PROTOCOL NUMBER: HS-15-00615

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TITLE: The effectiveness of IV/PO acetaminophen in the perioperative period in reducing opiate use after lumbar spine fusion: a prospective, randomized controlled trial

STUDY ARMS: Acetaminophen IV + Hydromorphone hydrochloride (A)
Acetaminophen PO+ Hydromorphone hydrochloride (B)
versus
Hydromorphone hydrochloride (control arm) (C)

IND OR IDE #:

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SPONSOR: Keck Medical Center USC

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AMENDMENTS/REVISIONS:

TABLE OF CONTENTS

1.	Background and Hypothesis	3
2.	Objectives and Purpose	3
3.	Study Design	4
4.	Drug and Device Information	4
5.	Selection and Withdrawal of Subjects	5
6.	Descriptive Factors, Stratification, Randomization Scheme	5
7.	Study Agent Administration or Intervention and Toxicity Management Plan	5
8.	Assessment of Efficacy and Safety	6
9.	Clinical and Laboratory Evaluations and Study Calendar	6
10.	Criteria for Evaluation and Endpoint Definitions	7
11.	Special Instructions	7
12.	Data Collection and Monitoring	7
13.	Statistical Considerations	7
14.	Registration Guidelines	9
15.	Biohazard Containment	9
16.	Ethical and Regulatory Considerations	9
17.	References	9
18.	Appendix	10

1.0 BACKGROUND AND HYPOTHESES

Recovery after spine surgery, especially spinal fusion surgery, is usually accompanied by severe pain. Traditionally, the mainstay of pain control after spinal surgery has been opioids. While opioids have been proven effective, they are associated with undesirable side effects including nausea, vomiting, pruritus, sedation, respiratory depression, ileus, and urinary retention. These effects lead to increased time required in PACU recovery and a decrease in patient satisfaction. For this reason, it is common practice to supplement opioid treatment with different classes of analgesics which work through alternative pain pathways and receptors in order to achieve an additive or synergistic effect while reducing the amount of opioids necessary for pain control.

Acetaminophen is a nonsteroidal anti-inflammatory medication. Specifically, it is a centrally-acting cyclooxygenase inhibitor that has minimal, if any, gastrointestinal and platelet-inhibiting side effects, and is better tolerated by patients than other cyclooxygenase inhibitors. This medication can be a beneficial supplemental analgesic to opioids for postoperative pain relief. Previously conducted studies demonstrate a rationale for the use of intravenous acetaminophen in a multimodal analgesic regimen to reduce postoperative analgesia. The bibliography of these of studies is below:

1. Cakan T, et al. Intravenous paracetamol improves quality of postoperative analgesia but does not decrease narotic requirements. *J Neurosurg Anesthesiol*, 2008;20:169-173
2. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. *J of Clin Neuroscience*, 2015 Jun;22(6):930-8
3. Emir E, et al. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. *Kaohsiung J Med Sci*, 2010;26(6):308-315
4. Garcia RM, et al. A multimodal approach for postoperative pain management after lumbar decompression surgery: a prospective randomized study. *J Spinal Disord Tech, 26:291-297, 2013*
5. Korkmaz Dilmen O, et al. Efficacy of intravenous paracetamol, metamizol and lomoxicam on postoperative pain and morphine consumption after lumbar disc surgery. *Eur J Anaesthesiol*, 2010;27(5):428-432
6. Toygar P, et al. Does IV paracetamol have preemptive analgesic effect on lumbar disc surgeries? Article in Turkish. *Agri*, 2008;20(2):14-19
7. Uzun S, Onguc Aycan I, et al. The addition of metamizole to morphine and paracetamol improves early postoperative analygesia and patient satisfaction after lumbar disc surgery. *Turk Neurosurg*, 2010 Jul;20(3):341-7
8. D. Dungy, J. Prince: When IV Acetaminophen Costs Skyrocketed, One Health System did Some New Math. *Drug Topics. Voice of the Pharmacist,*
9. J. Van Der Westhuizen, et al. Randomised controlled trial comparing oral and intravenous paracetamol (acetaminophen) plasma levels when given as preoperative analgesia. *Anaesth Intensive Care.*2011 Mar;39(2):242-6
10. Garcia, et al: A multimodal approach for Postoperative Pain Management after Lumbar Decompression Surgery. *J Spinal Disord Tech.* Volume 26(6), August 2013.

