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Satisfactory Analgesia with Minimal Emesis in Day Surgeries (SAME DayS): a protocol for a randomised controlled trial of morphine versus hydromorphone

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ABSTRACT

Introduction There has been an exponential increase in the number of ambulatory surgeries (AS). Pain and postoperative nausea vomiting (PONV) affects the recovery, discharge and overall satisfaction of patients having AS. Opioids remain the primary modality for moderate to severe pain. Since there is no perfect opioid, physicians should ideally use the opioid that optimally balances benefits and risks. Present decisions on the choice between morphine (M) and hydromorphone (HM) are based on individual experience and observation. Our primary objective is to compare the proportion of patients having AS achieving satisfactory analgesia without significant PONV when using M compared with HM. Secondly we will compare the proportion of patients with adverse events, analgesic used, patient satisfaction, time to discharge and postdischarge symptoms.

Methods and analysis This is a two-arm, multicentre, parallel group, randomised controlled trial of 400 patients having AS. Eligible patients undergoing AS of the abdominal and pelvic regions with a potential to cause moderate to severe pain will be recruited in the preoperative clinic. Using a computer-generated randomization, with a 1:1 allocation ratio, patients will be randomised to M or HM. Patients, healthcare providers and research personnel will be blinded. Study interventions will be administered in the recovery using equianalgesic doses of M or HM in concealed syringes. Patients will be followed in hospital and up to 3 months. Intention-to-treat approach will be used for analysis.

Ethics and dissemination This study has been approved by the Hamilton integrated research ethics board. We plan to publish our trial findings and present our findings at scientific meetings.

Trail registration number NCT02223377; Pre-results.

INTRODUCTION

The burden of pain and postoperative nausea vomiting (PONV) in ambulatory surgeries (AS)

It is estimated that currently around 70% of surgeries are being done as AS.1 Pain and PONV are recognised as the leading factors affecting its quality of AS,2 3 affecting the recovery, discharge and overall satisfaction of patients.4 5 Postsurgical pain is inadequately treated in 30%–40% of patients, and 20%–30% of patients having AS suffer from significant PONV.3 6 7 The time to discharge increases by 25% in patients having AS who develop PONV,8 and a single episode of PONV can prolong the postanaesthetic care unit (PACU) stay by 25 min.9 Studies also show that patients rate PONV to be the most undesirable outcome associated with anaesthesia4 and are willing to spend up to US$100 for an effective antiemetic treatment.10

Opioids and the challenge of pain relief without side effects

For the management of postoperative pain, multimodal analgesia is frequently employed. Despite efforts to increase the use of other options, opioids have remained the primary modality to manage moderate to severe pain.7 Opioids are potent analgesics. They also cause several side effects such as drowsiness, sedation, PONV, itching and respiratory depression. Morphine (M) has been

Strengths and limitations of this study

► This trial will inform the relative benefits and risks of morphine versus hydromorphone in patients having ambulatory surgeries.
► Our pragmatic design mirrors everyday practice, and this will facilitate knowledge translation and clinical applicability.
► This trial will also evaluate postdischarge symptoms, including persistent pain.
► The outcomes of pain and nausea, although measured using validated scales, suffer from their inherent subjective limitations.
► For equianalgesic dose ratio between morphine:hydromorphone, we have considered the most commonly used ratio of 1:5, although other ratios have been reported in literature.
considered the gold standard long-acting opioid, used widely for postoperative analgesia; however, hydromorphone (HM) is increasingly used in many centres and settings. Both M and HM are mu agonists and exert no ceiling effect for their analgesia; frequently, incomplete or inadequate analgesia is related to the appearance of side effects. HM is approximately five times more potent, and its distribution to cerebral tissues allows for easier titration.\textsuperscript{11} Presently, many believe that HM has a more favourable side effect profile compared with M,\textsuperscript{12,13} and at many centres, including ours, the use of HM is preferred as the first option for patient-controlled analgesia (PCA). It is also observed that healthcare providers may be willing to provide higher doses of HM compared with M in emergency departments as the actual quantity of drug is much smaller and therefore may cause less concern.\textsuperscript{14,15}

