**Study Title:**

Postoperative opioid use and pain scores in patients undergoing minimally invasive lumbar laminectomy and fusion after administration of preoperative followed by scheduled intravenous acetaminophen: A prospective, randomized, double blind, placebo-controlled trial.

**Primary Investigator:**

Jason Felton, MD Neurosurgeon, Department of Surgery Texas Tech University Health Sciences Center

**Co-Investigator:**

Jaime Villarreal, MD Orthopaedic Surgery Resident Department of Orthopaedic Surgery and Rehabilitation Texas Tech University Health Sciences Center

**Anesthesiology Contributor:**

Ashraf Farag, MD Anesthesiologist, Director of Neuroanesthesia, Assistant Professor

Department of Anesthesiology Texas Tech University Health Sciences Center

**Statistical Analysis:**

James G. Surles PhD, Associate Professor Department of Mathematics and Statistics at Texas Tech University

**University Medical Center Pharmacist:**

Scott Obanion Pharm D, BCNSP

**Study Coordinators:**

Nancy Swinford, Research Coordinator, Department of Orthopaedic Surgery and Rehabilitation Texas Tech Health Science Center

Amanda Romero, RN; Chris Scott Johnson, RN; Thu Fenno, RN, Melissa Leiker, RN, Cathy Lovett, RN, Ruth Gard, RN

Clinical Research Institute, Texas Tech Health Sciences Center

**Background**

*Significance of decreasing postoperative Opioid use*

Opioids are generally at the forefront in our treatment of postoperative patient's pain. But even short-term use of opioids can cause adverse effects on the postoperative patient such as:

nausea, ileus, constipation, pruritis, urinary retention, and respiratory depression (8). These may lead to under-treatment of postoperative pain (18).

Tolerance and dependence can develop as well, and although these are often thought of as chronic issues, in the postoperative period the patient is exposed to high doses of opioids in a relatively brief period of time. Tolerance and opioid induced hyperalgesia can develop even after short-term use of high-dose opioids (12). Opioid induced hyperalgesia, a paradoxical phenomenon in which patients on opioids become more sensitive to pain, can contribute to the development of chronic pain after surgery (10, 11).

In addition, postoperative inflammatory responses can lead to spinal cord sensitization and may result in chronic pain after surgery. This is thought to occur after surgical trauma to various tissues releases inflammatory mediators that can in turn cause the spinal cord to undergo an inflammatory response which leads to sensitization (9).

Reducing exposure to opioids is of utmost importance to help limit adverse effects. Recent trends toward finding opioid sparing analgesics, multimodal pain strategies, and minimally invasive surgical techniques reflect this realization.

*Why Intravenous Acetaminophen?*

Intravenous Acetaminophen is a very attractive and established medication for treating post-operative pain (2, 4, 24). A meta-analysis of randomized controlled trials confirmed the postoperative opioid sparing effect of acetaminophen (16). Intravenous pro-drugs of acetaminophen administered preoperatively have also proven to improve postoperative pain when analyzed by a meta-analysis (17). It has a relatively safe and well documented side-effect profile. Intravenous acetaminophen is preferred post-operatively because of its bioavailability compared to oral versions of the drug. Opioids can slow the gastrointestinal tract and in turn the ability to absorb the medication when taken by mouth (15).

Acetaminophen derives its analgesic effects not only by inhibiting prostaglandin synthesis, but also by a central serotonergic mechanism (5, 6). Prostaglandin E2 is a potent local inflammatory cytokine which plays an important role in postoperative pain and can hinder rehabilitation after Orthopaedic surgery (21).

Intravenous acetaminophen reaches peak effect within 1 hour of administration and duration of the effect lasts 4 to 6 hours (4, 13). The anti-nocioceptive properties of acetaminophen, work in part through inhibition of prostaglandin synthesis in the spinal cord (19). The concentration of acetaminophen in cerebrospinal fluid peaks at 3 hours and remains above the concentrations that are reached by oral or rectal routes 6 hours from administration (14).

