Most Effective Opioid Analgesia in Ambulatory Surgeries: a randomized control, investigator blinded, parallel group with superiority design study of Morphine versus Hydromorphone

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Abbreviations to terms used

M: Morphine	SAME: Satisfactory Analgesia with Minimal Emesis
HM: Hydromorphone	PACU: Post Anesthesia Care Unit
AS: Ambulatory Surgeries	PONV: Post Operative Nausea Vomiting
ER: Emergency Room	NAS: Numerical Analogue Scale
OR: Operating Room	VDS: Verbal Descriptive Scale
DSU: Day Surgery Unit	EMU: Equivalent Morphine Units
RA: Research Assistant	PCA: Patient Controlled Analgesia
CRF: Case Record Form	CPSP: Chronic postsurgical pain

Background and Rationale

There has been an exponential increase in the number of day case surgical procedures also called as ambulatory surgeries (AS), over the last 2 years.[1] Currently around 70% of procedures are being done as AS, with known benefits to patients and hospitals.[2] Its efficiency and cost effectiveness depends upon its organization and delivery of services. Pain and PONV are recognized as the leading factors affecting the quality of services delivered under AS,[1,3] and they affect the recovery, discharge, and overall satisfaction of patients.[4,5] According to literature, postsurgical pain could be inadequately treated in 30%-60% of patients and 30%-40% of AS patients suffer from significant PONV.[3,6,7] It is estimated that a single episode of PONV can prolong the PACU stay by 25 mins,[8] and patients rate PONV to be the most undesirable outcome associated with anesthesia.[4] Despite the increasing use of non-opioid analgesics, opioid analgesics have remained the primary modality in moderate to severe pain.[7] They cause several side effects such as drowsiness, sedation, PONV, itching and respiratory depression. Appropriate selection of opioid medications becomes significantly important to deliver safe and effective analgesia with minimal side effects. Although M has been the most commonly used medication, HM is also being increasingly used.[9] We do not yet know whether HM is more effective than M in AS patients. Both M and HM exert no ceiling effect for their analgesia, and by this nature incomplete or inadequate analgesia is related to the appearance of side effects.[10] Hence clinical effectiveness of opioids, relative to each other, is reflected not just by satisfactory analgesia, but by a combination of 'satisfactory analgesia with limited side effects'. Clinical observation suggests that HM is clinically better by providing superior or equivalent analgesia with decreased side effects.[9] HM is a semi-synthetic morphine derivative that differs from M in its position 6 of the benzol ring, where it has a keto-group instead of a hydroxy group, making it

5–10 times more potent and enhances its distribution to cerebral tissues, making for easier titration.[9] The t1/2 Ke0 (transfer life from plasma to effect site) is 1.6hr – 4 hr for M, compared to 18-38 min for HM.[9,10] It is observed that health care providers may be willing to provide higher dose of HM compared to M in EMU, as its actual quantity of drug is much smaller and therefore appears to cause less concern.[12, 13] Our literature review showed that there are no previous studies comparing these 2 medications in AS patients. The lone systematic review compared various acute and chronic pain studies, in various routes of drug administration.[9] Of the 11 studies identified; only 4 were done in acute pain settings.[13-16] Two of them were done by the same author in ER settings. Chang et al noted that HM reduced the mean pain scores by 1.3 units [95% CI= (-2.2 to -0.5)] compared to M in 198 adults treated in ER.[12,13]. However it did not show much difference in geriatric population.14 In perioperative settings, Hong et al studied the difference in nausea between the 2 medications in 50 patients using PCA and found no difference.[15] Rapp et al studied various effects between the 2 medications in 61 surgical patients using PCA. There is not much clarity about their primary outcome; however they found the effects to be similar.[16] Both these studies had smaller sample sizes. The meta-analysis performed demonstrated that the HM does provide better analgesia than M, with a small effect size; Cohen's d=0.266 (p=0.012).[9] Looked at acute pain alone it was statistically significant (p=0.006), compared to chronic pain (p=0.889). It was noted that that there is a definite lack of comparative studies between them in surgical settings.