**Literature review and limitations within the existing evidence**
Our comprehensive search (up to 2016 September) involving PubMed, Embase and Cochrane databases did not identify any randomised controlled trial (RCT) comparing M and HM in patients having AS. However, we identified four studies that compared the use of intravenous M and HM in acute pain settings,\textsuperscript{16-19} and two among them were conducted in perioperative settings.\textsuperscript{18,19} Hong et al studied the difference in nausea between the two medications in 50 patients using PCA and found no difference.\textsuperscript{19} The long-acting study drugs were administered intraoperatively, without any standardisation of anaesthetic techniques. The study was also not blinded. Rapp et al compared the analgesia and side effects between the two medications in 61 surgical patients using PCA. They did not include any sample size calculation and also did not specify the primary outcome; however, they found the effects to be similar.\textsuperscript{18} Felden et al attempted to summarise the evidence in a systematic review and meta-analysis, published in 2013.\textsuperscript{11} Notably, they considered the use of M versus HM in both acute and chronic pain scenarios and also as any route of administration. For acute pain, they identified seven studies out of which four used intravenous administration. For meta-analysis, using a random-effects model, they reported effect sizes as standardised difference in means using Cohen’s d.

They pooled acute and chronic pain studies separately. For acute pain they observed that the analgesia was better with HM than M, demonstrated by a small difference in effect size ($d=0.228, p=0.012$), without any such difference in chronic pain. Based on the above literature, we feel that there is uncertainty and limited data to make reasonable conclusions for clinical practice.

**Patients symptoms after discharge**
It is increasingly appreciated that research and healthcare delivery have not focused enough on the postdischarge symptoms after AS. In this direction, two crucial aspects are to be considered. Compared with inpatients, patients having AS have less efficient access to healthcare services, and it could be wrong to assume that the burden of pain, nausea and other symptoms, after patients having AS, is not substantial.\textsuperscript{20} A significant number of patients suffer from continuing pain even at 24 hours,\textsuperscript{21} and studies have shown that differences in anaesthetic management and choice of medications have made a difference in patients’ perception of pain in AS in the first 24 hours and beyond.\textsuperscript{22} The review by Wu et al has noted that only 30%–42% of studies on patients having AS assessed for pain or PONV after discharge.\textsuperscript{20} Most were not randomised trials and many had methodological limitations. It has been observed that up to 10%–50% patients and 2%–11% patients suffer from moderate and severe level of chronic postsurgical pain (CPSP), respectively.\textsuperscript{23} Not many studies have assessed the incidence of CPSP in AS trials. Our study will allow us to estimate the overall burden on CPSP at 3 months in patients having AS.

**Clinical hypothesis**
In patients who undergo AS causing at least moderate pain, HM increases the proportion of patients demonstrating ‘satisfactory analgesia with minimal or no postoperative nausea-vomiting (PONV)’ (satisfactory analgesia with minimal PONV: pain<$4/10$ in numerical analogue scale, with minimal or no PONV $<2/5$ in verbal descriptive scale) compared with M, when both are administered intravenously, in equianalgesic doses, and are compared at 2 hours or earlier after surgery, in PACU.

**OBJECTIVES**
The primary objective is to compare the proportion of patients with Satisfactory Analgesia and Minimal Emesis (SAME) after AS, when M is compared with HM during their stabilisation in PACU.

Secondary objectives include comparison of patients with severe itching, significant sedation and respiratory depression in PACU; comparison of time to discharge from PACU and hospital; comparison of analgesic doses used as equivalent morphine units (EMU); comparison of postdischarge symptoms of pain, nausea and vomiting within the first 24 hours; and incidence and type of CPSP at 3 months after discharge.

**METHODS**
**Sites**
The study will be conducted at three hospitals affiliated with McMaster University, Canada: St Joseph’s Hospital, McMaster University Medical Centre and Juravinski Hospital.

**Design**
This will be a multicentre RCT with a two-arm parallel design (figure 1).

**Patient selection**
Patients will be screened during their ‘pre-anaesthetic visit’ by a trained research assistant (RA) using the following
selection criteria. Informed consent of willing patients will be obtained along with their baseline parameters.

**Inclusion criteria**
Age 18–70 years; patients of elective day surgeries within the scope of general surgical, gastrointestinal and gynaecological specialties; surgeries with a potential to cause moderate to severe pain (cholecystectomy, appendectomy, ovarian cystectomy, hernia repair) and ability to communicate in English.

**Exclusion criteria**
Not consenting; allergy to M or HM; patients for surgeries with potential to cause minimal pain (tubectomy, diagnostic laparoscopy, dilation and curettage); surgeries with planned surgical time <1 hour; patients for orthopaedic, urological, plastic or other surgeries planned for a nerve block; patient on regular opioid medication (intake >3 days/week); severe obesity (body mass index (BMI) >35); history of schizophrenia or bipolar disease; current history of opioid drug addiction; and patients with confirmed sleep apnoea. The baseline parameters will include recording of the following variables. (1) Apfel Score (for PONV prediction) collected on four items\(^\text{24}\); (2) Hospital Anxiety Depression Scale score collected on 14 items\(^\text{25}\); (3) Pain Catastrophizing Scale collected on 13 items\(^\text{26}\); (4) presence of preoperative pain in the surgical area—yes/no; (5) if present: is it mild/moderate/severe; and (6) presence of chronic pain (>4 months) in other parts of the body.

