Enhanced Recovery After Spine Surgery: A Prospective Randomized Controlled Trial to Assess Quality of Recovery and the Biochemical Stress Response to Lumbar Fusion

FUNDER: Research & Education Fund, Department of Anesthesiology, Critical Care & Pain Management

PROTOCOL NO.: 2016-617

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PROTOCOL SYNOPSIS

Protocol Title:	Enhanced Recovery After Spine Surgery: A Prospective Randomized Controlled Trial to Assess Quality of Recovery and the Biochemical Stress Response to Lumbar Fusion
Protocol Number:	2016-617
Protocol Date:	5/4/2020
Sponsor:	N/A
Principal Investigator:	Ellen M Soffin, MD PhD
Products:	NA
Objective:	Our primary aim was to investigate the effect of the pathway on patient quality of recovery compared with usual care in a randomized controlled trial at an orthopedic specialty hospital.
Study Design:	Randomized Controlled Trial
Enrollment:	56
Subject Criteria:	1. Any patient presenting for 1 or 2 level posterior lumbar fusion with instrumentation. 2. Ages 21 and older.
Study Duration:	December 2016 – October 2018
Data Collection:	• Name • MRN ID • Age • Race • Ethnicity • Gender • Height • Weight • BMI • ASA • QoR40 Survey Scores • Details of nutritional, anesthetic, and PT management • Collection of Plasma

	• PT assessment for patient discharge • Surgical assessment of patient discharge • Postoperative complications
Outcome Parameters:	• The primary outcome is patient score on the Quality of Recovery 40 (QoR40) inventory, measured at POD3.
	1. Length of stay and time from surgery to meeting discharge and physical therapy goals (measured in days after surgery). 2. Pain control: opioid consumption and NRS rating scales of pain (measured in morphine equivalents, and numerically, respectively, daily). 3. Time to post-operative oral intake (measured in days after surgery; or hours, if on POD 0). 4. Post-operative nausea, vomiting and ileus (measured daily after surgery). 5. Levels of plasma markers of surgical stress (IL-6, cortisol, CRP and insulin resistance; post-operative days 0 [ie, PACU], 1 and 3). 6. Other post-operative complications: presence of delirium/confusion, infection, DVT/PE (will be assessed for the entire hospital admission, but measured at discharge. 7. QoR40 administered daily during the admission (starting at POD 0; ie, prior to PACU discharge) until POD 3, once on the day of discharge, and on PODs 14 and 56.

Statistical Analysis:	1. Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.): two-sample t-test 2. Alpha level: 0.05 3. Beta or power level: 80% 4. Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): mean +/- SD QoR40 on POD 3 in control group = 183.0 ± 14.1 (Bekker 2013) 5. Number of groups being compared (use 1 for paired analysis within the same subjects):2 6. Effect size or change expected between groups: 12 point difference in QoR40 score between groups (Myles et al., 2012 found a 12 point difference in mean QoR40 score between patients with and without severe postoperative nausea and vomiting) 7. Resulting number per group: 25 8. Total sample size required: 50 + ~10% to account for attrition = 56 • Adding 4 more patients to achieve 80% power which is a total sample size of 60 The primary outcome (QoR40 on POD3) will be compared between the ERAS and conventional perioperative management groups using a two sample *t*-test or Wilcoxon rank-sum test, depending upon the distribution of the data. As a secondary analysis, linear regression will be used to compare the primary outcome between groups while adjusting for number of spine levels fused. Secondary outcomes measured once per patient will be analyzed by *t*-test or Wilcoxon rank-sum test (continuous data) and $\chi 2$ or Fisher's exact test (categorical data). Outcomes measured multiple times per patient (e.g., plasma levels of IL-6, cortisol, CRP and the glucose:insulin) will be analyzed using regression based on a generalized estimating equation approach. Balance on demographics and baseline characteristics will be assessed by calculating standardized differences (difference in means or proportions divided by the pooled standard deviation) between groups. An absolute value of 0.2 or greater will be interpreted as more imbalance than would be expected by chance (Austin 2009). All analyses will be performed on an intention-to-treat basis.