Hypotheses:

1. Use of intravenous acetaminophen in the perioperative period will decrease TOTAL opioid intake after lumbar spinal fusion surgery by 30% while use of oral acetaminophen in the postoperative period will decrease TOTAL opioid intake by 30% as well.

2. Use of intravenous acetaminophen in the perioperative period will decrease postoperative pain by 25% and increase patient's satisfaction and wellbeing, while use of oral acetaminophen in the postoperative period will decrease postoperative pain by 25% as well.
3. Use of intravenous or oral acetaminophen in the perioperative period will lead to the reduction of opioid side effects.

2.0 OBJECTIVES AND PURPOSE

Primary objective:

- Determine the impact of administering a supplemental non-opioid analgesic drug such as IV acetaminophen or oral acetaminophen on total opioid dose administered over the perioperative period.

Secondary objectives:

- Impact of IV/oral acetaminophen on the level of postoperative pain
- Impact of IV/oral acetaminophen on patient satisfaction
- Impact of IV/oral acetaminophen on side effects secondary to opioids such as nausea, vomiting, pruritus, sedation, respiratory depression, ileus, and urinary retention, and PACU discharge time.

3.0 STUDY DESIGN

This is a prospective randomized clinical trial designed to evaluate the change in opioid intake, pain control, and patient satisfaction with the addition of IV/oral Acetaminophen during the postoperative period in patients undergoing minimally invasive spine surgery.

This study will include adult patients over the age of 18 years who are classified as ASA I-III, scheduled for elective one or two level minimally invasive lumbar fusions. Appropriate patients will be identified in the surgeons' clinic. Exclusion criteria will include patients requiring surgery for neoplastic processes, allergy to acetaminophen, liver dysfunction and elevated Liver Function Tests (LFTs), alcohol or drug dependency, mental retardation, patients with <50 kg of weight, and pregnant women. In addition, patients requiring long-acting opioid pain management (including fentanyl patch, oxycontin, etc) for over 3 weeks immediately prior to surgery will also be excluded. Informed consent for participation in this study will be obtained by the anesthesiology staff during the pre-operative anesthesia visit.

Once informed consent has been obtained, patients will either be randomized to group 1 with IV acetaminophen (A), group 2 with oral acetaminophen, or group 3 with Hydromorphone (control arm) (C). Patients in group A will receive 1 g of IV acetaminophen 15 minutes prior to wound incision, and every 4 to 6 hours postoperatively for a total of 4 grams in 24 hours. Patients in group B will receive 1 g of PO acetaminophen prior to surgery, and 1 g of oral acetaminophen every 4 to 6 hours postoperatively for a total of 4 grams in 24 hours. Patients in the control arm (Group C) will not receive acetaminophen for 24 hours. General anesthetic medications will be identical in each group, and will include:

- IV Propofol and IV Remifentanil (1 mcg/kg) will be used on induction.
- Local injection at the beginning of the procedure with Lidocaine 0.5% (maximum 5 mg/kg) with Epinephrine by the surgeon.
- Remifentanil infusion (0.05-0.4 mcg/kg/hr) and Propofol infusion (75-200 mcg/kg/min) for maintenance of anesthesia.
- Bupivacaine 0.5% (maximum 3mg/kg) injected into the wound by the surgeon before closure.
- Hydromorphone PCA (0.2-0.4 mg Q10 min, up to 2 mg/hr with no basal rate) for postoperative pain control for 24 hours after surgery.

Postoperative assessments will be done at 0, 30, and 60 minutes, 6 hours, 12 hours and 24 hours after surgery. Patients will be evaluated for pain (using a numeric rating scale), total opioid consumption, and

for opioid side effects including drowsiness (using the Ramsey sedation scale and the Aldrete score at the time of arrival to and discharge from recovery room), respiratory depression, nausea, vomiting, and pruritus. Patient satisfaction will also be assessed using a numeric rating scale. Example evaluation forms are in the appendix. Side effects of IV/oral acetaminophen will be monitored in the postoperative period.

