Optimizing outpatient anesthesia

(OSPREy: Outpatient Surgery Pain Relief Enhancement)

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1. SYNOPSIS

Study Title	**Optimizing outpatient anesthesia**
Objective	In separate cohorts of patients undergoing moderately painful outpatient surgery ("short-stay" requiring overnight hospitalization with intended next day discharge and "same-day" surgery), compare the influence of general anesthesia with long-duration vs short-duration opioids on 1. short-term (before discharge) and intermediate term (1-30d post-discharge) opioid consumption. 2. short-term (immediate postoperative), intermediate term (1-30d post-discharge), and chronic (6 and 12 mo) postoperative pain. 3. short-term (immediate postoperative), intermediate term (1-30d post-discharge) opioid-related side effects 4. intermediate (30d post-discharge), and long-term (6 and 12 mo) quality of recovery.
Study Period	Approximately 30 days per subject, plus 6 and 12 month follow-up Total enrollment duration: Approximately 4 years
Number of Patients	600 evaluable subjects. Estimated number to be studied is 750 with 25% loss to follow-up. Estimated enrollment is 1000 to account for schedule changes, withdrawals, etc.
Inclusion and Exclusion Criteria	Inclusion Criteria 1. Age 18-65 years 2. Undergoing general anesthesia and moderately painful ambulatory surgery with anticipated postop stay of < 24 hours 3. Signed, written, informed consent Exclusion Criteria 1. History of liver or kidney disease. 2. Females who are pregnant or nursing. 3. Chronic opioid use (e.g. preoperative daily use of methadone, buprenorphine, fentanyl transdermal patches, or ≥ 3 oxycodone pills)
Study Design	Single-center, randomized, double blinded, parallel-group, 2-cohort investigation. Patients receive standard monitoring for anesthesia and postoperative care. Surgical and anesthesia care (except for intraoperative opioid use) are not altered for study purposes. In each cohort, subjects are randomized 1:1 to either long-duration opioid (IV methadone HCl) or typical short-duration opioid (IV e.g. fentanyl, morphine or hydromorphone at anesthesia provider discretion) intraoperatively and postoperatively in the recovery room. Intraoperative methadone doses are 15 mg in "short-stay" patients (10 mg if ≤55kg) and 10 mg in "same-day" surgery patients.
Study Drug Administration	In each of two cohorts ("short-stay" and "same-day" outpatients), 375 patients are randomized 1:1 (187 each) to receive long-duration opioid (IV methadone HCl) or typical short-duration opioid (e.g. fentanyl, morphine or hydromorphone at anesthesia provider discretion) intraoperatively & postoperatively in the recovery room (PACU).
Measurements	Patients complete a questionnaire about current pain, past 7 day average pain, pain interference with activities of daily living, and expected level of postoperative pain. Total intraoperative and postoperative opioid administration during hospitalization will be recorded from the medical record. Pain intensity will be assessed using a verbal Numeric Rating Scale (NRS). Pain relief will be assessed using five point scale (0-no relief, 4-complete pain relief). Postoperative sedation will be recorded using Modified Observer`s Assessment of Alertness/Sedation (MOAA/S). Opioid-related side effects will be assessed using the Opioid-Related Symptom Distress Scale (ORSDS). Daily opioid consumption and pain self-assessments using a NRS and ORSDS will be recorded for approximately 30

	days after surgery using anemailed REDCap or paper survey tool. Pain (PROMIS Pain Intensity and Pain Interference) and recovery (patient-reported quality of life, functional independence, health status, ability to return to work and normal activities; PROMIS global health, PROMIS-29, Veterans RAND 12-item VR-12 survey, Barthel index of activities of daily living, Quality of Recovery QoR-15) will be assessed at 7d, 14d, 21d, 30d, 6mo and/or 1yr postoperatively. Blood will be collected for future DNA analysis (CYP2B6 or pain-related genes).
Statistical Methodology	Both cohorts are analyzed separately. Demographic data including race, sex, and age will be analyzed using chi-square. Post-discharge opioid use (30d) is compared using Chi-square tests and multiple logistic regression, with opioid group as a predictor and adjusting for covariates. Total pill consumption is compared with a GEE model and Poisson link function. A time-to-event (survival) model will compare time to opioid discontinuation. Opioid use during intraop, in-hospital post-op, and post-discharge periods will be evaluated using appropriate model and data transformation. Pain reduction effectiveness of long- vs short-duration opioids is compared using repeated measures models to adjust for multiple measures on each subject. Side effects will be compared using Chi-squared or Fisher exact tests. Overall recovery will be assessed using chi-square tests for categorical outcomes and t-tests for continuous outcomes as well as a repeated measures model.
Outcomes	Primary: total 30d post-discharge home opioid use (number of tablets) Secondary: 1. Total 7d post-discharge home opioid use 2. Total intraoperative non-methadone opioid administration 3. Total PACU opioid administration 4. Total hospital non-methadone opioid administration Exploratory: 1. Total day of surgery nonmethadone IV opioid administration 2. Total day of surgery nonmethadone IV and oral opioid administration 3. Total day of surgery opioid administration 4. Postoperative day 1 total IV oral and opioid administration (short-stay cohort only) 5. Total hospital opioid administration 6. PACU pain scores (NRS) and pain relief score; at time-specific intervals 7. Duration of intraoperative analgesia (median time to request for re-medication with opioid) 8. PACU side effects and adverse events: respiratory depression (4 events occurrence per above), sedation (MOAA/S score), nausea/vomiting (number of events); at time-specific intervals and total 9. PACU duration of stay 10. 7d and 30d total post-discharge home opioid use (in morphine equivalents) 11. 7d and 30d post-discharge pain scores (NRS) and pain relief score; daily 12. Total pain relief, calculated as the area under the curve of pain relief score vs time 13. 7d and 30d post-discharge opioid side effects (ORSDS); daily, weekly and total (summed and average) 14. Time to cessation of post-discharge opioid use 15. 7d and 30d post-discharge unused opioid tablet count 16. Quality of recovery at 7d, 14d, 21d, 30d, 6 mo, and/or 12 mo (PROMIS global health, PROMIS-29, VR-12, Barthel index, QoR-15, functional independence, return to work) 17. Surgeons' opioid prescribing patterns