**Control of bias**

**Randomisation and allocation**
Treatment allocation will be done using a random, computer-generated table, with an allocation ratio of 1:1, using random permuted block sizes, with stratification based on each centre (three sites).

**Allocation concealment**
Study allocation will be handled by the respective pharmacy at each hospital site and concealed by providing sequentially coded and numbered syringe packets of study medications, labelled with serial numbers and no identifiers for the medication. The study packets (containing prepared study medication syringes) will be made available in a safe drug locker within a fridge at the respective PACU.

**Achievement of randomisation**
The randomisation for each patient would happen on the day of surgery, inside the PACU, by allotting the next available medication packet. To ensure that the respective
patient and medication is matched for subsequent analysis, the PACU nurse will attach the medication sequence number on the patient study records and also note down the patient hospital ID on the medication record log.

Achievement of blinding
Since the medication syringes contain clear solutions of study medications in EMU units, physicians, patients, the PACU nurses and RA are effectively blinded.

Application of interventions
The operating room (OR)
Patients included in the study would be managed according to the OR protocol. Patients will have preoperative dexamethasone as an intravenous infusion. As the nature of the included surgeries demands, patients will only have a general anaesthetic, without the use of study medications. The protocol would allow for the appropriate use of sedation, intravenous or inhalational anaesthetics, and intraoperative analgesia using any short-acting opioids. The use of study medications during surgery will not be allowed. All patients will have local anaesthetic infiltration as 20–30 mL using 0.25% bupivacaine with or without epinephrine, at the end of surgery.

PACU protocol
The PACU nurse will administer the medications to provide postoperative analgesia with equianalgesic doses of M or HM, administered in titrated doses. Syringes will be pre-prepared from the pharmacy in EMU; 1 mL=1 mg of M or 0.2 mg of HM. We have considered a potency ratio of 1:5 (M:HM), considered equivalent in literature. Analgesia will be provided according to the following guideline. A similar method has been advised to be safe and effective for titrated analgesia in PACU.

PACU protocol (titrate the opioid medication to achieve the desired pain score)
► Patient to be asked for their pain score, and if it is >4 out of 10 (NAS): to receive the first dose within 5 min after coming to PACU: 0.04 mg/kg morphine units (rounding off to the nearest 1 mL or 0.5 mL); with a maximum of 3 mg of morphine equivalents.
► Repeat doses: 0.02 mg/kg morphine units every 5–10 min to titrate for analgesia and side effects (rounding off to the nearest 1 mL or 0.5 mL).
► If no side effects observed, titrate to have analgesia: NAS<4/10.
► PONV observed: record it and treat it with antiemetics (ondansetron 1–4 mg intravenous, dimenhydrinate 25–50 mg).
► Sedation observed (<3 Ramsay Sedation Scale)—withhold the next dose and restart the bolus if the score is >3.
► Respiratory depression: withhold the next dose, treat with naloxone if necessary.
► Use ketorolac intravenous 15–30 mg as the rescue medication if the patient does not tolerate the study opioid or if the patient does not satisfy the success of satisfactory analgesia even at 1 hour.

Day surgery unit (DSU) protocol
The DSU nurse will follow patient and collect the relevant outcomes before hospital discharge. In DSU, patients shall be offered oral analgesia (oxytocet (oxycodeone+acetaminophen), or tylenol #3 (codeine+acetaminophen)) and antiemetics as necessary. Relevant secondary outcomes are noted before the discharge of patients.

Follow-up
Patients will be followed up by a phone call and a mailed letter at 24 hours post surgery and at 3 months, respectively. Participant flow through the study is shown in figure 1 (Consolidated Standards of Reporting Trials (CONSORT) flow chart).

Outcomes
Primary outcome and measurement
Proportion of patients achieving SAME, compared between the two groups, at or before 2 hours after surgery. Patient should satisfy a pain score ≤4/10 in numerical rating scale (NRS) (0–10) with minimal nausea vomiting <2/4 in verbal descriptive scale (VDS). These observations will be made by the PACU nurse with clear guidance on deciding whether a patient satisfied the outcome or not.