Patients Symptoms after Discharge

It is being appreciated that, research and health care delivery have not focussed much on the post discharge symptoms after day surgeries. In this direction, two crucial aspects are to be considered. Compared to inpatients, ambulatory surgery patients have less efficient access to health services.[18] It is wrong to assume that the burden of pain, nausea and other symptoms, after ambulatory surgery patients, is not substantial. A significant number of patients suffer from continuing pain even at 24 hours, or a week after surgery.[19] Up to 1/3rd or more number of patients suffer from nausea or vomiting after surgery. Studies have shown that differences in anesthetic management, and choice of medications (even with non-analgesic medications such as propofol or sevoflurane) have made a difference in patient's perception of pain in ambulatory surgeries in the first 24 hrs, and beyond.(19) A systematic review noted that only around 30%-42% of studies on ambulatory surgery patients, assessed for pain, nausea, and vomiting after discharge.[20] Due to significant heterogeneity, and study limitations, appropriate figures of observed incidence could not be calculated. Several of the included studies were also not well designed. Similarly, day surgery patients can also suffer from chronic postsurgical pain (CPSP), at 1 year or more after surgeries. It has been observed that up to 10%-50% patients, and 2%-11%

patients, suffer from moderate and severe level of CPSP.[21] The definition of CPSP, in terms of the duration after surgery, has not been clearly identified. However, persistence beyond 2 months is normally considered as CPSP.[22] Specific to day surgeries, not many studies have assessed the incidence of CPSP and its predictive factors. A recent, large observational study, involving 908 patients, observed a CPSP (moderate to severe) rate of 15.3% after day surgeries. [23] They found that surgical specialty, preoperative pain, preoperative analgesic use, acute postoperative pain, surgical fear, lack of optimism and poor preoperative quality of life, as factors predictive of CPSP.

Hence, we will also look for any differences in pain, nausea and vomiting over the first 24 hrs after the surgery, along with chances of readmission or ER visits within the same period, post discharge. At 3 months, we will look for the incidence of persisting pain after surgery.

Hypothesis

In patients who undergo ambulatory surgical procedures causing at least moderate pain, hydromorphone (HM) increases the proportion of patients who would demonstrate 'satisfactory analgesia [=<4/10 NAS] with minimal or no postoperative nausea-vomiting (PONV) [<2/5 VDS]' as compared to morphine (M), when both are administered intravenously, in equianalgesic doses, and are compared at 2 hours after surgery in PACU.

2. Specific Objectives

The primary objective of this study is to compare the proportion of patients with SAME (satisfactory analgesia and minimal emesis) after AS, when using M compared with HM, during the immediate postoperative hospital stay.

Secondary objectives include:

1. Total dose of analgesic used in PACU, in morphine equivalents,
2. Time to discharge or readiness to discharge from the DSU,
3. Proportion of pain, and its comparison after discharge, within 24 hours,
4. Proportion of nausea, and its comparison after discharge, within 24 hours,
5. Proportion of vomiting, and its comparison after discharge, within 24 hours,
6. Incidence of CPSP at 3 months after discharge

The tertiary objectives include:

1. Proportion of patients with severe itching,

2. Proportion of patients with significant sedation,
3. Proportion of patients with significant respiratory depression,
4. Patient satisfaction score at the time of discharge,
5. Time to discharge or readiness to discharge from the PACU,
6. Use of ketorolac as a rescue medication,

METHODS

The study is designed as a multisite, 2 arm, parallel, superiority design with randomization of patients and blinding of patients, health care providers (physicians and nurses) and research personnel (research coordinator and data analyst). Patients will be stratified based on site and laparoscopic/open surgeries. Intention to treat approach will be used for design and analysis.