2. STUDY PROTOCOL

2.1 Background and Significance

Anesthesiologists and surgeons face two challenges: (1) More than 80% of surgical patients report inadequately treated pain. Chronic postsurgical pain develops in 10-50%, and acute postoperative pain is the single greatest risk factor. Treating pain in outpatient surgery is particularly challenging. Unfortunately, no meaningful progress has been made in postsurgical pain treatment in the last 20 yr.[1,2] (2) The USA is awash in opioids, with skyrocketing prescribing, diversion, abuse, addiction, and fatal overdose.[3] There is a growing reservoir of unused opioids (some originally prescribed for postoperative pain) being diverted and misused. Shrinking the opioid pool is a public health imperative,

Opioids remain the primary therapy for intraoperative and postoperative analgesia. Over the past decades progressively shorter-duration opioids have been used intraoperatively.[4] In contrast, accumulated evidence strongly establishes that a single intraoperative dose of a long-duration opioid (i.e. methadone), which sustains therapeutic drug concentrations, produces better analgesia than repeated doses of short-duration opioids, and reduces further opioid requirements.[5,6] Nevertheless, this has only been evaluated for inpatients.

Intraoperative anesthesia and postoperative analgesia are most commonly achieved with the opioids morphine, hydromorphone, fentanyl, and methadone. Methadone has several therapeutic advantages compared with these other opioids, including more rapid onset, absence of active metabolites, lack of P450 (CYP2B6) genetic influence on the disposition of intravenous methadone, and longer elimination half-life and duration of effect.[5,7-9] For example, the elimination half-life of methadone is 1-2 days, compared with remifentanil (0.5 hr), morphine and hydromorphone (2-3 hr), and fentanyl (8-10 hr), although the actual duration of effect of these latter opioids is much shorter due to rapid redistribution. Methadone is both a μ-opioid receptor agonist and an N-methyl-D-aspartate (NMDA)-receptor antagonist, which may confer additional therapeutic benefit. In addition, even when given intraoperatively, even in a single dose, methadone, compared with shorter-duration opioids, results in lower pain intensity, better postoperative pain relief, longer duration of analgesia, and, *of particular importance and relevance to the opioid epidemic,* need for fewer postoperative opioid doses, and lower cumulative postoperative opioid use.[5,6,10-13] Moreover, these clinical advantages do not come at a cost of greater opioid side effects (respiratory` depression, nausea, vomiting).

2.2. Preliminary Data

We conducted two WUSTL IRB-approved (201408002), prospective, randomized, double-blind clinical pilot studies, with separate outpatient cohorts (both termed outpatients per CMS definitions; Medicare Benefit Policy Manual, Chapter 6, Rule 20.2).

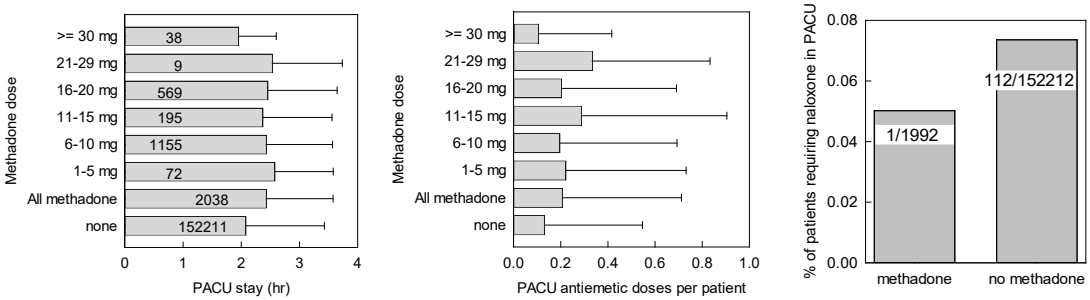
- Patients undergoing short-stay (overnight stay, <24 hr) outpatient surgery
- Patients undergoing true same-day discharge outpatient surgery

Two cohorts were studied because their operations may have different pain intensities and opioid requirements. Inclusion and Exclusion Criteria were identical to those for the present investigation. Subjects were randomized to receive short-duration (IV fentanyl, morphine or hydromorphone at anesthesia provider discretion) or a single dose of a long-duration (IV methadone HCl) opioid intraoperatively. Because methadone anesthesia for outpatient surgery had not previously been studied, these pilot studies used escalating dose groups (typically ~20 per group) to determine the optimal methadone dose for each cohort (short-stay, same-day). The methadone bolus at anesthetic induction was 0.1, 0.2, 0.25, or 0.3 mg/kg ideal body weight for short-stay cases and 0.1 or 0.15 mg/kg ideal body weight for same-day cases. The specific objective was to evaluate intraoperative, immediate postoperative (Post-Anesthesia Care Unit, PACU), and 30d postoperative opioid consumption; immediate and 30d postoperative pain intensity and pain relief; and postoperative opioid-related side effects. And to determine the optimal dose for subsequent large-scale studies.