*Intravenous Acetaminophen in Spinal procedures*

There have been studies on post-operative pain and opioid use in patients undergoing laminectomy/fusion procedures given intravenous acetaminophen and pro-drugs of acetaminophen (1,3). These have not included pre-operative dosing and the pro-drug used is not approved for use in the U.S. A study by Cakan et al did demonstrate a significant difference in

pain scores favoring intravenous paracetmol (acetaminophen), but no difference in opioid use was detected in patients who had undergone multilevel lumbar laminectomy and diskectomy (1). Hernandez-Palazon et al. were able to detect a difference in morphine use between intravenous propacetamol (a pro-drug of acetaminophen), and placebo groups at all-time data points within a 72-hour period in patients undergoing lumbar laminectomy and spinal fusion. In contrast to the study by Cakan et al, which showed a difference in pain scores at the $12^{th}$, $18^{th}$, and $24^{th}$ hour, the Palazon study only showed a difference in pain scores at the $40^{th}$ and $56^{th}$ hours post-operatively.

Concerning intravenous propacetamol verus acetaminophen, a study by Moller et al found similar pain relief with both, but found that administration of propacetamol had significantly greater adverse events in terms of pain at the infusion site causing interrupted infusions in some patients. This was attributed to longer infusion times as 2g propacetamol = 1g acetaminophen (20).

The use of preoperative Intravenous acetaminophen in spinal surgery as part of a multimodal pain regimen in minimally invasive spine surgery has been suggested in the literature in a review by Buvanendran et al, but as a 1g oral administration preoperatively followed by 1g orally every 12 hours (8). This contradicts the basic pharmacology of acetaminophen. Intravenous administration has immediate bioavailability, thus is preferred versus the oral route, and the recommended dosing based on plasma concentration and peak effect is once every 6 hours, maximum dose of 4 grams in 24 hours.

Kesimci et al tested preoperative oral paracetamol versus dexketoprofen in controlling posteroperative pain and opioid use after elective lumbar disc hernia operation. In the study a preoperative single oral dose of 500 mg paracetamol did not show an opioid sparing effect (22). Much like the recommendations in the review by Buvanendran et al, this study did not adhere to the optimal pharmacologic regimen, which consists of intravenous administration followed by scheduled dosing at six-hour intervals.

*Pre-operative Intravenous Acetaminophen*

When considering prophylaxis against pain in postoperative patients it is logical to consider initiating a postoperative regimen, preoperatively. Specifically, with medications that act to inhibit synthesis of inflammatory pain mediators. If we can reach therapeutic concentrations prior to surgical trauma, this may curtail the painful inflammatory response (8). Increased preoperative concentrations of a COX-2 inhibitors in the cerebrospinal fluid in patients undergoing hip surgery was found to suppress prostaglandin E2 synthesis and decrease postoperative pain (21). Similarly, acetaminophen has also been found to inhibit spinal cord prostaglandin E2 release (19).

*Minimally Invasive Spine Surgery*

Minimally invasive surgical techniques decrease tissue damage and the subsequent inflammatory response versus traditional surgical techniques. The goals of minimally invasive spine surgery are to decrease surgical injury, pain, promote faster recovery, and decrease hospital stay. The use of Intravenous acetaminophen in spine surgery as part of a multimodal pain regimen in minimally invasive spine surgery has been suggested in the literature (8).

**Significance of the study:**

The purpose of this project is to study the effects of preoperative followed by scheduled intravenous acetaminophen on pain control for 24 hours postoperatively after minimally invasive 1 or 2 level laminectomy, and fusion. The advantages of intravenous acetaminophen are well known in the literature and its opioid-sparing effects have been documented in multiple surgical studies.

Multimodal regimens are now being advocated in the literature to decrease opioid use (8, 23). This is especially significant in spine surgery patients who often have chronic pain requiring long-term use of these habit-forming drugs as well as in patients who may not be able to tolerate opiods due to health status.