Patient Selection and Recruitment: Patients', who undergo AS of the abdominal and pelvic regions, within the scope of general surgical (GS), gastrointestinal (GI) and gynecological (GYN) specialties, shall be considered. Patients shall be considered for the study if they fulfill the following selection criteria. They would be screened on the day of their preoperative appointment, assessed for eligibility and then if they agree, obtain consent.
The inclusion criteria will include: age 18 yrs to 70 yrs-; ambulatory surgeries producing at least moderate pain-such as cholecystectomy, appendicectomy, ovarian cystectomy, inguinal hernia repair, abdominal wall hernias; and an ability to communicate in English.
Exclusion criteria will include: allergy to M or HM; patient on regular chronic opioid medication; patient uncontrolled systemic disease; severe obesity with a BMI >35; significant psychological impairment; history of drug addiction or dependence; any planned regional or nerve block other than local anesthesia infiltration; patients with confirmed sleep apnea; emergency surgeries and urological surgeries.
Suitable patients will be screened before their visit to 'pre-anesthetic visit'. During their visit, they will be approached by a trained RA, involved with the study. Relevant information will be provided, along with a letter of information about the research study. Consent of willing patients will be obtained, along with their baseline, and demographic variables. The consent will include the study process, and also willingness to be followed, and contacted at 24 hours and at 3 months after surgery.
On the day of surgery, at DSU, patients' consent will be confirmed. Relevant baseline variables of the recruited patients shall be noted (appendix 1). The concerned OR anesthesiologist is informed of the patient's inclusion to the study and reinforced about the study methodology (appendix 2).

Allocation and Randomization: Treatment allocation will be done using a random, computer generated table, with an allocation ratio of 1:1, using random permuted block sizes. Stratification based on each centre (3 sites). These syringes (4*10 mls)-in sealed packages, labelled with serial numbers and no identifiers for the medication, shall be deposited in a safe drug locker, within the fridge, at the respective PACU. The actual randomization, for each patient happens as they enter into the PACU after surgery. The PACU nurse allotted for that patient will obtain the next medication package in series to be used for that patient. To ensure that the respective patient and medication is matched for subsequent analysis, the nurse will attach the medication sequence number on the patient study records, with no identifiers of actual drug. The PACU nurse shall also note down the patient hospital ID on the medication syringe, once it is taken out, to ensure there is no mix up.

Blinding: The study allocation will be blinded to patients, treating nurses, physicians, research assistant and investigators. The allocation order will be available only to the person responsible for randomizing and the pharmacists involved in the study at each centre.

Application of Intervention:
The Operating Room Protocol: Patients included in the study need to be managed according the OR protocol provided in Appendix 2. In brief, the patient will only have a GA, with local infiltration provided at the end of the surgery. Long acting opioid medications (morphine and hydromorphone) are not administered in the OR. LA infiltration is done within a range of 20-30 mls (based on laparoscopic or open surgeries) using 0.25% bupivacaine with or without adrenaline.

PACU Stay: The actual study intervention (hence randomization) will only become applicable once the patient is moved to the PACU. Every patient will be treated as per the protocol during the intraoperative management, which primarily restricts the use of any study opioids. The details are provided in appendix 2. The nurse looking after the study patient in PACU will administer the medication as per the study protocol. This would include analgesia with equipotent doses of M or HM administered in titrated doses. Syringes will be pre-prepared from the pharmacy in EMUs; 1ml=1mg of morphine or 0.2 mg of hydromorphone. We shall consider a potency ratio of 1:5 (M: HM), considered equivalent in literature.[9] 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.[24] Readiness to discharge from PACU and outcomes are noted at 2 hrs, or at the time of discharge to DSU.

PACU Protocol (titrate the opioid medication to achieve desired pain score)

- Patient to be asked for their pain score, and if it is more than 4 out of 10 (NAS): to receive the 1st dose within 5 minutes after coming to PACU: 0.04mg/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 minutes 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.
- If Nausea-Vomiting observed: record it in the CRF provided and treat it with antiemetics (Ondansetron 1-4 mg IV, Dimenhydrinate 25-50 mg)
- If patient is too sedated (<3-Ramsey Sedation Scale)-withhold the next dose and restart the bolus if the score is >3
- If respiratory depression present, withhold the next dose, treat with Naloxone if necessary.
- Ketorolac IV 15-30 mg as rescue medication if patient does not tolerate the study opioid or if the patient does not satisfy the success of satisfactory analgesia at more than 1 hr.