Results for the short-stay surgery (<24hr) cohort show that a single intraoperative methadone dose (17 ± 2 mg) reduced intraoperative and post-operative in-hospital opioid requirement. Average PACU opioid use was 4 ± 5 mg morphine equivalents after 17 ± 2 mg/kg methadone (not different vs other groups). Methadone did not cause any greater postop sedation or other adverse effects (nausea, emesis). Based on these preliminary intraoperative + PACU opioid use data, a single 15 mg intraoperative dose of methadone will be used in this protocol for the short-stay surgery (<24hr) cohort. This is the typical dose for patients staying in the hospital.[5]

Results for the same-day surgery cohort showed that a single intraoperative methadone dose (9 ± 1 mg) reduced intraoperative, PACU, and post-operative opioid requirement. Average PACU opioid use was 2 ± 3 mg morphine equivalents after 9 ± 1 mg methadone. A single intraop methadone dose also decreased 30d postop opioid use, with less opioids consumed and earlier cessation of use. Despite using less opioid, 30d pain scores were no different in the patients receiving methadone. Patients receiving intraop methadone were also more comfortable (less pain) on arrival in PACU. Methadone did not cause any greater postop sedation or other adverse effects (nausea, emesis). Based on these intraoperative + PACU opioid use preliminary data, a single 10 mg intraoperative dose of methadone will be used in this protocol for the same-day surgery cohort.

Because methadone has a longer elimination half-life, there is natural and appropriate concern about potential respiratory depression. Studies published to date show that postop respiratory effects of methadone are *no different* than other opioids. The above studies found similarly. Nevertheless, we also performed a large-scale QA analysis. We reviewed 3 yr of general anesthetics (n=154,249) with regard to the intraoperative opioid and side effects and safety (Figure). There was no difference between patients receiving methadone (and no methadone dose-effect relationship) vs other opioids (e.g. morphine, fentanyl, hydromorphone) with regard to PACU discharge (duration of stay), nausea/emesis (using antiemetic therapy as an indicator), or respiratory depression (using naloxone administration as an indicator). Thus, we are fully assured of methadone safety for outpatient anesthesia.



Retrospective QA analysis of opioid safety and side effects in general anesthesia (n=154,249 over 3 yr). There was no difference between pts receiving methadone (and no methadone dose-effect relationship) vs other, short-duration opioids (e.g. morphine, fentanyl, hydromorphone) intraoperatively with regard to (*left*) PACU discharge time (duration of stay), (*center*) nausea/emesis (using antiemetic therapy as an indicator), or (*right*) respiratory depression (using naloxone administration as an indicator).

2.3. Objective

The overall goal of this research is to improve perioperative pain treatment, decrease post-operative opioid consumption, diminish opioid related side effects, and reduce postop opioid prescribing (and hence opportunity for diversion, abuse, addiction, and fatal overdose). This protocol will test the innovative, paradigm-shifting hypothesis that anesthesia for outpatient surgery with long-duration opioids (methadone), compared with conventional short-duration opioids, achieves better analgesia, with similar or diminished side effects, may reduce development of chronic postsurgical pain, improves recovery, and importantly, decreases postoperative opioid consumption and could hence diminish take-home opioid prescribing and shrink the population reservoir of unused opioids available for diversion and misuse.

Specific Aims: In separate cohorts of patients undergoing moderately painful outpatient surgery ("short-stay"

requiring overnight hospitalization with intended next day discharge and "same-day" surgery), compare the influence of general anesthesia with long-duration vs short-duration opioids on

1. short-term (before discharge) and intermediate term (1-30d post-discharge) opioid consumption.
2. short-term (immediate postoperative), intermediate term (1-30d post-discharge), and chronic (6 and 12 mo) postoperative pain.
3. short-term (immediate postoperative), intermediate term (1-30d post-discharge) opioid-related side effects
4. intermediate (30d post-discharge), and long-term (6 and 12 mo) quality of recovery.

In ambulatory surgery patients, methadone is expected to decrease the need for additional opioids in the immediate postoperative period, decrease 30d opioid consumption, decrease opioid-related side effects, improve postoperative pain relief, decrease the occurrence of chronic postoperative pain, reduce opioid quantities routinely prescribed upon discharge, and improve overall patient recovery

2.4. Overall study design

Both trials ("short-stay" and "same-day" surgery cohorts) will test the same hypothesis, and have the same protocol aims, inclusion and exclusion criteria, procedures, assessments, methods of data analysis, and hypothesis testing, but are otherwise separate (and separately analyzed). Two cohorts are studied because their operations may have different pain intensities and opioid requirements. The protocol is very similar (hypothesis, aims, inclusion/exclusion, procedures, assessments, data analysis, hypothesis testing) to that of the dose-finding Pilot (Preliminary Studies). In each cohort, patients will be randomized to general anesthesia with methadone or short-duration opioids. Patients are followed in-hospital, then queried daily for 30d after discharge through emailed REDCap or paper surveys . Additional REDCap surveys will be emailed at 6 and 12mo.

Target enrollment is 300 evaluable subjects per cohort (150 control, 150 methadone). A 25% overall drop-out rate prior to 30d follow-up is conservatively assumed, thus 375 subjects in each cohort will be studied (750 total).

2.5. Patient Selection

Patients undergoing outpatient surgery at Duke University Hospital and Ambulatory Surgery Centerwill be recruited. Selection criteria are the same for both "short-stay" and "same-day" cohorts. If enrollment lags, or for strategic advantage, we will add Duke Regional or Duke Raleigh Hospitals, at which point we will amend the protocol. Sex and minority composition will approximate that of the greater Duke patient population, depending on the surgical cases available.