1.0 INTRODUCTION

The concept of ERAS was first introduced by Henrik Kehlet in the 1990s (Kehlet, 1997). The goal of ERAS pathways is to promote faster recovery by maintaining pre-operative organ function and reducing the profound stress response that follows surgery. Early studies in colorectal surgery patients established that "organ dysfunction", (expressed as pain, nausea, vomiting, ileus, fatigue and cognitive dysfunction), together with prolonged immobilization, and logistical issues all contribute to slow post-operative recovery. Kehlet hypothesized that it was unlikely any single surgical technique, anesthetic intervention or medication could significantly impact organ dysfunction individually. However, a better recovery could be achieved with a multimodal approach directed towards modulating the surgical stress response. This led to the introduction of ERAS for colorectal surgery in which a number of pre-, intra- and postoperative interventions are delivered together in order to produce improvements in overall clinical outcomes and healthcare resource utilization. A recent study published in *JAMA* highlights the clinical and economic gains that can be achieved with an ERAS-for-colorectal surgery pathway: compared to historic controls, after introducing the ERAS pathway, hospital stay was reduced by 3 days, without an increase in readmission rates; opiate consumption was reduced by 50%; and a cost saving of almost $7000 per surgery was achieved (Geltzeiler et al., 2014). Given the quality improvements found in colorectal patients, ERAS pathways have been quickly implemented in a range of surgical specialties, including total joint arthroplasty (hip and knee; Aasvang et al., 2015), gynecologic oncology (Nelson et al., 2014), urology (Melnyk et al., 2011), vascular (Podore & Throop, 1999) and thoracic surgery (Tovar et al. 1998).

There is a strong theoretical case for the introduction of ERAS principles to major spine surgery. The demand for spine surgery is increasing, and there are wide variations in length of stay, complication rates, post-operative pain and functional recovery. In particular, spinal procedures are associated with especially high levels of pain. Indeed, in a recent prospective study of pain intensity across 179 different surgical procedures, lumbar fusion and complex spinal reconstruction were ranked 3 of the 6 most painful (Gerbershagen et al., 2013). Similar to colorectal procedures, ileus is a frequent complication limiting recovery and increasing length of stay after spinal fusion (Motasem et al., 2014). Additionally, rates of lumbar fusion are increasing rapidly, particularly for spinal stenosis and degenerative spondylolisthesis. The *US Spinal Surgery Market Outlook to 2017* indicates that advanced technologies and an aging population will lead to further increased demand for these procedures (Ken Research, 2013). At the same time, evidence derived from Medicare patients suggests that aggregated hospital charges are increasing while the overall procedure cost is falling, suggesting greater surgical complexity and/or longer length of stay (Deyo et al., 2010).

Thus, there are clinical and economic imperatives to develop strategies to improve outcomes after spine surgery. To date, ERAS principles have not yet been applied to spine surgery. Given the success of ERAS in so many surgical disciplines, here we ask whether an ERAS pathway can also improve quality of recovery and reduce complications after multi-level lumbar fusion.

A major assumption underlying the efficacy of ERAS pathways is modulation of the systemic inflammatory response (SIR) to surgery (Kehlet, 1997). The stress of surgery leads to well-characterized metabolic, endocrine and immune responses, which together promote physiological stability and healing (Marik & Flemmer, 2012). The major responses to surgical injury include the release of proinflammatory cytokines (most importantly, IL-6) and acute phase proteins (C-reactive protein), elevated cortisol, and the development of insulin resistance (Desborough, 2000). CRP and IL-6 have the strongest association with the magnitude of the surgical injury (Watt et al., 2015a). A recent meta-analysis of the effect of ERAS on markers of SIR after colorectal surgery concluded that overall, objective evidence is limited, with the exception that a laparoscopic approach is associated with reduction in IL-6 and CRP (Watt et al., 2015). There is limited data regarding inflammatory markers after spine surgery: percutaneous lumbar discectomy is associated with lower levels of inflammatory cytokines compared to open discectomy (Pan et al., 2014), and glucocorticoids modulate levels of most cytokines after osteotomy (Reikeras et al., 2009). Bekker et al (2013) described reduced IL-10 and cortisol after dexmedetomidine infusion in patients undergoing lumbar fusion, but to date, the relationship between perioperative interventions and effects on SIR remains an underexplored area of research.

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Tovar, E.A., Roethe, R.A., Weissig, M.D. et al. (1998). One-day admission for lung lobectomy: an incidental result of a clinical pathway. *Ann Thorac Surg*. 65:803-6.
Watt, D.G., Horgan, P.G. & McMillan, D.C. (2015a). Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. *Surgery* 157:362-80.

2.0 PRODUCT DESCRIPTION

N/A

3.0 OBJECTIVE OF CLINICAL STUDY

The specific aims are to determine if placing patients on the ERAS for spine pathway will:

1. Improve the quality of recovery after spine surgery.
2. Accelerate recovery.
3. Be associated with fewer post-operative complications.
   Attenuate the stress response to surgery.