DSU Stay and Protocol:

At the end of 2 hours or after satisfactory completion of primary endpoints, patients shall be transferred to DSU. At the DSU, in both groups, patients shall be given oral Oxycocet (combination of oxycodone and paracetamol) or Tylenol 3 (combination of codeine and paracetamol), as a PRN medication, if necessitated by the patient's pain. Nurses shall note down the occurrence of any pain and nausea necessitating treatment in the patient's CRF. Readiness to discharge home is noted down for each patient. The RA shall collect the CRFs from PACU and DSU and deposit safely in a locked filing cabinet.

Planned Outcomes: Our combined primary outcome will be proportion of patients with SAME, as compared between the 2 groups. Analgesia will be based on NAS 0-10 (appendix 3), and PONV will be based on VDS 0-5 (appendix 3). These observations will be made at the end of 2 hrs or before (corresponding to the time of discharge from PACU), by the PACU nurse, in the specified CRF. All the other outcomes to be recorded within the hospital, along with the time of their measurement and proposed analysis method are noted in table 1.

Sample Size Calculation: It was calculated based on the primary, binary outcome of proportion of patients with SAME, which will be compared using a chi-square test. According to literature,

approximately 30%-40% of patients are provided with inadequate analgesia after their AS,[25, 26] with a similar number also known to suffer from PONV after AS.[3, 24] Our chart reviews suggests that approximately 20% of patients suffer from inadequate analgesia with PONV using morphine. For a 2-sided test, with an alpha of 0.05 and a power of 90%, and with an estimated effect size of 10% (p1= 80% and p2= 90%), a sample size of 266 per group was calculated. However, for recruitment we shall have a target of 275 per group, for a total of 550 patients (rounding off). For the primary outcome analysis, we expect minimal loss through attrition as the study involves a follow up of few hours. The expected recruitment is approximately 20 cases per month at each of the 3 sites. We expect the trial to run for 10-12 months.

Table 1: Study Outcomes, and their Measurement and Analysis

OUTCOME MEASURE	**TYPE**	**MEASUREMENT**	**TIME OF MEASUREMENT**	**ANALYSIS METHOD**
Primary outcome **Satisfactory Analgesia with minimal PONV**	Binary	NAS=<4/10 VDS<2/5	At 2hrs or at the time of discharge from PACU	**Chi-square**
Severe Itching	Binary	VAS>5/10	At 2hrs or at the time of discharge from PACU	**Chi-square or Fisher's test (as appropriate)**
Severe Sedation	Binary	Ramsey Score >3/6	At 2hrs or at the time of discharge from PACU	**Chi-Square or Fisher's test (as appropriate)**
Severe Respiratory Depression	Count	All cases needing treatment as counts	At 2hrs or at the time of discharge from PACU	**Chi-square or Fisher's test (as appropriate)**
Use of Ketorolac	Continuous	Total dose used per patients as a rescue therapy	At 2hrs or at the time of discharge from PACU	**T test**
Mean dose of Analgesic Used	Continuous	Dose of Analgesic used per patient in EMU	At the time of hospital discharge	**T test**

Patient Satisfaction-Mean score (0-10)	Continuous	Mean Score calculated between 0 to 5 scale	At the time of hospital discharge	**T test**
Time to discharge from PACU	Continuous	Mean time in hrs	At 2hrs or at the time of discharge from PACU	**T test**
Time to discharge from the hospital	Continuous	Mean time in hrs	At the time of hospital discharge	**T test**

Outcomes at Post-operative Day 1:
Patients will be approached by 1-2 phone calls shall be done during the next day; if unanswered, a repeat call will be made on the subsequent day (2nd day after discharge); for responders, the following questions will be asked.

1. What was your average pain score over the last 24 hrs, in 0-10 NAS scale, after you were discharged home?

2. After discharge, did you have nausea-severe enough to require medications at home?

3. After discharge, did you have vomiting-severe enough to require medications at home?

4. After discharged home, did you require a visit to ER, or readmission?

Outcomes at 3 months:
Patients will be contacted by a mailed package at 3 months after surgery to collect the following outcomes.