Secondary outcomes and measurement
The following secondary outcomes will be captured during the in-hospital follow-up of study patients:
► Proportion of patients with severe itching: measured as visual analogue scale (VAS) >5/10.
► Proportion of patients with severe sedation: measured as Ramsay sedation score >5/6.
► Proportion of patients with respiratory depression: patients needing naloxone treatment.
► Differences in total analgesic used in PACU: mean differences in EMU.
► Differences in time to discharge (or readiness) from PACU: time in hours.
► Differences in time to discharge (or readiness) from hospital: time in hours.
► Differences in patient satisfaction scores: mean differences in 0–10 VAS.

Tertiary outcomes and measurement
All outcomes after hospital discharge will be considered as tertiary outcomes and collected at two different time points: 24 hours after surgery and at 3 months.

Outcomes at 24 hours
Patients will be approached by 1–2 phone calls done the next day; if unanswered, a repeat call will be made on the subsequent day (second day after discharge) to ask the following questions.
1. What was your average pain score over the last 24 hours in 0–10 NRS scale after you were discharged home?
200 per group for a total of 400 patients. This was estimated using power and sample size software program by Vanderbilt University (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize#PS:_Power_and_Sample_Size_Calculation), V.3.0.43.

### Statistical analysis

The trial will be reported as per the CONSORT standards for reporting randomised trials.\(^3^0\) The study will be analysed using an intention-to-treat (ITT) approach. For ITT, we will analyse patients within their randomised groups. We will use multiple imputation strategy to account for missing outcomes in ITT. Since we used a randomisation stratified on the basis of site, binary outcomes will be compared using Mantel-Haenszel \(\chi^2\) test and continuous outcomes using analysis of variance (ANOVA).\(^3^1^\)

Among the baseline variables, higher BMI, higher Apfel score, anxiety, depression, catastrophising, presence of moderate to severe preoperative pain in the surgical area and presence of chronic pain in other parts of the body are known to be associated with higher pain or increased chances of PONV.\(^3^2^\) Similarly, intraoperative factors such as dose of dexamethasone, total intraoperative opioid used (morphine equivalents), duration and type of surgery (laparoscopic vs open) are known to influence postoperative outcomes of analgesia and PONV. Sensitivity analysis will be conducted to explore the influence of these factors on the outcomes with multivariable logistic analysis using logistic regression for binary outcomes and linear regression continuous outcomes. For the regression model, we will use appropriate interaction terms between the subgroup variable and the treatment group. We will check for the residual to assess model assumptions and goodness of fit. Up-to-date versions of SAS and SPSS will be used to conduct all analyses. For all analyses, we will use a two-sided test with alpha=0.05 for significance. Dichotomous outcomes will be reported as relative risk and relative risk reductions and continuous outcomes as difference in means with SD. Precision will be reported using 95% CI. List of outcomes and their analysis is provided in table 2.

### Project coordination and reporting

This trial will be coordinated from the research office, Department of Anesthesia, and conducted at three hospital sites affiliated with McMaster University, Hamilton: St Joseph’s Hospital, McMaster University Medical Centre and Juravinski Hospital.

### Data management and quality control

All study data including case record forms (CRFs) of each patient shall be securely stored at the central office. A summary table indicating study timeline from enrolment to final follow-up (http://www.spirit-statement.org/title/) shall be included for each patient. CRFs will be collected as paper forms. They shall be periodically cross-checked for completeness and entered into a suitable electronic master file. All reports of incorrect randomisations, protocol violations or incomplete data shall be noted.
### Table 2  List of outcomes, measurement and analysis