4.0 STUDY HYPOTHESES

Hypothesis 1: ERAS pathway patients will experience greater quality of recovery after multilevel spine fusion.
Hypothesis 2: ERAS patients will demonstrate accelerated recovery after surgery, as evidenced by faster time to discharge readiness.
Hypothesis 3: Use of the ERAS pathway will be associated with fewer post-operative complications.
Hypothesis 4: The pathway will modulate the surgical stress response.

5.0 STUDY DESIGN

5.1 Study Duration

12/2016-10/2018

5.2 Endpoints

5.2.1 Primary Endpoint

- The primary outcome is patient score on the Quality of Recovery 40 (QoR40) inventory, measured at POD3.

5.2.2 Secondary Endpoints

- Length of stay and time from surgery to meeting discharge and physical therapy goals (measured in days after surgery).
- Pain control: opioid consumption and NRS rating scales of pain (measured in morphine equivalents, and numerically, respectively, daily).
- Time to post-operative oral intake (measured in days after surgery; or hours, if on POD 0).
- Post-operative nausea, vomiting and ileus (measured daily after surgery).
- Levels of plasma markers of surgical stress (IL-6, cortisol, CRP and insulin resistance; post-operative days 0 [ie, PACU], 1 and 3).
- Other post-operative complications: presence of delirium/confusion, infection, DVT/PE (will be assessed for the entire hospital admission, but measured at discharge.
- QoR40 administered daily during the admission (starting at POD 0; ie, prior to PACU discharge) until POD 3, once on the day of discharge, and on PODs 14 and 56.

5.3 Study Sites

Hospital for Special Surgery – Main Campus

6.0 STUDY POPULATION

6.1 Number of Subjects

56

6.2 Inclusion Criteria

Subjects of either gender will be included if they:

- Any patient presenting for 1 or 2 level posterior lumbar fusion with instrumentation.
- Ages 21 and older.

6.3 Exclusion Criteria

Subjects will be excluded from the study if they:

- Cognitive impairment (baseline dementia, cognitive dysfunction or inability to consent to participate).
- Kidney disease: GFR <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause (Levey et al., 2012).
- Liver disease: transaminitis, cirrhosis, hepatitis, hypoalbuminemia, coagulopathy.
- Pre-existing bowel disease (inflammatory bowel disease, colectomy/ colostomy/diverticular disease).
- Allergy/intolerance/contraindication to any medication or component included in the ERAS pathway protocol.

- Diabetes mellitus (types I and II).
- Planned minimally invasive surgical technique including use of the Coflex device.
- Patients whose primary or preferred language is not English.
- Patients planned to be discharged to rehab facility post-operatively.
- Planned procedures involving revisions of instrumented posterior lumbar fusions, xtreme lateral interbody fusions, and/or removals.

6.4 Randomization

The randomization schedule will be created using SAS software by a member of the Healthcare Research Institute not otherwise involved in the trial. The randomization schedule will be stratified by number of spine levels fused (50 1-level fusions vs. 10 2-level fusions to account for the relative frequency of each procedure) and contain permuted blocks within each stratum. Randomization will be performed after the patient has signed informed consent to be in the study but prior to interventions and observations.

7.0 PROCEDURES

7.1 Surgical Procedure

- 1 or 2 level posterior lumbar fusion

7.1.1 Investigational Product Application

N/A

7.2 Data Collection

Data will be collected by an investigator or research assistant. Sources of data include medical records and patient physical assessments conducted by study personnel. Data will be recorded and managed using REDCap electronic data capture tools hosted at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Connection to REDCap occurs via the hospital's encrypted cable and wireless networks, and data will be entered through a password-protected computer terminal or iPad.

7.3 Schedule of Assessments

Study Visit #	Randomization	Surgery	Administration of IV Study Medication	Administration of Topical Study Medication	Blood Draw (from existing catheter)	Collection of Drained Blood from Wound
#1 OR, Before TQ onset	X	SOC	X		X	
#2 OR, Before final TQ release				X	X	X (Surgeon collects pooled blood around wound)
#3 PACU, 1 hour after TQ release			X		X	
#4 PACU, 4 hours after TQ release					X	X (Taken from surgical drain)

X= Research Procedures

SOC= Standard of care (care you would receive if you were not participating in this study)

OR = Operating Room; PACU = Post-Anesthesia Care Unit; TQ = Tourniquet; IV = Intravenous