Inclusion Criteria

- Age 18-65 years
- Undergoing general anesthesia and moderately painful, ambulatory surgical procedures with anticipated postop hospital stay of < 24 hours
- Signed, written, informed consent

Exclusion Criteria

- History of or known liver or kidney disease
- Females who are pregnant or nursing
- Chronic opioid use (e.g. preoperative daily use of methadone, buprenorphine, fentanyl transdermal patches, or ≥ 3 oxycodone pills)

Patients will be approached prior to surgery in the Center for Preoperative Assessment and Planning or identified through IRB-approved review of the surgical schedule prior to their surgery, at which time they will be contacted and asked if they are interested in participating. An IRB-approved phone screen may be conducted and a consent visit scheduled in advance of surgery for subjects that wish to participate. This visit may also occur on day of surgery, allowing sufficient time for explanations, questions and answers. If interested and willing, subjects might also be fully consented using IRB approved electronic Informed Consent Form (eICF). All enrolled subjects must provide informed consent, evidenced by signing an informed consent document. They will be consented for participation and enrolled by trained study staff.

2.6 Design and Procedures

2.6.1 Study Design

Single-center, randomized, double blinded, parallel-group, 2-cohort investigation. Patients receive standard monitoring for anesthesia and postoperative care. Surgical and anesthesia care (except for intraoperative opioid use) are not altered for study purposes. In each cohort, subjects are randomized 1:1 to either typical short-duration or long-duration opioid.

2.6.2 Randomization

Subjects in each cohort will be randomized 1:1 to either short-duration or long-duration opioid using randomization tables generated by the hospital Investigational Pharmacy. Each subject is assigned the next number. Anesthesia practitioners are instructed on study procedures, and receive a sealed envelope with Group (drug) assignment and group-specific instructions. To ensure full double-blinding, subjects, investigators, and study team members evaluating patients will be blinded to drug treatment. Dropouts (after treatment) will not be replaced, in case this is not random but outcome-related. Enrollment is increased to account for dropouts.

2.6.3 Preoperative

Patients will complete a questionnaire about current pain, past 7 day average pain, pain interference with activities of daily living, and expected level of postoperative pain (NIH PROMIS-29 Profile v2.0, PROMIS Global Health Scale 1.2, http://www.nihpromis.org/). Quality of life indices will be assessed using the Veterans RAND 12-item health survey (VR-12),[14] the Barthel index of activities of daily living,[15] and the Quality of Recovery QoR-15.[16] Demographic data will be recorded. Additional questions will query patients' current employment, level of normal activities, and expectation of time to return to work and normal activities. Demographic data including patient zip codes, employment status, education status, will be recorded. Patient information (demographics, medical history, procedure, medications, pain scores) will be extracted form patient's electronic medical records.

2.6.4 Intraoperative and postoperative care and study drug administration

Anesthesia and surgical care are not altered for this study, except for randomization to intraoperative and recovery room opioid (all opioids are currently used as part of standard anesthesia care). Anesthetic induction and maintenance are per usual, and at practitioners' discretion.

Patients in the short-duration opioid group receive typical short-duration opioids (IV fentanyl, morphine, and/or hydromorphone), given as needed throughout the intraoperative period, at practitioners discretion, per usual practice. Patients in the long-duration opioid group receive IV methadone HCl 15 mg in "short-stay" patients (1.5 cc of 10 mg/ml) (10 mg, 1.0 cc if ≤55kg) and 10 mg in "same-day" patients (1 cc of 10 mg/ml)). These subjects receive methadone only as their intraoperative opioid, given as a single bolus at anesthetic induction.

For analgesia in the Post-Anesthesia Care Unit (recovery room, PACU), patients in the short-duration group continue to receive typical short-duration opioids (fentanyl, morphine, hydromorphone), at practitioners discretion. It is not necessary that patients receive the same short-duration opioid postoperatively as intraoperatively. Methadone patients continue to receive methadone (2 mg increments). Post-op opioids are given by PACU MDs and nurses, based on patient pain reports, per standing orders and institutional practice.

Practitioners will have the discretion to administer additional opioid at the end of surgery on emergence, while still in the operating room or during transport, to ensure patient comfort. Patients in the short-duration group would continue to receive typical short-duration opioids (fentanyl, morphine, hydromorphone), and patients in the long-duration group would receive methadone. For study purposes, these will be recorded as PACU doses.

Approximately 24 ml of blood will be collected from an existing IV catheter for later genotyping (CYP2B6 or pain-related genes). Genotyping will be performed by an appropriate laboratory

As a safety measure, in the remote event that patients experience repeated respiratory-specific PACU events or at PACU discharge, they will be sent to a monitored (pulse oximetry) bed (`short-stay` cohort) or observed in the PACU for additional time (`same-day` cohort).

2.6.5 Post-Discharge

Post-discharge care is not altered for purposes of this study. Both groups in both cohorts will receive standard of care post-discharge analgesics as determined by their treating surgeon. These include NSAIDs and opioids (oxycodone, oxycodone+acetaminophen (Percocet,Tylox), hydrocodone+acetaminophen (Norco, Vicodin), tramadol, and codeine+acetaminophen (Tylenol#3)). Selection and quantity of opioids dispenses will be at surgeons' discretion.

Opioids will be dispensed in a medication monitoring system, to measure drug utilization during the 30d post-discharge follow-up period. After discharge, patients record their pain self-assessments, home opioid use, and side effects each day through emailed REDCap or paper surveys, allowing real time data recording. Additional REDCap surveys will be emailed at 6 and 12 mo.

For approximately 30d postop, patients will be queried once daily (evening) regarding pain (average at rest, with activity, with coughing, using NRS), pain relief and pain interference with eight activities of daily living (5-point Likert scale) using the NIH PROMIS Pain Intensity 3A and Pain Interference 6A questionnaires. Recovery is assessed using the QoR-15. Patients also record opioid and non-opioid analgesic use, sedation, and time to return to work and ADLs, and opioid side effects (ORSDS). This electronic-based system has improved daily data capture, improved reliability, and can trigger patient contact if necessary to ensure maximal data capture.