To our knowledge there are no studies done in the U.S. on the opioid sparing and pain reducing effects of intravenous acetaminophen on patients undergoing elective 1 or 2 level lumbar laminectomy and fusion. Investigating intravenous acetaminophen, particularly its pain reducing and opioid sparing effects, may give surgeons another medication for use in a multimodal approach to pain.

**Specific Aims:**

The primary specific aims of this study is to test the hypothesis that the use of preoperative, combined with scheduled postoperative, intravenous acetaminophen after minimally invasive 1 or 2 level lumbar laminectomy and fusion; will reduce patients' use of opioid narcotic needed for pain control and that they will have better postoperative pain scores assessed by the Visual Analog Scale (VAS) versus controls.

The secondary specific aims of this study are to assess quality of pain control, as well as sedation and adverse outcomes.

**Hypothesis:**

We hypothesize that the use of intravenous acetaminophen both pre-operatively and post-operatively will result in improved VAS scores, less opioid, narcotic usage, better quality pain control, and similar adverse events, when compared to placebo.

## Research Plan

**Study design:**

Prospective, randomized, double-blind, placebo controlled trial

**Patient population:**

Male and female adult patients undergoing elective 1 or 2 level minimally invasive lumbar laminectomy and fusion for spinal stenosis

Inclusion criteria:

1. Age ≥ 18 years old
2. Being scheduled to have elective primary 1 or 2 level lumbar laminectomy and fusion for spinal stenosis
3. ASA I, II, or III
4. Informed consent form signed

Exclusion criteria:

1. Hypersensitivity or contraindication to intravenous acetaminophen or opioids
2. Allergy to Methocarbamol; morphine sulfate, sevoflourane, or fentanyl
3. Impairment of liver function-- defined as the inability to receive intravenous acetaminophen without dose adjustment as determined by the investigator; or history of chronic liver disease defined as history of hepatitis of any kind as recorded in the patient's chart
4. Mental retardation recorded as a diagnosis in the patient's chart
5. History of chronic pain (defined as currently receiving treatment from a specialist for pain)
6. History of pain recalcitrant to intravenous morphine
7. Impaired kidney function (defined as creatinine > 1.5)
8. Anyone who is not a candidate for general anesthesia or any other portion of the Investigator's standard of care.

***Subject recruitment:***

Upon TTUHSC IRB approval, patients will be identified and recruited from Dr. Jason Felton's Neurosurgical practice.

**Study procedures:**

All patients will be given informed consent as approved by the TTUHSC IRB. The study will begin on the day of surgery. Study medication (intravenous acetaminophen/placebo) will be provided to study participants free of charge. All other medications used are the standard of care and will be paid for by the patient or their insurance.

Visit 1:

Patient will be seen in clinic and informed consent for inclusion in the study will be obtained, then baseline characteristics: Age, Sex, weight, American Society of Anesthesiologists classification and pre-operative VAS scores, will be recorded.

The patient will also be randomized to intravenous acetaminophen or placebo group prior to surgery.

Visit 2:

Pre-op dose of IV acetaminophen/Placebo will be administered intravenously over a period of 15 minutes, 15 minutes (+/- 10 minutes) prior to the anticipated time of incision.

Visit 3:

Patient will be treated and evaluated in the post-anesthesia care unit according to the study protocol.

Visit 4 through Final Visit:

This and all other visits will take place post-operatively; they will be treated and evaluated according to the study protocol for 24 hours (+/- 30 minutes). Specifically, the following will occur:

- Every 4 hour assessments of pain with a VAS and VRS
- Every 4 hour sedation assessment
- Morphine usage
- Every 4 hour post-operative vital signs
- Adverse Event monitoring

**Randomization procedure:**

Treatment allocation will be assigned by the unblinded pharmacist who will assign a "1" or "2" as the treatment group. Patients will be randomly allocated by sealed envelope into group 1 or 2 by the pharmacist using preordered sealed envelopes which will be randomized to contain a "1" or "2" using randomization software owned by the UMC Pharmacy.

Upon designation to a group the pharmacist will fill identical IV bags with either 1g acetaminophen or 100 mL 0.9% NaCl saline for administration and label the bag appropriately.