4.0 DRUG AND DEVICE INFORMATION

Acetaminophen
IND number:
IDE number: DB00316 (APRD00252)
The supplier: Cadence Pharmaceuticals, Inc.

OFIRMEV® (acetaminophen) Injection (1000 mg / 100 mL, 10 mg / mL)
Acetaminophen injection, is indicated for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever. The FDA approval of OFIRMEV was based on data from clinical trials in approximately 1,020 adult and 355 pediatric patients. These trials included two studies evaluating the safety and effectiveness of OFIRMEV in the treatment of pain, and one study evaluating OFIRMEV in the treatment of fever. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients less than 2 years of age.

Safety Information. The maximum recommended daily dose of acetaminophen (4 g) should not be exceeded. Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. OFIRMEV is contraindicated in patients with severe hepatic impairment, severe active liver disease or with known hypersensitivity to acetaminophen or to any of the excipients in the formulation. Acetaminophen should be used with caution in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment. OFIRMEV should be administered only as a 15 minute intravenous infusion. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients. The antipyretic effects of OFIRMEV may mask fever in patients treated for post-surgical pain.

ACETAMINOPHEN
ID/FEI: 19 41239 8 0

The Supplier: Physician Total Care, Inc

ACETAMINOPHEN EXTRA STRENGTH- acetaminophen tablet (500 mg)
Acetaminophen is indicated for the management of minor pain and the reduction of fever.
Safety information: The maximum recommended daily dose of acetaminophen (4 g) should not be exceeded. Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury and severe hepatotoxicity. It cannot be use with other medications containing acetaminophen.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Inclusion Criteria: Patients of the age of 18 and over, ASA I-III, English or Spanish speakers, scheduled for elective one or two level minimally invasive lumbar fusions, selected from the neurosurgical outpatient clinic at the Keck Hospital of USC.

Exclusion Criteria: Patients requiring surgery for neoplastic processes, allergy to acetaminophen or hydromorphone, liver dysfunction, alcohol or drug dependency, mental retardation, and pregnant women. In addition, patients requiring long-acting opioid pain management (including fentanyl patch, oxycontin, etc) for over 3 weeks immediately prior to surgery will also be excluded.

Withdrawal Criteria: Patients may withdraw from the study at any time during the pre-operative or data collection period (the first 24 hours post-operatively) or later, should they no longer wish to participate. Patients experiencing severe post-operative pain not controlled by the post-operative pain protocol may withdraw should they require alternate pain management. Any patient experiencing discomfort or adverse reaction to the study drug, or the hydromorphone PCA may withdraw at any time to receive alternative pain control.

6.0 DESCRIPTIVE FACTORS, STRATIFICATION, RANDOMIZATION SCHEME

Once informed consent is obtained, patients will be randomized to either the treatment with IV acetaminophen (A), with oral acetaminophen (B), or hydromorphone only (control arm) (C) group. For randomization, we will have 126 opaque envelopes (42 for group A, 42 for group B, and 42 for group C) which will be randomly distributed and opened in the preoperative area before surgery. Patients in group A will receive IV acetaminophen + IV hydromorphone. Patients in group B will receive oral acetaminophen + IV hydromorphone. Patients in group C will receive hydromorphone only. Patient characteristics that are important to stratify and control include age, ASA classification, operative level, and number of spinal levels fused.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

Patients will be randomized to either the treatment with IV acetaminophen (A), PO acetaminophen (B), or hydromorphone (C) group. Before entering the operating room, patients may be pre-medicated with benzodiazepines. Patients in PO acetaminophen group (B) will receive 1000mg of PO acetaminophen 15 minutes before entering the operating room. All Patient will be receiving propofol as the induction agent, remifentanil as the induction opioid, and a muscle relaxant of choice. During the case, patients will only receive propofol and remifentanil as continuous infusions, which can be supplemented with up to 0.5 MAC of an inhalational anesthetic (sevoflurane or desflurane). Patients who are randomized to group A will receive 1 g of IV acetaminophen 15 minutes prior to wound incision. Patients who are randomized to group A will receive IV acetaminophen every 4 to 6 hours postoperatively for a total of 4 g in 24 hours. Patients who are randomized to Group B will receive PO acetaminophen every 4 to 6 hours postoperatively for a total of 4 g in 24 hours. Patients who are randomized to group C will not receive acetaminophen. Post-operatively, patients in both groups will also receive IV hydromorphone PCA only for 24 hours for pain.