2.6.7 Observations and Measurements

All assessment scales are the standard in perioperative methodology, and are conducted by a trained member of the research team, blinded to randomization allocation. Assessments are conducted after PACU admission, every 15 min for the first hour, hourly for the next 4 hr, at bedtime, and ~~24 hr after surgery or prior to hospital discharge (whichever is first), using established protocols.[17,18] We use the standard, well-defined, reliable, recommended patient-reported outcome measures to assess pain.[19] Pain intensity is assessed (at rest/while coughing/with activity) using the validated 0-10 Numeric Rating Scale (NRS).[20] Pain relief is assessed using the standard 5 point scale (none=0, slight=1, moderate=2, good=3, complete=4). Observed sedation (Modified Observer's Assessment of Alertness/Sedation, MOAA/S) and subject's self-assessment of sedation are recorded concurrently with pain assessments.[21] Opioid side effects are assessed prior to discharge using the Opioid-Related Symptom Distress Scale (ORSDS).[22] ORSDS uses 4-point Likert scales to characterize 12 opioid side effects (nausea, vomiting, constipation, difficulty urinating, difficulty concentrating, drowsiness, dizziness, confusion, fatigue, itchiness, dry mouth, and headache) according to frequency, severity, and bothersomeness. Twelve symptom-specific ORSDS scores (0-4) are the average of the 3 distress dimensions (frequency, severity, and bothersomeness). The composite ORSDS (0-4) is the mean of the 12 individual scores. ORSDS has both construct reliability and content validity.[22] Drug administration for prophylaxis/treatment of opioid side effects (e.g. antiemetics) during hospitalization is recorded from the electronic medical record. Particular attention will be paid to opioid-related adverse events, most importantly respiratory depression. During PACU recovery, four types of respiratory-specific events will be assessed:[23]

1. Hypoventilation (3 episodes of <8 respirations/min)
2. Apnea (episode of apnea >=10 seconds)
3. Hypoxemia (3 episodes of oxyhemoglobin saturation <90% for 30 sec with/without nasal oxygen)
4. "Pain/sedation mismatch" (defined as MOAA/S 0-2 and a numeric pain score > 5

Postoperative opioid use will be quantified from the medication monitoring system, patients' daily questionnaire, and residual pill counts, and recorded both as the number of tablets used and total morphine equivalents using standard opioid conversion tables.[24]

Recovery from surgery/anesthesia will be assessed at 7d, 14d, 21d, 30d, 6mo and/or 1yr postoperatively, by assessing patient-reported quality of life, functional independence, health status, and ability to return to work and normal activities. We will assess quality of life (Veterans RAND 12-item health survey VR-12,[14] functional independence (Barthel index of activities of daily living[15], recovery (QoR-15).[16] QoR-15 assesses 5 domains of patient-reported health status: pain, physical comfort, physical independence, psychological support and emotional state using an 11-point numerical rating scale with results summed from 0 (poor recovery) to a maximum of 150 (excellent recovery). These are among the most commonly used instruments, are extensively validated and normed, and are our hospital standards, used locally for several years. Thus we can compare postop with preop metrics, but also with our entire patient database. VR12 is a short form based on the Veterans SF36 version, has 2 domains and 8 dimensions leading to 12 questions, and generates two aggregate summary scores (Physical Component & Mental Component summaries), which are standardized using weights derived from the general population survey and calibrated so that 0.50 is the threshold defining the status of the respondent. Washington University has standing approval (Dr. Lewis Kazis) to use the VR12 and scoring algorithm. The Barthel questionnaire assesses functional independence (able to complete 10 specific normal activities like bathing, feeding, dressing, with any help). It generates a weighted aggregate score 0-100 (100=highest independence). We will evaluate patients' return to employment (defined as work for pay or volunteer work outside home). If applicable, specific questions targeting the reason (pain, addiction, etc) for not returning to work will be asked at 30d, 6mo and 1yr.

Throughout the investigation, any adverse events will be described, recorded and reported according to GCP and IRB regulations.

Medical records are used to calculate the amount of morphine equivalents administered during surgery and until discharge, as well as other drug administration for treatment and/or prophylaxis of possible opioid side effects.

Baseline measurements that will be obtained from patients or the medical record are age, sex, ethnicity, vital signs, weight, height, and peripheral oxygen saturation by pulse oximetry.

Subjects will be compensated $400 for the time and effort to complete 1-30d daily data entries, and use and return of medication monitoring pill bottle, and 6 and 12mo survey responses.

Patient Surveys/Self-Assessments

	Baseline	Discharge	Daily POD 1-3	Daily POD 4-30	POD 7	POD 14	POD 21	POD 30	6 mo	12 mo
PROMIS Global Health Scale 1.2 08.22.2016	✓							✓	✓	✓
PROMIS -29 Profile 2.0	✓							✓		
RAND VR12 v4	✓				✓	✓	✓	✓	✓	✓
Barthel Index ADLs	✓				✓	✓	✓	✓	✓	✓
QoR-15	✓	✓	✓		✓	✓	✓	✓		
PROMIS Pain Intensity 3A v1.0					✓	✓	✓	✓		
PROMIS Pain Interference 6A v1.0					✓	✓	✓	✓		
OSPREy Survey-Baseline	✓									
OSPREY Survey 1 mo								✓		
OSPREY Survey 6 mo									✓	
OSPREY Survey 12 mo										✓
Home diary			✓	✓						

2.6.8 Primary and secondary outcome measures

Primary outcome measure: Total 30d post-discharge home opioid use (number of tablets). This is because surgeons prescribe a variety of post-op opioids (oxycodone, tramadol, oxycodone+acetaminophen, hydrocodone+acetaminophen, codeine+acetaminophen), we avoid any confounding by use of opioid conversion tables, and the most important factor in opioid diversion and misuse is the number of left-over tablets.