8.0 STATISTICAL ANALYSIS

1. Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.): two-sample t-test
2. Alpha level: 0.05
3. Beta or power level: 80%
4. Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): mean +/- SD QoR40 on POD 3 in control group = 183.0 ± 14.1 (Bekker 2013)
5. Number of groups being compared (use 1 for paired analysis within the same subjects):2
6. Effect size or change expected between groups: 12 point difference in QoR40 score between groups (Myles et al., 2012 found a 12 point
difference in mean QoR40 score between patients with and without severe postoperative nausea and vomiting)
7. Resulting number per group: 25
8. Total sample size required: 50 + ~10% to account for attrition = 56
    - Adding 4 more patients to achieve 80% power which is a total sample size of 60

The primary outcome (QoR40 on POD3) will be compared between the ERAS and conventional perioperative management groups using a two sample *t*-test or Wilcoxon rank-sum test, depending upon the distribution of the data. As a secondary analysis, linear regression will be used to compare the primary outcome between groups while adjusting for number of spine levels fused. Secondary outcomes measured once per patient will be analyzed by *t*-test or Wilcoxon rank-sum test (continuous data) and $\chi 2$ or Fisher's exact test (categorical data).
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Balance on demographics and baseline characteristics will be assessed by calculating standardized differences (difference in means or proportions divided by the pooled standard deviation) between groups. An absolute value of 0.2 or greater will be interpreted as more imbalance than would be expected by chance (Austin 2009).
All analyses will be performed on an intention-to-treat basis.

9.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report. Definitions for Adverse Event (AE) used in this study are listed below and are based on FDA and international guidelines:

9.1 Adverse Event (AE)

All of the components included in the proposed ERAS pathway have evidence of benefit, no evidence of harm, and are used routinely in the care of patients undergoing lumbar fusion at HSS. The objective of this study is to ensure that those assigned to the ERAS pathway will receive these standard of care components. Patients who are assigned in the no-treatment (usual care) group will be receiving conventional perioperative management and will thus be considered standard of care, as well. Prior to enrollment at their pre-operative surgical clinic appointment, patients will be thoroughly screened to determine eligibility by a study

investigator. However, if after enrollment, the clinical judgment of the healthcare provider(s) deems the patient to be unfit to continue the study procedures specific to his/her ERAS group assignment, he/she will thereafter proceed through the conventional perioperative pathway. The risks of collecting plasma for this study are similar to the risks of a routine blood draw, including - mild pain, bruising, and very rarely infection at the place of needle insertion. However, the likelihood of these risks occurring is rare, as an arterial line catheter is routinely placed in patients undergoing this class of spine surgery in order to continuously monitor the patient's hemodynamics perioperatively. The study team expects to draw samples using the pre-existing catheter. Patients can decline to participate in further blood draws at any point after enrollment should discomfort become a concern.

Participation in this research involves the potential risk of a break of confidentiality to stored health information. HSS tries to minimize those risks by (i) removing some direct identifiers from stored information (i.e., names, social security numbers, medical record numbers); (ii) securing, in a separate location, and limiting access to information that would be identifiable; and (iii) limiting access to information stored to HSS investigators.

The likelihood of a breach of confidentiality is minimal.

9.2 Serious Adverse Events (SAE)

N/A

9.3 Subsequent Surgical Interventions Definitions

N/A

9.4 Adverse Event Reporting

All adverse events will be reported to the DSMB and IRB within five working days of the event.

10.0 INVESTIGATOR RESPONSIBILITIES, RECORD AND REPORTS

10.1 Subject Consent and Information

Written/signed consent will be collected from participants in the holding area before surgery.

10.2 Subject Data Protection

- HSS tries to minimize those risks by (i) removing some direct identifiers from information stored [(i.e., names, social security numbers, medical record numbers)]; (ii) securing, in a separate location, and limiting access to information linking codes (i.e., linkage codes) assigned to the registry information with direct participant identifiers; and (iii) limiting access to information stored to HSS investigators.
- Access to the REDCap program is password-protected, and access to a specific study's information within the program is limited to the research assistant and other IRB-approved study personnel who have been given permission to view and/or enter study data. REDCap program access is authorized by the CTSC; particular study access is granted by the research assistant. For data exports, fields marked as protected health information (PHI) in REDCap will be de-identified, if feasible.

- All transmission of data will occur via encrypted networks in password-protected files. Any paper-based data sheets utilized for the study will have personal identifiers removed whenever possible and will be stored in the department's locked office. Each subject will be assigned a unique study number for identification, and that number will not be derived from or related to information about the individual. Presentations and publications that result from this study will not contain any individual identifiers (at most the unique study numbers may be referred to). Thus our research presents a minimal risk of harm to subjects' privacy.