Placebo group:

1. 0.9% NaCl 100 mL over will be administered intravenously over a period of 15 minutes, 15 minutes (+/- 10 minutes) prior to the anticipated time of incision and every 6 hours (+/- 30 minutes) after the initial dose for 24 hours.

2. 750 mg of intravenous Methocarbamol will be administered within 60 minutes of admission to the postanesthesia care unit and every 6 hours (+/- 30 minutes) post-operatively, this is the standard of care for Dr. Felton's practice.

3. Intravenous morphine PCA pump connected to the patient within 60 minutes of admission to the postanesthesia care unit programmed to give 1 mg boluses on demand with 10 minute lock out intervals, and a 20 mg 4-hour limit, post-operatively. Morphine use in Milligrams will be recorded at 4 hour time intervals (+/- 30 minutes) for 24 hours post-operatively; this is the standard of care for Dr. Felton's practice.

Acetaminophen group:

1. 1 gram of intravenous Acetaminophen will be administered intravenously over a period of 15 minutes, 15 minutes (+/- 10 minutes) prior to the anticipated time of incision and every 6 hours (+/- 30 minutes) after the initial dose for 24 hours; maximum dose of 4 grams in 24 hours. **NOTE: this drug is being used "on label" as approved by the FDA.**

2. 750 mg of intravenous Methocarbamol will be administered within 60 minutes of admission to the postanesthesia care unit and every 6 hours (+/- 30 minutes) post-operatively, this is the standard of care for Dr. Felton's practice

3. Intravenous morphine PCA pump connected to the patient within 60 minutes of admission to the postanesthesia care unit programmed to give 1 mg boluses on demand with 10 minute lock out intervals, and a 20 mg 4-hour limit, post-operatively. Morphine usage in Milligrams will be recorded at 4 hour intervals (+/- 30 minutes) for 24 hours post-operatively, this is the standard of care for Dr. Felton's practice

**Rationale for timing of Pre-op dose of study drug:**

Peak serum doses, as well as efficacy of acetaminophen, is reached within 1 hour of administration. Therefore, the timing of administration, 15 minutes (+/- 10 minutes) prior to the anticipated time of incision, will coincide with synthesis of pain cytokines caused by the surgical approach and instrumentation. If we gave the medication 60 minutes before incision, there would be a fall from peak serum levels as the incision is made (and a continued fall as the bony work and instrumentation take place).

**General Anesthesia protocol:**

General endotracheal anesthesia will be implemented for all patients as is the investigators' standard of care. Intraoperative anesthetic management will be maintained with:

Morphine sulfate loading dose of 0.15 mg/kg, intraoperative general anesthesia: sevoflourane, in addition to intravenous fentanyl of 1 to 2 mcg/kg. Intravenous fentanyl, due to its short half, does not add a confounding analgesic effect in the postoperative period.

**Outcome Measures:**

Pain will be evaluated at 4-hour intervals (+/- 30 minutes) post-operatively for 24 hours with a Visual analog scale, VAS (0 = no pain to 10 = worst possible pain).

Pain relief will also be rated by patients on a 4 point verbal rating score, VRS at 4-hour intervals: 0 no pain relief; 1 partial pain relief; 2 good pain relief; and 3 excellent relief and complete

analgesia. The VRS recorded during the 24-h period will be summed to yield the Total Pain Relief (TOTPAR) score for that period.

The Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) are among the most commonly used, and validated, measures of pain intensity in clinical and research settings (25).

Sedation will be measured on a scale of 1 to 5 at 4-hour intervals as follows: 1-completely awake; 2-awake but drowsy; 3 asleep, but responds to verbal commands; 4-asleep but responds to tactile stimuli; and 5-asleep and not responding to any stimuli.

VAS, Sedation, and morphine usage will be documented in the patients' chart by nurses blinded to the patients' treatment status.