| Outcome measure                                      | Measurement                                      | Time of measurement                                      | Analysis method       |
|------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------|-----------------------|
| **Primary outcome**                                  |                                                  |                                                           |                       |
| Satisfactory analgesia with minimal PONV             | Number of patients with NRS<4/10 and VDS<2/5    | At 2 hours or at the time of discharge from PACU         | M-H $\chi^2$          |
| **Secondary outcomes**                               |                                                  |                                                           |                       |
| Severe itching                                       | Number of patients with VAS>5/10                 | At 2 hours or at the time of discharge from PACU         | M-H $\chi^2$ or Fisher's test |
| Severe sedation                                      | Number of patients with Ramsay score>3/6        | At 2 hours or at the time of discharge from PACU         | M-H $\chi^2$ or Fisher's test |
| Severe respiratory depression                        | Number of patients needing treatment             | At 2 hours or at the time of discharge from PACU         | M-H $\chi^2$ or Fisher's test |
| Use of rescue analgesia                              | Total dose used per patients as a rescue therapy | At 2 hours or at the time of discharge from PACU         | ANOVA                 |
| Mean dose of opioid analgesic used in PACU           | Dose of analgesic used per patient in EMU       | At the time of hospital discharge                        | ANOVA                 |
| Patient satisfaction—mean score (0-10)               | VAS 0-10; 0=completely unsatisfied; 10=extremely satisfied | At the time of hospital discharge                        | ANOVA                 |
| **Tertiary outcomes**                                |                                                  |                                                           |                       |
| Average pain score over the last 24 hours            | Comparison of mean pain scores NRS 0-10          | 24 hours after surgery                                    | ANOVA                 |
| Nausea severe enough to need treatment after discharge| Number of patients                              | 24 hours after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Vomiting severe enough to need treatment after discharge| Number of patients                              | 24 hours after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Requiring a ER visit or readmission                  | Number of patients                              | 24 hours after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Persistent pain in the surgical area                 | Number of patients                              | 3 months after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Intensity of pain                                    | NRS 0-10                                        | 3 months after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Interference in daily activities                     | Comparison of mean BPI seven items with 0-10 scale| 3 months after surgery                                    | ANOVA                 |
| Global impression of change                          | 0-7 Likert scale                                 | 3 months after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Analgesic use for>1 month                            | Number of patients                              | 3 months after surgery                                    | M-H $\chi^2$ or Fisher's test |
| Sensitivity analysis                                 |                                                  |                                                           | Multivariable regression |

ANOVA, analysis of variance; EMU, equivalent morphine units; ER, emergency room; M-H, Mantel-Haenszel; NRS, numerical rating scale; PACU, postanaesthetic care unit; PONV, postoperative nausea vomiting; VAS, visual analogue scale; VDS, verbal descriptive scale.
Risk assessment and protocol adherence
This trial does not entail any higher risk than the standard of care to the patients. This is a pragmatic trial and involves the use of medications of known benefit and in clinically acceptable doses. It also involves use of intraoperative short-acting opioids in the form of fentanyl or sufentanil or remifentanil in small boluses or infusion. Although this may be a slight departure from the normal practice for some, we do not anticipate this to be a major issue as the surgeries would be of 1–2 hours duration. Patients can be effectively and safely managed with short-acting opioids until patients are shifted to PACU. The protocol also involves the use of study medications in PACU at an initial dose of 0.05 mg/kg, followed by 0.03 mg/kg EMU boluses. Studies have shown that intravenous morphine titration in PACU after moderately painful surgeries requires a mean morphine dose of 0.17±0.10 mg/kg. Only doses as high as 0.15 mg/kg were found to be associated with significant adverse effects.

Patient and public involvement
Patients and public were not directly involved in the development of this study protocol. However, our study outcomes were guided by patient preferences expressed in previous studies, especially as it concerns AS. We will disseminate results to the study participants through the journal publication, as well as from our research website.

DISCUSSION
This RCT looks at the use of M and HM in patients having AS and compares the clinical effectiveness in achieving effective analgesia with minimal PONV. It allows for physicians to make a choice based on evidence rather than individual observations. The perceived advantages of the study include better analgesia, fewer side effects, early discharge, reduced use of medications, less overall cost and better patient satisfaction. These are noted to be reflective of the most ideal outcomes for an AS setting. The study will also provide an estimate of incidence of pain, nausea and vomiting after discharge, within the first 24 hours after surgery, and PPSP at 3 months.

Potential pitfalls
The primary outcome of SAME is being measured using subjective pain scale of NRS and VDS for nausea vomiting. Although there are inherent limitations of such scales, they are widely used in practice and are well validated. For equianalgesic dose ratio between M:HM, we have considered the most commonly used ration of 1:5, although other ratios have been reported in literature.

ETHICS AND DISSEMINATION
The study has been approved by the Hamilton integrated research ethics board. We plan to report and publish our study findings in a high-impact medical journal, with online access. We also plan to present it in select conferences and scientific meetings.

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Contributors
HS: primary investigator involved in the study design, protocol writing and study conduct. JP: co-primary investigator involved in the study design, protocol writing and study conduct. PL: co-investigator involved in protocol writing and study conduct. PJD, MB and LT: co-investigators involved in assisting with study methodology, protocol writing, supervision and interpretation of the trial.

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Competing interests
None declared.

Patient consent
Not required.

Ethics approval
Hamilton Integrated Research Ethics Board, McMaster University, Canada.

Provenance and peer review
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