Secondary outcome measures:

1. Total 7d post-discharge home opioid use (number of tablets).
2. Total intraoperative non-methadone opioid administration
3. Total PACU opioid administration
4. Total hospital non-methadone opioid administration

Exploratory outcomes:

1. Total day of surgery nonmethadone IV opioid administration
2. Total day of surgery nonmethadone IV and oral opioid administration
3. Total day of surgery opioid administration
4. Postoperative day 1 total IV oral and opioid administration (for short-stay cohort only)
5. Total hospital opioid administration
6. PACU pain scores (NRS) and pain relief score; at time-specific intervals
7. Duration of intraoperative analgesia (median time to request for re-medication with opioid)
8. PACU side effects and adverse events: respiratory depression (4 events occurrence per above), sedation (MOAA/S score), nausea/vomiting (number of events); at time-specific intervals and total
9. PACU duration of stay
10. 7d and 30d total post-discharge home opioid use (in morphine equivalents)
11. 7d and 30d post-discharge pain scores (NRS) and pain relief score; daily
12. Total pain relief (TOTPAR), calculated as the area under the curve of pain relief score vs time
13. 7d and 30d post-discharge opioid side effects (ORSDS); daily, weekly and total (summed and average)
14. Time to cessation of post-discharge opioid use
15. 7d and 30d post-discharge unused opioid tablet count
16. Quality of recovery at 7d, 14d, 21s, 30d, 6 mo, and/or 12 mo (VR-12, Barthel index, QoR-15, functional independence, return to work)
17. Surgeons' opioid prescribing patterns

2.7 Sample size justification

Sample size is based on the primary outcome measure, total 30d post-discharge home opioid use (number of opioid tablets). Based on available reports (Background) and the Preliminary Results, an ideal state of post-discharge opioid use is defined as ≤5 pills in 30 days. In the Preliminary data, the rate of "high" post-discharge opioid use (defined as >5 pills in 30d) was 45% in the short-duration opioid group. With a conservative assumption of a relative risk of 65% for the long-duration group (30% rate of "high" opioid use), a total of 300 subjects (150 per group) will be needed to achieve 80% power assuming alpha = 0.05.

2.8 Hypothesis testing

For all Aims, the two cohorts ("short-stay" and "same-day" surgery) are analyzed separately. Subgroup analysis may also explore specific surgical procedures (procedure-specific analgesia[25]).

Aim 1: Compare the influence of methadone vs short-duration opioids on short-term (before discharge) and intermediate term (1-30d post-discharge) opioid consumption.

30d post-discharge opioid use (>5 pills) will be compared between arms using Chi-square tests and multiple logistic regression, with opioid group as a predictor and adjusting for the important clinical and demographic covariates. Total pill consumption will be compared used using GEE model with Poisson link function. In addition, a time-to-event (survival) model will be fit to compare time to opioid discontinuation between the two groups,

adjusting for the appropriate covariates. Opioid use during intraop, in-hospital post-op, and post-discharge periods will be evaluated using appropriate model and data transformation, depending on the distribution of the data. It is common in some analgesic trials that subjects dropping from different treatment groups differ with respect to reasons for early discontinuation (i.e. not random but outcome-related). Therefore analysis will not be "completers only" .[19] Drop-out rates will be compared between the drug groups, and 30d opioid consumption (>5 vs ≤5 pills) analyzed with and without drop-outs. Drop-outs will be censored at the time of dropping out in time to discontinuation analysis. A corollary of opioid consumption by patients is opioid prescribing by surgeons. It is possible that surgeons' prescribing practices (# tablets per patient) may change during the study (coincidentally or as a result thereof) and this will be explored.

Aim 2: Compare methadone vs short-duration opioids in reducing short-term (immediate postoperative), intermediate term (1-30d post-discharge), and chronic (6-12 mo) postoperative pain.

Pain reduction effectiveness of methadone vs short-duration opioids will be compared using repeated measures models to adjust for multiple measures on each subject. Depending on the distribution of NRS, VAS and pain relief data, data will be analyzed as normal, or transformed into an ordinal or other scale.

Aim 3: Evaluate major and bothersome short-term (before discharge) and intermediate term (1-30d post-discharge) opioid-related side effects with methadone vs short-duration opioids.

Side effects (respiratory-specific events, composite ORSDS) will be compared between the groups using Chi-squared or Fisher exact test, as appropriate, and using logistic models to adjust for important clinical and demographic covariates.

Aim 4: Compare overall recovery after surgery/anesthesia with methadone vs short-duration opioids, as defined by changes in reported Health-related Quality of Life, functional independence, and ability to return to work and normal activity.

Overall recovery will be assessed using chi-square tests for categorical outcomes and t-tests for continuous outcomes as well as a repeated measures model to adjust for multiple time points.