Routine postoperative vital signs will be collected at 4-hour intervals (+/- 30 minutes) postoperatively respiratory rate, oxygen saturation, mean arterial pressure, and heart rate. Any reports of headache, dizziness, nausea, vomiting, pruritis, agitation, constipation, insomnia, bradycardia (Heart rate below 60 beats per minute), hypotension (MAP less than 30% of baseline), or urinary retention will be recorded throughout the study and will be treated appropriately as they occur, and the treatment medication will be stopped if determined to be a causative factor.

Age, Sex, ethnicity, weight, American Society of Anesthesiologists classification, pre-operative VAS score, intraoperative and postanesthesia unit use of opioids, surgical time, estimated blood loss, and the number of lumbar spine levels decompressed will be recorded.

**Statistical Analysis:**

Intent to treat analysis will be done. Assuming a 30% difference in Visual Analog Pain Scale scores between groups, with a type I error of 0.05 and type II error 0.20, 15 subjects are needed in each group, 30 subjects total. Morphine use, VAS scores, and TOTPAR scores will be compared between groups.

Age, Sex, American Society of Anesthesiologists classification, intraoperative and postanesthesia unit use of opioids, surgical time, estimated blood loss, and the number of lumbar spine levels decompressed will be recorded and compared between groups.

Reports of headache, dizziness, nausea, vomiting, pruritis, agitation, constipation, insomnia, bradycardia (Heart rate below 60 beats per minute), hypotension (MAP less than 30% of baseline), or urinary retention, will be recorded and compared between groups.

**Risks:**
The most common adverse reactions in adult patients treated with intravenous acetaminophen are: nausea, vomiting, headache, constipation, pruritus, agitation, and insomnia

- The antipyretic effects may mask fever in patients treated with intravenous acetaminophen for postoperative pain
- Hypersensitivity to acetaminophen or to any of the excipients in the formulation

- Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity, and in extreme cases death

**Adverse Events Reporting:**

Any event deemed as an Adverse Event that is possibly related or unexpected to the study will be assessed at each data gathering point and will be reported to the TTUHSC IRB as described in the IRB policies and procedure manual. Any Serious Adverse Event will be reported to the IRB within two days of the study team being aware of the event as per TTUHSC IRB policy. Monitoring of adverse events will start on the day of surgery.

**Benefits:**

There is no guarantee that taking part in this study will provide any benefit to the participants. We hypothesize, that patients will experience less pain, use less narcotic pain medication, and have better quality pain control. No monetary compensation will be provided to study participants.

**Confidentiality Measures:**

HIPAA rules will be followed at all times. Patients' names will not be used in the study results. Subjects' signed informed consent, completed questionnaires and/or data collection forms will be stored in a secure location in the study coordinator's office. All data collected will be coded with the identifier assigned to the participant, and contain no identifying information.

**Specific Roles:**

**Primary Investigator**

- Responsible for over-all conduct of the study
- Assist in identifying potential study participants for the study
- Administration and oversight of the study activities including obtaining informed consent, randomization and dispensing of study drug, data collection, preparation of manuscripts for publications, monitoring of adverse events and determination of causality and relatedness to study intervention
- Perform standard of care surgical intervention

**Sub-Investigator(s)**

- Assist PI in the over-all conduct of the study
- Assist PI in the performance of standard of care surgical intervention

- Any activity delegated to them by the PI and within their scope of practice

**Anesthesiology Contributor**

- Approve anesthesia protocol
- Monitor adherence to the anesthesia protocol

**Statistician**

- Statistical analysis of collected data
- Design randomization protocol
- Assist to preserve the statistical integrity of the study

**Study Coordinator (s):**

- Screen potential study participants for study eligibility
- Obtain & document informed consent
- Maintain study documents
- IRB submissions
- Completion of data collection forms/Data entry
- Any activity delegated to them by the PI and within their scope of practice

**Research Pharmacist(s):**

- Preparing, packaging, and dispensing of study medications
- Randomization
- Investigational Product (IP) accountability
- All documentation related to the above activities

References:


1. Cakan et al. “Intravenous Paracetamol Improves the Quality of Postoperative Analgesia but Does not Decrease Narcotic Requirement.” J Neurosurg Anesthesiol 2008;20: 169-173

