose in two consecutive days. Additionally, participants may request to withdraw from the study at any time. Once a participant is removed from the study, no additional data is collected.

**Primary and secondary outcomes**

The primary outcome will be the average change in daily opioid consumption, reported as morphine milligram equivalents (MME), from POD 2 to POD 5 between treatment arms. Opioid consumption was chosen as the primary outcome, over pain severity, given its association with survival outcomes in this patient population.\(^1\) The secondary outcomes will be pain levels as assessed by VAS\(^2\) and FPS\(^2\), answers to questions about PPP and NOSE\(^3\) surveys. A secondary exploratory outcome will be the proportion of participants in each group with persistent opioid use 1, 2, 3 and 6 months after surgery. These comparisons will be adjusted for the proportion of participants undergoing or having completed adjuvant radiation at each timepoint.

**Statistical analyses**

**Sample size calculation**

We aim to enrol 62 individuals in this study. Our objective is to obtain a sample size that will provide adequate power to detect a clinically significant difference in change from baseline MME in participants in the TAU vs COLP group.\(^8\) This will be calculated as the change in daily MME from POD 2 to POD 5. Review of historical data on a cohort of patients comparable to the TAU group at our institution showed an average change in daily MME consumption from POD 2 to POD 5 of 124.2±43.8%. Assuming a power of \(\beta=0.20\), a sample size of 44 participants would be required for a 30% change in MME from POD 2 to POD 5 in the COLP group to be statistically significant. A goal change in 30% of baseline MME per day was chosen based on results from prior studies of COLPs for acute spinal trauma and following spinal surgery.\(^8\)\(^3\)\(^4\) Historical data showed an average rate of complications requiring return to the operating room of 15%. Approximately 10% of participants may also undergo a different surgical procedure than initially planned, which no longer meets study criteria. Assuming these conditions that would result in removal from the study and an additional 5% dropout rate, total initial enrolment will be 62 participants (31 TAU, 31 COLP). The JHH Otolaryngology – Head & Neck Cancer Surgery Division performs, on average, over 1000 surgeries per year, of which over 100 meet study inclusion and exclusion criteria. With a goal enrolment rate of at least 40%, study recruitment should take ~18 months.

**Descriptive analyses**

Statistical analysis will be performed using Stata V.16 (StataCorp). Descriptive statistics will be given for each group and continuous and categorical variables will be compared with Student’s t-test and \(\chi^2\) test, respectively. Average absolute daily MME, VAS, FPS, PHQ-9 and NOSE scores will be compared between groups through 6 months and changes in average daily MME from baseline MME (POD 2) will be compared between groups through 14 days after surgery using generalised estimating equations to account for repeated measures over time and potential missing data. The primary outcome, short-term change in baseline MME will be defined as the change in average daily MME from POD 2 to POD 5. The secondary outcome, long-term opioid use will be evaluated by calculating average daily MME as well as the proportion of patients within each group with persistent opioid use 1, 2, 3 and 6 months following surgery. A linear mixed model will be used to evaluate for potential differences in primary and secondary outcomes between study groups to account for missing data and to control for covariates, including participants’ age, sex, comorbidities and adjuvant treatment.\(^3\)

**Data monitoring and confidentiality**

A data monitoring committee was not required by our IRB given the minimal risk associated with this protocol. The study team will monitor participants on a daily basis while they are admitted to the hospital. The participant’s primary clinical care team will be responsible for making changes to the standard multimodal analgesia regimen, when medically indicated. A member of the study team will communicate with the participant and their clinical care team on a daily basis while inpatient to discuss changes to the participant’s pain regimen, side effects or concerns related to study interventions or continued participation, and any other adverse events. All adverse events that occur while a patient is enrolled in the trial will be recorded and reported to the IRB in 6-month intervals, or immediately in the case of a severe adverse event. An interim analysis of the study will also be performed after the first 10 participants are enrolled. The study protocol will be reassessed if more than half of the initial 10 participants are removed from the study within 5 days after surgery.

To protect the confidentiality of participants in this trial, data is recorded and maintained in a HIPAA-compliant REDCap project. Following study completion, all identifiable information is removed. This application also incorporates data value checks for each entry to ensure accuracy of data collection. Given the small number of participants in this trial, participant-level data will only be available to study investigators. Access to the full study protocol, aggregate data and statistical code can be requested by contacting the principal investigator of the study.