AGENT	DOSE	ROUTE	DAYS	Rx INTERVAL	NOTES
B (acetaminophen PO)	500 mg, 2 tablets	PO	1	4-6 hours (maximum 4 g/24 h)	1st dose 15 min prior to going to the OR
A (acetaminophen IV)	1 g/100mL	IV over 15 min	1	4-6 hours (maximum 4 g/24 h)	1st dose intra-op 15 minutes prior to wound incision

Treatment will be discontinued if a patient experiences any side effects related to the medication. A patient may always be removed from the treatment whenever he/she wishes for reasons including but not limited to inadequate pain control or adverse reactions to treatment medications.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

Side effects and toxicities that the patient will be asked about at each evaluation during the treatment include: nausea, vomiting, headache, and insomnia. If symptoms associated with allergy or hypersensitivity occur, the medication will be discontinued immediately. Maximum recommended daily dose of acetaminophen will not exceed 3.75g for patients <50 kg or 4g for patients > 50 kg. Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. Patients will not receive doses higher than recommended. Serious adverse events will be monitored up to 2 days following the last Study Medication dosing and followed to resolution or stabilization. Investigators will keep all safety-related documentation in site files.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Study Calendar

Parameter	Pretreatment	15 min prior to incision	Arrival to PACU	30 min after arrival to PACU	60 min after arrival to PACU	In 6 hours	In 12 hours	In 18 hours	In 24 hours
Comprehensive History & Physical Examination	X								
IV Agent administration		X				X	X	X	
PO Agent administration	X					X	X	X	
Ramsey Sedation Scale			X						
Numeric pain scale			X	X	X		X		X
Aldrete score			X		X				
Respiratory depression scale			X	X	X		X		X
PONV			X	X	X		X		X
Pruritus			X	X	X		X		X
Patient discharge time from PACU					X				
Patient satisfaction scale					X				X

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Endpoint Definitions: The primary study endpoint will be determined by the impact of IV/oral acetaminophen on total opioid dose administered over the perioperative period. The impact of IV/oral acetaminophen on the level of postoperative pain, patient satisfaction, and side effects from opioids such as nausea, vomiting, pruritus, sedation, respiratory depression, ileus, and urinary retention, and PACU discharge time of all eligible patients will also be investigated. All eligible patients who are enrolled will be included in the analysis of the impact of IV/oral acetaminophen administration over the perioperative period.

11.0 SPECIAL INSTRUCTIONS

Only standard laboratory tests or additional laboratory results necessary for the patient will be obtained. No additional blood samples for study purposes will be obtained from the patient.

12.0 DATA COLLECTION AND MONITORING

- Case Report Forms: will be in the chart for every patient and will include all data collected for the patient. They will be held by the Study Coordinator and locked in the office after data is collected.
- Source Documentation and Timeliness of CRF Completion will be completed immediately after data collection is complete.
- Study Records: Will be locked by the Study Coordinator in the office.
- Data Management: Data will be labeled with a code that the research team can link to personal identifying data.
- Data Monitoring: The PI will monitor the study methods and procedures, and will be meeting with investigators for data monitoring on a bimonthly basis.

13.0 STATISTICAL CONSIDERATIONS

All sample size calculations with reference to:

"Specific Aim 1", i.e. reduction of TOTAL opioid intake by at least 30% between the Control (Group 3) and Intervention Group (Group1 or Group 2), meaning Group 1 versus Group 3 and Group 2 versus Group 3
and
"Specific Aim 2", i.e. improvement of Pain Score (within 12 hours) by at least 25% between the Control (Group3) and the Intervention Group (Group 1 or Group2), meaning Group 1 versus Group 3 and Group 2 versus Group 3,

were based on data from [Garcia et al, 2013; 26:291-297, J Spinal Disord Tech]. (manuscript attached). Also, on the grounds of literature from Westhuizen et al (Anaesth Intensive Care 2011; 39: 242-246) and D. Dungy, J. Prince (Voice of the Pharmacist), it is suggested that IV-Acetaminophen and Oral-Acetaminophen should have comparable effects. Thus, in our sample size calculations we assumed that the comparison between Group 1 vs Group 3 and Group 2 vs Group 3 would be similar. We have no further information regarding the distribution of the data (no own pilot studies) and have no further references other than the literature.