3.0 Recruitment strategy and feasibility

Subjects will be 18-65 yr. Because this is the first evaluation of methadone for outpatient anesthesia, children and older patients will not be studied (because of declining methadone elimination and increased risk of respiratory depression with age[26,27]). Such studies may ensue after safety is established in the present investigation. Sample size calculations show that 300 evaluable (completing 30d follow-up) patients are needed in each of the 2 study cohorts (600 total). Change in scheduled operation, prolonged (>1d) stay of scheduled short-stay (next day discharge) patients, unanticipated admission of same-day patients, or patient withdrawal has occurred in ~10% of our study patients to date. This, combined with post-op loss to follow-up (see below), suggests a potential overall drop-out rate before completion of 30d follow-up of <15%. Hence, to ensure 300 pts evaluable at 30d, a conservative 25% drop-out is estimated and 375 pts in each of the 2 study cohorts will be randomized (750 total). The Duke Department of Anesthesiology provides anesthetics for >66,000 procedures per year. The main campus of Duke University Health System includes Duke University Hospital which is a 957 bed facility. In 2016 there were 41,408 patients admitted and 1,119,151 outpatient visits. Duke University Hospital includes the Duke North Hospital/Duke Medical Pavilion (~54 ORs), the Children's Health Center, the Duke Eye Center (6 ORs), and Ambulatory Surgery Center (9 ORs). Between the Duke North Hospital/Duke Medical Pavilion and Ambulatory Surgery Center there were 34,492 anesthetics performed in 2017. These included, for example, 375 laparoscopic cholecystectomies and 269 laparoscopic hysterectomies ± salpingoopherectomies, further supporting specific feasibility. If enrollment lags, or for strategic advantage, Duke Regional and/or Duke Raleigh Hospitals can be added as future sites.

4.0 Management of Intercurrent Events

4.1 Adverse Experiences

The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported

and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

4.2 Premature Discontinuation

If a subject withdraws from the study before the administration of study drug, or there is a protocol violation, the subject will be replaced in order to provide the required number of subjects. Dropouts and withdrawals (after study drug administration) will not be replaced, in case this is not random but outcome-related. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study.

4.3 Potential Risks

Risks of being in this study are not materially different from those of surgery and anesthesia in general. Clinical opioid side effects are expected to be no different between the various opioids administered during and after anesthesia. The most common side effect of intraoperative and postoperative opioids such as methadone, fentanyl, hydromorphone and morphine is mild sedation, the magnitude of which is not different between the various opioids to be used, at the expected doses. The most common adverse effect of opioids is nausea and/or vomiting, which is not different between the various opioids to be used. Postoperative nausea and/or vomiting are also influenced by other drugs used intraoperatively. Respiratory depression is a potential concern with all opioids, but has not been problematic or different between opioids at the doses of methadone that have been used in similar previous studies, and not materially different than that from morphine, fentanyl and hydromorphone. Clinical data are collected for all enrolled patients, so there is also a potential risk of breach of protected health information.

4.4 Procedures to Minimize Potential Risks

a. Recruitment and Informed Consent. The study will be conducted under appropriate Duke University IRB protocol and consent form approvals. The study will be conducted under the supervision of the PI, who is a Board-Certified anesthesiologist with decades of experience in the conduct of human volunteer studies, and Co-Investigators, who are Board-Certified Anesthesiologists or Surgeons. Potential subjects will be approached in the pre-operative assessment clinic, or identified through IRB-approved review of the surgical schedule prior to their surgery, at which time they will be contacted and asked if they are interested in participating. An IRB-approved phone screen will be conducted and a consent visit scheduled in advance of surgery for subjects that wish to participate. This visit may also occur on day of surgery when allowing sufficient time for explanations, questions and answers. If interested and willing, subjects might also be fully consented using IRB approved eICF. All enrolled subjects must provide informed consent, evidenced by signing an informed consent document.

b. Protections against Risk.

i) Eligibility criteria exclude patients with known renal or hepatic disease, which may affect opioid disposition, as well as pregnant or nursing females. Patients with known history of hypersensitivity to opioids or, conversely, are opioid tolerant (e.g. preoperative methadone therapy or use of fentanyl or buprenorphine transdermal patches) are also excluded. For safety reasons, children and patients older than 65 yr are not studied, because of declining methadone elimination and increased risk of respiratory depression with age.

ii) Methadone dosing is fixed, using ideal body weight, rather than actual body weight, to obviate risk of excessive dosing due to obesity. The investigational pharmacist will be unblinded.

iii) Patients will have only clear liquids 6 hours before anesthesia, per standard of care. If nausea and/or vomiting occur, they will be treated using the standard of care for all post-anesthesia nausea and vomiting. Mild respiratory depression is defined as respiratory rate <8/min in adults. Severe depression will be defined as a patient with respiratory rate < 6/min. If treatment is required, naloxone will be used. Patients in the hospital are routinely periodically monitored by blood pressure and/or pulse oximetry, and receive supplemental oxygen if dictated, according to standard anesthesia practice.

iv) Research subjects will receive pre-operative, intra-operative and post-operative routine monitoring by anesthesiology and nursing staff.

v) The risk of breach of protected health information will be minimized by limiting the number of people within the research group who have access to identified data. Data are collected and stored via REDCap. The REDCap servers are securely housed in an on-site limited-access data center managed by the Division of Biostatistics. All web-based information transmission is encrypted, and the data is stored on a private, firewall protected network. No identifiable data will be stored on personal computers or laptops. Data will be exported from REDCap for statistical analysis with patient identifying information removed. The consent form, medical information, flow-sheets, will be stored under lock and key (office, file cabinet) and only the PI, physician investigators, and research team will have access.
vi) With regard to determination of CYP2B6 (or other) genotype: 1) CYP2B6 is not associated with any disorder(s), syndrome(s), or adverse condition. 2) Samples will be kept confidentially. They will be coded, with a key to the code linking code numbers to names kept at a separate location, under lock and key. 3) The link to identifiers will be destroyed at the end of the study. 4) Testing will not provide evidence of previously undiagnosed or unrecognized illness, or susceptibility to illness. 5) Samples will not be used for any purpose other than to study genes related to study drug disposition and response. 6) Blood samples will not be used to establish permanent cell lines. 7) Data will be stored under lock and key (office, file cabinet) and only the investigators will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 8) Genetic study data will not be entered in subjects' medical records. 9) Studies are not likely to result in findings that meet the National Bioethics Advisory Commission criteria for disclosure. 10) Genetics counseling will not be available to subjects, as they will not be informed of results and there are no know implications with respect to disease. 11) DNA samples will stripped of identifiers and given a separate code numbers unrelated to the subjects' study identification numbers. The code key will be kept by the PI under lock and key.