1	Do you have Persistent Pain (which started with or after surgery), at or near the surgical area?	Yes or No
2	Intensity of Pain	NAS: 0-10
3	Brief Pain Inventory-Interference Items 7 Items: each item scored between 0-10	
4	Global Impression of Change	Likert scale 1-7

5	Analgesic Use: Did you have to use any pain medications for more than 1 month, to help with pain, which started with or after Surgery?	Yes or No

Statistical Analysis: The study will be analyzed using an intention to treat approach. The individual outcomes along with their respective analyses method have been listed within the table 1. Broadly the dichotomous outcomes will be reported as proportions and analyzed using a chi-square test to detect a significant difference ($p<0.05$). Precision will be reported using 95% CI. Continuous outcomes will be analyzed using an unpaired 2-tailed student t test for significance ($p<0.05$). Means and standard deviations shall be reported along with 95% CI. We also plan to perform logistic multivariable regression analysis to account for the influence of baseline covariates, which are listed in appendix 1. A sensitivity analysis will be performed to compare the effects of laparoscopic surgeries vs open surgeries.

Trial Management: This trial will be conducted at 3 hospital sites affiliated with McMaster University, Hamilton: St Joseph's Hospital, McMaster University Hospital and Juravinski Hospital.

Data Management and Quality Control: All study data including CRFs of each patient, shall be securely stored at the central office. A summary table indicating study timeline from enrollment to final follow-up (http://www.spirit-statement.org/title/) shall be included for each patient.[27] CRF's 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 randomizations, protocol violations or incomplete data shall be noted.

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 using only short acting opioids in the form of fentanyl or sufentanyl or remifentanyl in small boluses or infusion. Although for some this might differ from their normal practice, we do not anticipate this to be a major issue as the surgeries would be of 1-2 hrs duration and can be effectively and safely managed with short acting opioids until patients are shifted to PACU. Protocol also involves the use of study medications in PACU at an initial dose of 0.05mg/kg, followed by 0.03/mg/kg EMU boluses. Studies have shown that IV Morphine titration in PACU, after moderately painful surgeries

require a mean morphine dose of 0.17 +/- 0.10 mg/kg.[17,28] Only doses as high as 0.15mg/kg were found to be associated with significant adverse effects.[29]

Potential Pitfalls (Study Limitations): Despite being a randomized study, there exists the possibility of bias due to unequal distribution of unknown covariates**.** The primary outcome of SAME is being measured using subjective pain scale of NAS and VDS for emesis. Although there are inherent limitations of such scales, we think they are widely used in practice and are well validated. We have considered a potency ratio of 1: 5 (M: HM) as it is commonly used and supported by the literature. However, we do accept that there is a much wider range described in some studies.

STUDY SIGNIFICANCE:

The potential impact of the study could change the routine practice for anesthesiologists and other care providers. By choosing a better medication, physicians can be confident of their choice based on clear evidence, instead of a trial and error method in PACU management which usually leads to increased time with inferior results. The perceived advantages include better analgesia, less side effects, early discharge, reduced use of medications, less overall cost, and better patient satisfaction. These are truly reflective of what are proposed to be the most ideal outcomes for AS setting. [2] These results could facilitate early discharge will require lesser costs due to savings on manpower. The study will also provide an estimate of incidence of pain, nausea and vomiting after discharge, within the first 24 hrs after surgery. The burden of such a problem will help to organize better health service provision in future, for patients of day surgeries. The study will also give us an indication of incidence of persistent postoperative pain; and also whether better control of their acute pain makes an impact on the incidence and severity of persistent pain at 3 months.