On the basis of the above assumptions and for our statistical calculations as primary endpoint is the reduction by 30% of the total opioid used, i.e. 53.3 ± 28.9 to 37.3 mg, thus, with 0.1 type I alpha error probability and 80% power we will need 42 patients per arm, meaning, 126 patients in total which we will use to compare IV Acetaminophen vs Control groups and Oral Acetaminophen vs Control groups.

Regarding the secondary/pain endpoint we postulate 25% decrease within 12-hours, meaning 7.0 ± 2.9 to 5.25, thus with 0.05 type I alpha error probability and 80% power we will need 24 patients per arm. Due to the above, we feel comfortable that by enrolling 126 patients, in total, we should be able to prove our hypotheses.

Similar studies have demonstrated that the dropout rate is 0% for patients in this condition. Also, medical charts in our hospital have demonstrated that over 100 patients are treated in this condition every year. Thus, it is postulated that a final sample of 126 patients can be enrolled within a year and a half.
All sample size calculations are based on assumptions from published data in the literature. Therefore, we would like to conduct an interim analysis once 21 patients per arm i.e. 63 total have been collected and if necessary to account for any potential differences (in our patient population descriptives and or distribution vs literature) that may be observed.
Patients will be randomized into 2 groups, Control and Intervention as per a 1:1 ratio to satisfy equal enrolment at any time and until the targeted sample has been reached.

Statistical References

1. Ostle, B. and Malone, L.C. 1988. Statistics in Research. Iowa State University Press. Ames, Iowa.
2. Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.
3. Garcia, et al: A multimodal approach for Postoperative Pain Management after Lumbar Decompression Surgery. *J Spinal Disord Tech.* Volume 26(6), August 2013.

14.0 REGISTRATION GUIDELINES

14.1 Specify phone number to register the patients: 213-287-0038. Also identify whether the patients will be randomized or stratified: Patient will be randomized at the day of the surgery.

14.2 Specify the forms and records needed for registration: Informed Consent, Registration/Eligibility Worksheet, Flow Sheet.

Note: At the time of registration, two copies of a signed and dated patient Informed Consent form with Bill of Rights must be available (an original for patient's medical chart; one copy for the patient; and the other for the PI's file).

15.0 BIOHAZARD CONTAINMENT

N/A

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to the ICH Good Clinical Practice Guidelines.

17.0 REFERENCES

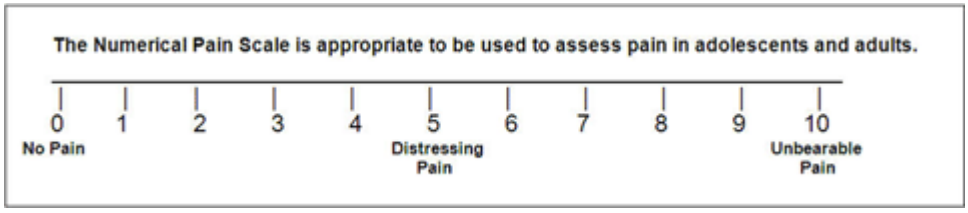
1. Cakan T, et al. Intravenous paracetamol improves quality of postoperative analgesia but does not decrease narotic requirements. *J Neurosurg Anesthesiol*, 2008;20:169-173

2. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. *J of Clin Neuroscience*, 2015 Jun;22(6):930-8
3. Emir E, et al. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. *Kaohsiung J Med Sci*, 2010;26(6):308-315
4. Garcia RM, et al. A multimodal approach for postoperative pain management after lumbar decompression surgery: a prospective randomized study. *J Spinal Disord Tech, 26:291-297, 2013*
5. Korkmaz Dilmen O, et al. Efficacy of intravenous paracetamol, metamizol and lomoxicam on postoperative pain and morphine consumption after lumbar disc surgery. *Eur J Anaesthesiol*, 2010;27(5):428-432
6. OFIRMEV® (acetaminophen) Injection Package Insert
7. Ostle, B. and Malone, L.C. 1988. Statistics in Research. Iowa State University Press. Ames, Iowa.
8. Toygar P, et al. Does IV paracetamol have preemptive analgesic effect on lumbar disc surgeries? Article in Turkish. *Agri*, 2008;20(2):14-19
9. Uzun S, Onguc Aycan I, et al. The addition of metamizole to morphine and paracetamol improves early postoperative analygesia and patient satisfaction after lumbar disc surgery. *Turk Neurosurg*, 2010 Jul;20(3):341-7
10. Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.
11. D. Dungy, J. Prince: When IV Acetaminophen Costs Skyrocketed, One Health Systed did Some New Math. *Drug Topics. Voice of the Pharmacist,*
12. J. Van Der Westhuizen, et al. Randomised controlled trial comparing oral and intravenous paracetamol (acetaminophen) plasma levels when given as preoperative analgesia. *Anaesth Intensive Care.*2011 Mar;39(2):242-6

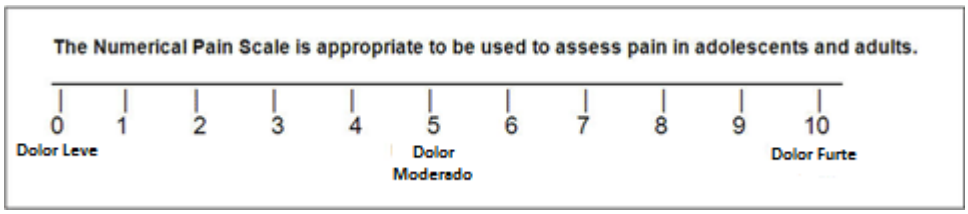
18.0 APPENDIX

Appendix I: Toxicity Scale (if applicable)
Appendix II: Informed Consent
Appendix III: Questionnaires &/or Survey Forms

Numerical Pain Scale (1-10)



Spanish version of Numerical Pain Scale (1-10)



Patient Satisfaction Scale

	1 – Very poor	2 – Poor	3 – Okay	4 – Good	5 – Very good
Pain Control					
Drowsiness					
PONV					
Pruritus					
Overall satisfaction					

Spanish version of Patient Satisfaction Scale

	1 – Muy mal	2 – Mal	3 – Bueno	4 – Bien	5 – Muy bueno
Control del dolor					
Somnolencia					
Náusea y vómitos					
Prurito					
Satisfacción general					

Ramsay Sedation Scale*

Response to verbal command	**Score**
Anxious, agitated, or restless	1
Cooperative, oriented, tranquil	2
Responds only to auditory stimulus	3
Brisk response to light glabellar tap or loud auditory stimulus	4
Sluggish response to light glabellar tap or loud auditory stimulus	5
Does not respond to test stimulus	6

*Performed using a series of steps: observation of behavior (score 1 or 2), followed (if necessary) by assessment of response to voice (score 3), followed (if necessary) by assessment of response to loud auditory stimulus or light glabellar tap (score 4 to 6)

Modified Aldrete Score

Parameter	**Description of Patient**	**Score**
Activity level	Moves all extremities on command/voluntarily	2
	Moves 2 extremities	1
	Cannot move extremities	0

Respirations	Breathes deeply and coughs freely	2
	Dyspneic, shallow, limited breathing	1
	Apneic	0
Circulation	20 mm Hg BP ± 20% of preanesthetic level	2
	20-50 mm Hg BP ± 20-50% of preanesthetic level	1
	50 mm Hg BP ± 50% of preanesthetic level	0
Consciousness	Fully awake	2
	Arousable to verbal stimuli	1
	Non-responsive	0
Pulse Oximetry	Maintains >92% on room air	2
	Requires supplemental oxygen to maintain >92%	1
	<92% on supplemental oxygen	0

Respiratory depression assessment

Heart rate	
Blood pressure	
Respiration rate	
Pulse oximetry (%)	

Post-operative Nausea and Vomiting (PONV scale)

No N/V	**0**
Nausea Only	**1**
Both N/V	**2**

Total opioid consumption

Remifentanil intra-operatively	
Hydromorphone postoperatively (24 hrs)	

End of study.