4.5 Data and Safety Monitoring Plan

The specific monitoring plan for this investigation is commensurate with the risks, size and complexity of the investigations planned. The potential risks are attributable to the use of opioids (fentanyl, hydromorphone, morphine, methadone) intraoperatively and postoperatively (recovery room). Based on literature reports, use of standard-of-care drugs throughout the investigation, sample size, the relatively low risk nature of the protocol, and clinical experience to date with this protocol (Preliminary Results), the PI and any CoIs are involved in the monitoring plan, rather than a full DSMB. These individuals will review the annual summary of adverse events. In addition, they will review all reports of an Unexpected Serious Adverse Event, or an Unexpected Adverse Event as soon as they are known.

All adverse events will be described, recorded and reported according to GCP and IRB regulations. All subjects' actual reasons for study discontinuation (not just other, subject request, investigator request, other nonspecific designation) will be captured accurately to provide data for a risk-benefit assessment. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events - CTCAE (v4.03 or 5.0 as appropriate).

5. HUMAN SUBJECTS RESEARCH

5.1 Protection of Human Subjects

This is a randomized clinical trial in which patients comprising two cohorts undergoing elective short-stay or same-day surgery will be randomized to receive one of two standard opioid regimens: intraoperative and postoperative (recovery room) long-duration methadone or as needed short-duration opioids (e.g. fentanyl, hydromorphone, morphine) intraoperatively and postoperatively (recovery room). Two cohorts (short-stay and same-day surgery) are studied because of potential differing opioid requirements or outcomes, potentially related to surgical intervention. The study will be conducted under appropriate Duke University IRB protocol and consent forms, and under the supervision of the PI, a Board-Certified and GCP-certified anesthesiologist with several decades experience in human studies.

5.2 Sources of Materials

The electronic medical record will be used to determine opioid amounts (morphine equivalents) administered during surgery, until discharge, and after discharge, as well as other drugs for treatment and/or prophylaxis of possible opioid side effects. Data collected will include demographics, co-morbidities and diagnoses, vital signs, laboratory results, and medications. Only the research team will have access to individually identifiable patient information, and clinical data will be de-identified after analysis. Data will be collected from medical records by a study team member who has completed appropriate training in HIPAA and clinical research and who is approved by the IRB at Duke University. Data from the electronic (REDCap) data capture system employed to assess daily drug dosing history, pain, and side effects from after hospital discharge until the postop clinic visit at approximately 30 days will be stored on secure servers. A manual pill count is performed, by subjects and recorded in a REDCap survey. Data are collected from the medication monitoring bottles which provides date/time stamp for pill bottle openings. Subjects will receive emailed REDCap surveys at 6 and 12 months after discharge to inquire about pain, opioid, use, return to work, ADLs, and quality of recovery.

5.3 Recruitment and Informed Consent

Potential subjects will be approached in the pre-operative assessment clinic, or identified through IRB-approved review of the surgical schedule prior to surgery, at which time they will be contacted and asked if they are interested in participating. An IRB-approved phone screen will be conducted and a consent visit scheduled in advance of surgery for subjects that wish to participate. This visit may also occur on day of surgery allowing sufficient time for explanations, questions and answers. If interested and willing, subjects might also be fully consented using IRB approved eICF. All enrolled subjects must provide informed consent and evidenced by signing a written informed consent document.

5.4 Potential Benefits of the Proposed Research to Human Subjects and Others

Long-duration vs short-duration opioids may decrease the need for additional opioids in the immediate postoperative period, decrease possible side effects of opioids, improve immediate postoperative pain relief and may decrease the occurrence of chronic postoperative pain.

Successful completion of this research is expected to result in improved outpatient surgical care, enhanced patient recovery and pain management requiring less post-operative opioids, and a concomitant decrease in risk of persistent post-surgical pain. Anesthetic risks associated with long-duration and short-duration opioids are similar, and, in light of improved pain relief demonstrated in preliminary studies and the opportunity to improve the management of post-surgical pain, the potential benefits outweigh potential risks, and there is sufficient clinical equipoise to justify conducting this research.

5.5 Importance of Knowledge to be Gained

This research addresses critical questions in medicine that have profound implications to society. By seeking improved methods of post-surgical pain management, this work has implications for developing one arm of a national strategy for potentially affecting opioid misuse and the addiction epidemic is a reality. Outcomes of this research may shift the prevailing anesthesia paradigm away from short-duration opioids to long-duration opioids, which potentially would optimize patient recovery as well as decrease requirements for postoperative opioids.

5.6 Inclusion of Women and Minorities

Studies actively encourage the participation of women. Women of childbearing potential are not excluded. Pregnancy testing is performed as standard of care for surgical patients. Studies actively encourage the participation of minorities. Sex and minority recruiting typically matches the demographic composition of the Barnes-Jewish Hospital patient population from which subjects will be recruited (72% Caucasian, 24% African American, 4% Asian), subject to the actual ethnic, sex, and racial makeup of the surgical population.

5.7 ClinicalTrials.gov Requirements

The research will be registered in ClinicalTrials.gov once the protocol has been reviewed and approved by the Duke University IRB.

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