REFERENCES

1. Sarin P, Philip BK, Mitani A, Eappen S, Urman RD. Specialized ambulatory anesthesia teams contribute to decreased ambulatory surgery recovery room length of stay. Ochsner J. 2012 Summer;12(2):94-100.
2. Troy AM, Cunningham AJ. Ambulatory surgery: an overview. Curr Opin Anaesthesiol. 2002 Dec;15(6):647-57.
3. Shnaider I, Chung F. Outcomes in day surgery. Curr Opin Anaesthesiol. 2006 Dec;19(6):622-9.
4. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg. 1999 Sep;89(3):652-8.
5. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiol Res Pract. 2011;2011:748031.
6. Lovatsis D, José JB, Tufman A, Drutz HP, Murphy K. Assessment of patient satisfaction with postoperative pain management after ambulatory gynaecologic laparoscopy. J Obstet Gynaecol Can. 2007 Aug;29(8):664-7.
7. White PF. Pain management after ambulatory surgery - where is the disconnect? Can J Anaesth. 2008 Apr;55(4):201-7.
8. Habib AS, Chen YT, Taguchi A, Hu XH, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. Curr Med Res Opin. 2006 Jun;22(6):1093-9.
9. Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, Geisslinger G,Lötsch J. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011 Sep;107(3):319-28.
10. Tramèr MR. Strategies for postoperative nausea and vomiting. Best Pract Res Clin Anaesthesiol. 2004 Dec;18(4):693-701.
11. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. Br J Anaesth. 2012 Feb;108(2):193-201.
12. Patanwala AE, Keim SM, Erstad BL. Intravenous opioids for severe acute pain in the emergency department. Ann Pharmacother. 2010 Nov;44(11):1800-9.
13. Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C, Gallagher EJ. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. Ann Emerg Med 2006; 48: 164–72.
14. Chang AK, Bijur PE, Baccelieri A, Gallagher EJ. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: a prospective, randomized, clinical trial. Am J Geriatr Pharmacother 2009; 7: 1–10.

15. Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 2008; 107: 1384–9.
16. Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW, Ching JM. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 1996; 82: 1043–8.
17. Odom-Forren J, Rayens MK, Gokun Y et al. The Relationship of Pain and Nausea in Postoperative Patients for One Week after Ambulatory Surgery. Clin J Pain. 2014 Nov 3. [Epub ahead of print], Anesthesiology 2002; 96:994–1003).
18. Wu CL, Berenholtz SM, Pronovost PJ, Fleisher LA. Systematic review and analysis of postdischarge symptoms after outpatient surgery. Anesthesiology. 2002 Apr;96(4):994-1003.
19. Ogurlu M, Sari S, Küçük M, Bakis M, Ugur B, Eshraghi YE, Galimberti F, Turan A. Comparison of the effect of propofol and sevoflurane anaesthesia on acute and chronic postoperative pain after hysterectomy. Anaesth Intensive Care. 2014 May;42(3):365-70.
20. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006 May 13;367(9522):1618-25.
21. Macrae WA. Chronic pain after surgery. Br J Anaesth 2001; 87(1): 88-98.
22. Hoofwijk DM, Fiddelers AA, Peters ML, et al. Prevalence and Predictive Factors of Chronic Postsurgical Pain and Poor Global Recovery One Year after Outpatient Surgery. Clin J Pain.2015 Jan 6.
23. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. Br J Anaesth. 2012 Feb;108(2):193-201.
24. Schug SA, Chong C. Pain management after ambulatory surgery. Curr Opin Anaesthesiol. 2009 Dec;22(6):738-43.
25. Rawal N. Analgesia for day-case surgery. Br J Anaesth. 2001 Jul;87(1):73-87.
26. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586.
27. Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. Anesthesiology. 2003 Jun;98(6):1415-21.
28. Aubrun F, Amour J, Rosenthal D, Coriat P, Riou B. Effects of a loading dose of morphine before i.v. morphine titration for postoperative pain relief: a randomized, double-blind, placebo-control study. Br J Anaesth. 2007 Jan;98(1):124-30.
29. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. Acta Anaesthesiol Scand. 2000 Apr;44(4):470-4.

APPENDIX 1: Study Patient Case Record Form with Details to be Recorded

DEMOGRAPHICS AND PATIENT INFORMATION TO BE OBTAINED FROM PATIENT RECORDS

Study Number: Site: SJH MUMC JH

1	Patient's Hospital ID Number		
2	Age		
3	Gender	M F	
4	Height		
5	Weight		
6	Allergy to NSAIDS	Y N	
7	Allergy to LAs	Y N	

INFORMATION TO BE GAINED FROM THE PATIENT MEETING

1	APFEL Score (for PONV prediction)		Collected on 4 items- separately
2	HADS Score (Hospital Anxiety Depression Scale)		Collected on 14 items- separately
3	PCS (Pain Catastrophizing Scale)		Collected on 13 items - separately
4	Presence of Preoperative Pain in the Surgical Area	Y N	
5	If YES: is it Mild/ Moderate/ Severe		
6	Presence of Chronic Pain (>4 months) in Other Parts of the Body	Y N	