2. Ortiz-Cardona et al. “Perioperative Pain Management in the Neurosurgical Patient.” Anesthesiology Clin 2007;25: 655-674

3. Hernandez-Palazon et al. “intravenous Administration of Propacetamol Reduces Morphine Consumption After Spinal Fusion Surgry.” Anesth Analg 2001; 92: 1473-1476

4. Sinatra et al. “Efficacy and Safety of Single and Repeated Administration of 1 Gram Intravenous Acetaminophen Injection (Paracetamol) for Pain Management after Major Orthopedic Surgery.” Anesthesiology 2005; 102: 822-831

5. Pickering et al. “Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism.” Clinical Pharmacology & Therapeutics 2006; 79(4): 371-378

6. Sandrini. “Central Effects of Non-Opioid Analgesics.” CNSDrugs: 1999; 12(5): 337-345

7. Alford, “Chronic Back Pain With Possible Prescription Opioid Misuse.” JAMA: 309; 9: 919-925

8. Buvanendran et al. “Preoperative and Postoperative Anesthesia Techniques for Minimally Invasive Surgery of the Spine.” SPINE: 2010; 35 (26): 274-280

9. Melzack et al. “Central neuroplasticity and pathological pain.” *Ann N Y Acad Sci* 2001;933: 157–74

10. Kehlet et al. “Persistent postsurgical pain: risk factors and Prevention.”*Lancet* 2006;26: 1618–1625

11. Brush “Complication of Long-Term Opioid Therapy for Management of Chronic Pain: the Paradox of Opioid-Induced Hyperalgesia.” J Med. Toxicol 2012;8: 387-392

12. Angst et al. “Opioid-Induced Hyperalgesia: a qualitative systematic Review.” *Anesthesiology* 2006;104: 570–587

13. Moller PL, Juhl GI, Payen-Champenois C, et al. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its pro-drug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg*. 2005;101:90-96.

14. Data on file. Cadence Pharmaceuticals, Inc.

15. Berger MM, Berger-Gryllaki M, Wiesel PH, et al. Intestinal absorption in patients after cardiac surgery. *Crit Care Med*. 2000;28:2217-2223.

16. Remy C, Marret E, and Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. British Journal of Anesthesia. 2005:94(4):505-513.

17. McNicol et al. Single-dose intravenous paracetamol or proacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. British Journal of Anesthesia. 2011:106(6):764-775.

18. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: A systemic review. *J Pain.* 2002;3:159 180.

19. Muth-Selbach et al. Acetaminophen Inhibits Spinal Prostaglandin E2 Release after Peripheral Noxious Stimulation. Anesthesiology 1999; 91:231-239.

20. Moller et al. Intravenous Acetaminophen (Paracetamol): Comparable Analgesic Efficacy, but Better Local Safety than Its Prodrug, Propacetamol, for Postoperative Pain After Third Molar Surgery. Anesth Analg 2005;101:90–96.

21. Buvanendran A, Kroin JS, Berger RA, et al. Up regulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. *Anesthesiology* 2006;104:403–410.

22. Kesimci et al. Comparison of efficacy of dexketoprofen versus paracetamol on postoperative pain and morphine consumption in laminectomy patients. AĞRI 2011;23(4):153-159.

23. Garcia et al. A Multimodal Approach for Postoperative Pain Management After Lumbar Decompression Surgery A Prospective, Randomized Study J Spinal Disord Tech 2012; Volume 00:Number 00.

24. White, P. The Changing Role of Non-Opioid Analgesic Techniques in the Management of Postoperative Pain Anesth Analg 2005;101:S5–S22.

25. Maria Alexandra Ferreira-Valente, José Luís Pais-Ribeiro, Mark P. Jensen, Validity of four pain intensity rating scales, PAIN, Volume 152, Issue 10, October 2011, Pages 2399-2404, ISSN 0304-3959, http://dx.doi.org/10.1016/j.pain.2011.07.005. (http://www.sciencedirect.com/science/article/pii/S0304395911004453)

# Visual Analog Pain Scale