**ETHICS AND DISSEMINATION**

This is the first randomised controlled trial to evaluate COLP for adjunctive pain management in head and neck cancer surgery patients. This trial will specifically investigate whether short-term treatment with COLP can reduce baseline opioid requirements while maintaining adequate...
pain control in the perioperative setting and whether this intervention can reduce the risk of developing chronic opioid dependence in this patient population.

Patients with head and neck cancer represent a unique population in that surgical resection involves particularly painful areas of the body. Surgery for head and neck cancer can also significantly impair a patient’s ability to perform daily activities, such as speaking and eating, with potential psychosocial consequences; in fact, up to 50%6 of these patients also suffer from depression and anxiety.4 5 Together, these factors inherently increase the risk of opioid dependence in this patient population, which may be as high as 20%–60% of patients after surgery for head and neck cancer.31 36–38 Additionally, both depression and chronic opioid use in cancer patients have been associated with poorer disease-free and overall survival.31–33

Recent efforts have been made to address the issue of over-prescription of opioids and opioid dependence across surgical specialties.2 39 The American Society of Anesthesiologists Task Force on Acute Pain Management published updated guidelines for pain management in the perioperative setting, which advocate for greater use of multimodal analgesia regimens.39 Similarly, in 2021 the American Academy of Otolaryngology published Clinical Practice Guidelines outlining expected durations and severity of pain and expected postoperative opioid requirements for common otolaryngological procedures.40 However, studies suggest there remains significant room for improvement,1 41 and novel methods are required to minimise opioid risks in patients with head and neck cancer after surgery.

Concerns over deception and safety associated with placebo opioid medications understandably persist.42 43 However, recent evidence has delineated that the psychological and neurobiological effects of placebo can be observed without blinding of patients (ie, as OLPs), essentially eliminating these concerns.34 44 This success has been demonstrated across different clinical applications and medical fields, including oncology.8 45 A recent study by Flowers et al, also demonstrated significant reduction in opioid consumption with COLPs for treatment of acute pain following spinal surgery, supporting its efficacy in the postoperative setting.34 While an open-label study design may inherently be at risk for bias, many prior high-quality studies have been performed with this design.8 14 19 Potential bias from clinicians or study team members in this study is limited by having participants directly enter their survey responses into REDCap. Any interaction with the research assistant during this task will follow a prewritten script to ensure equivalent instructions are given to all participants. Furthermore, nursing staff will document opioid consumption and pain severity directly in the EMR, as is standard of care.

Conditioning takes advantage of the assumption that patients have a positive experience taking an active medication, and it has been combined with placebo as studies show it may further enhance the desired treatment effect.43 This is an important factor to consider as its efficacy may depend on the validity of this assumption.43 As highlighted in a follow-up study of a recent randomised controlled trial, a proportion of patients that received COLP endorsed negative experiences with opioids and pill taking in general.42 Therefore, it may be essential to consider patients’ perceptions of active treatments when interpreting future studies employing COLP. Our study design incorporates surveys about patients’ perceptions of pain, opioids, and placebo, adapted from participant responses in the aforementioned study,42 prior to surgery and after completion of COLP to address this potential source of implicit bias. Overall, these encouraging results of prior studies support further investigation of COLPs for other clinical applications.

Despite efforts to improve multimodal analgesia regimens and limit opioid prescribing, the risk of chronic opioid use following surgery persists in patients with head and neck cancer. This randomised, controlled, open-label trial is an initial and essential step to determine if treatment with conditioned open label placebo is a feasible solution to this problem. We expect that incorporation of COLPs into standard pain regimens following surgery is feasible in the inpatient setting and have designed the study protocol to minimise burden on the nursing staff. However, additional studies would be required to determine if COLPs would be effective in the outpatient setting for patients who are discharged from the hospital on the same day or a few days after surgery. This would likely require additional oversight of patients after discharge from the hospital to ensure adherence to the protocol. Following completion of this study, results will be presented at a national medical conference and published in a peer-reviewed journal to support further investigation of COLP for adjunctive pain management for patients with head and neck cancer in additional perioperative settings.

Contributors DRT, LC and PSV designed the study, research tools and strategies for drug manufacturing and delivery, CF, MT and ZK provided critical feedback about the protocol. DRT, LC, PSV, CF, MT and ZK drafted and revised the manuscript. All the authors reviewed and agreed with the latest version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Provenance and peer review Not commissioned; externally peer reviewed.

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**ORCID iDs**

Daniele A Trakimas http://orcid.org/0000-0003-1974-1880
Luana Colloca http://orcid.org/0000-0002-6503-4709

**REFERENCES**