7	If YES: is it Mild/ Moderate/ Severe		

SURGICAL DETAILS TO BE OBTAINED FROM THE SURGICAL RECORDS

1	Date of Surgery		
2	Diagnosis (Intraoperative)		
3	Actual Surgical Procedure		
4	Laparoscopic or Open	L O	
5	Surgeon		Initials
6	Start Time of Surgery		
7	End Time of Surgery		
8	Duration of Surgery		
9	Total Local Anesthetic Infiltration (mls)		

ANESTHESIA DETAILS TO BE OBTAINED FROM THE ANESTHETIC RECORD

1	Anesthesiologist		Initials
2	Dexamethasone 4mg or 8mg	Y N	
3	Midazolam	1 mg 2 mg	
4	Propofol (total dose used)		
5	Remifentanyl (total dose used)		
6	Fentanyl (total dose used)		
7	Sufentanyl (total dose used)		

8	Any continuous infusion used	Propofol ☐ Remifentanyl ☐	
9	Ondansetron Prophylaxis Dose		Given prior to extubation
10	Was there a delay in transferring patient to the PACU (applicable when the PACU is on hold-and protocol needs to be initiated by the OR anesthesiologist)	Y N	

APFEL SCORE: for Prediction of Post-Operative Nausea Vomiting

RISK FACTOR	SCORE (each gets 0 or 1)
Postoperative Opioids	
Non-smoker	
Female Gender	
History of PONV or Motion Sickness	
Total Score	

PCS: Patient Catastrophyzing Score:

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

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0 – not at all; 1 – to a slight degree; 2 – to a moderate degree;

3 – to a great degree; 4 – all the time

When I'm in pain ...

1☐ I worry all the time about whether the pain will end.

2☐ I feel I can't go on.

3☐ It's terrible and I think it's never going to get any better.

4☐ It's awful and I feel that it overwhelms me.

5☐ I feel I can't stand it anymore.

6☐ I become afraid that the pain will get worse.

7☐ I keep thinking of other painful events.

8☐ I anxiously want the pain to go away.

9☐ I can't seem to keep it out of my mind.

10☐ I keep thinking about how much it hurts.

11☐ I keep thinking about how badly I want the pain to stop.

12☐ There's nothing I can do to reduce the intensity of the pain.

13☐ I wonder whether something serious may happen.

...Total

Updated 11/11

HADS: HOSPITAL ANXIETY DEPRESSION SCORE

This questionnaire is designed to help us know how you feel. Read each item and place a firm tick in the box opposite the reply, which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick one box only in each section

1 I feel tense or wound up:
- Most of the time (3) ☐
- A lot of the time (2) ☐
- Time to time, occasionally (1) ☐
- Not at all (0) ☐

2 I still enjoy the things I used to enjoy:
- Definitely as much (0) ☐
- Not quite so much (1) ☐
- Only a little (2) ☐
- Hardly at all (3) ☐

3 I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly (3) ☐
- Yes, but not too badly (2) ☐
- A little, but it doesn't worry me (1) ☐
- Not at all (0) ☐

4 I can laugh and see the funny side of things:
- As much as I always could (0) ☐
- Not quite so much now (1) ☐
- Definitely not so much now (2) ☐
- Not at all (3) ☐

5 Worrying thoughts go through my mind:
- A great deal of the time (3) ☐
- A lot of the time (2) ☐
- From time to time but not too often (1) ☐
- Only occasionally (0) ☐

6 I feel cheerful:
- Not at all (3) ☐
- Not often (2) ☐
- Sometimes (1) ☐
- Most of the time (0) ☐

7 I can sit at ease and feel relaxed:
- Definitely (0) ☐
- Usually (1) ☐
- Not often (2) ☐
- Not at all (3) ☐

8 I feel as if I am slowed down:
- Nearly all the time (3) ☐
- Very often (2) ☐
- Sometimes (1) ☐
- Not at all (0) ☐

9 I get a sort of frightened feeling like "butterflies" in the stomach:
- Not at all (0) ☐
- Occasionally (1) ☐
- Quite often (2) ☐
- Very often (3) ☐

10 I have lost interest in my appearance:
- Definitely (3) ☐
- I don't take so much care as I should (2) ☐
- I may not take quite as much care (1) ☐
- I take just as much care as ever (0) ☐

11 I feel restless as if I have to be on the move:
- Very much indeed (3) ☐
- Quite a lot (2) ☐
- Not very much (1) ☐
- Not at all (0) ☐

12 I look forward with enjoyment to things:
- As much as I ever did (0) ☐
- Rather less than I used to (1) ☐
- Definitely less than I used to (2) ☐
- Hardly at all (3) ☐

13 I get sudden feelings of panic:
- Very often indeed (3) ☐
- Quite often (2) ☐
- Not very often (1) ☐
- Not at all (0) ☐

14 I can enjoy a good book or radio or TV programme:
- Often (0) ☐
- Sometimes (1) ☐
- Not often (2) ☐
- Very seldom (3) ☐

ANXIETY SCORE _____ DEPRESSION SCORE _____

OUTCOMES AT 24 HOURS

24 hours after surgery (telephonic follow up)

- One-two calls shall be done during the next day; if unanswered, a repeat call will be made on the subsequent day (2nd day after discharge)
- For responders, the following questions will be asked.

1. What was your average pain score over the last 24 hrs, in 0-10 NAS scale, after you were discharged home?

2. After discharge, did you have nausea-severe enough to require medications at home?

3. After discharge, did you have vomiting-severe enough to require medications at home?

4. After discharged home, did you require a visit to ER, or readmission?

OUTCOMES AT 3 MONTHS AFTER SURGERY

1. **Persisting pain after Surgery**: Yes or No

2. **If Yes: Intensity of Pain:** a score between 0-10

3. **Brief Pain Inventory Items Score:**

Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:			
1	General Activity	0-does not interfere 10-completely interferes	
2	Mood	0-does not interfere 10-completely interferes	
3	Walking Ability	0-does not interfere 10-completely interferes	
4	Normal Work (includes both work outside the home and housework)	0-does not interfere 10-completely interferes	
5	Relations with people	0-does not interfere 10-completely interferes	

6	Enjoyment of life	0-does not interfere 10-completely interferes	
7	Sleep	0-does not interfere 10-completely interferes	

4. **Patient Global Impression of Change:**

Since surgery, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

5. Analgesic Use:
Did you have to use any pain medications for more than 1 month, to help with pain, which started with or after Surgery?

Yes:

No:

APPENDIX 2: STANDARD ANESTHESIA PROTOCOL

- Only General Anesthetic
- No regional other than local infiltration as appropriate-to be documented
- Midazolam 1-2 mg –to be given as appropriate-to be documented
- Propofol-Induction in titrated doses
- Rocuronium-Muscle relaxant in titrated doses
- Intraop opioids: Remifentanyl-bolus or infusion
  Fentanyl-25-50 mcg bolus
  Sufentanyl-5-20 mcg bolus
- No long acting opioids to be given during the surgery
- No NSAIDS to be given during the surgery
- Antiemetic prophylaxis with Dexamethasone 4mg to 8mg soon after induction in all patients, except with history of allergy.

APPENDIX 3: Outcome Measurement Scales

1. **Numerical Analogue Scale for Pain (NAS)**

2. **Verbal Descriptive Scale for PONV**: the presence and severity of PONV (reference 9)

0	no nausea
1	mild nausea
2	moderate nausea-may need treatment
3	frequent vomiting –controlled with antiemetics
4	severe vomiting-uncontrolled with antiemetics.

3. Severity of Respiratory Depression: Presence of one or both of the following
   - presence of Respiratory Rate below 10
   - Presence of Oxygen saturation <90\

4. Ramsay Sedation Scale

Response to verbal command	Numerical Score
Agitated	6
Responds readily to name spoken in a normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to test stimulus	0

5. Patient Satisfaction Score and Severity of Itching: Visual Analogue Scale