

**Randomized Controlled Trial of Postoperative Thoracic Epidural Analgesia
Versus Intravenous Patient Controlled Analgesia (3:1) in Patients
Undergoing Liver and/or Pancreatic Resection**

• Table of Contents	1
• Study Personnel	2
• List of Abbreviations	3
1.0 Objectives	4
2.0 Background and Rationale	4
3.0 Patent Eligibility	10
4.0 Treatment Plan: Analgesic Regimens	11
5.0 Treatment Plan: Perioperative Monitoring	12
6.0 Postoperative Assessments	13
7.0 Measure Outcomes	14
8.0 Statistical Considerations	16
9.0 Data and Protocol Management	18
10.0 Data Safety and Monitoring Board	18
11.0 Confidentiality	16
• References	20
• Appendix A – Inpatient IVPCA Orders	25
• Appendix B – Inpatient Thoracic Epidural Orders	26
• Appendix C – Motor Block Scale	27
• Appendix D – Dermatome Sensory Block Map	28
• Appendix E – Richmond Agitation Symptom Scale	29
• Appendix F – Numeric/Visual Analog Pain Scale	30

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LIST OF ABBREVIATIONS

APS	Acute Pain Service
aPTT	Activated Partial Thromboplastin Time
CBC	Complete blood count
cc	Cubic Centimeter
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
GI	Gastrointestinal
HORQ	Health Outcomes Recovery Questionnaire
Hr	Hour
HR	Heart Rate
ICU	Intensive Care Unit
ICU	Intensive Care Unit
INR	International Normalized Ratio
IV	Intravenous
IVPCA	Intravenous Patient Controlled Analgesia
MAP	Mean Arterial Pressure
MCS	Mental Health Component Summary
MDACC	MD Anderson Cancer Center
mg	Milligram
MH	Mental Health
ml	Milliliter
NK	Natural Killer
NO	Nitric Oxide
OR	Operating Room
PACU	Post Anesthesia Care Unit
PCA	Patient Controlled Analgesia
PCS	Physical Component Summary
PPS	Postoperative Pain Survey
PPV	Pulse Pressure Variation
prn	As Needed
PT	Prothrombin Time
Q/q	Every
QOL	Quality of Life
QOR	Quality of Recovery
RASS	Richmond Agitation Symptoms Scale
SBP	Systolic Blood Pressure
SDS	Symptom Distress Scale
SICU	Surgical Intensive Care Unit
SV	Stroke Volume
SVV	Stroke Volume Variation
TEA	Thoracic Epidural Analgesia
Th1	T-Helper Lymphocyte
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

1.0 Objectives

1.1 Primary Objective:

1.1.1 - To compare postoperative pain control and quality of life in patients undergoing liver and/or pancreatic resection between those receiving thoracic epidural analgesia (TEA) versus intravenous patient-controlled analgesia (IVPCA).

1.2 Secondary Objectives:

1.2.1 - To compare postoperative/surgical outcomes between TEA and IVPCA groups.

1.2.2 - To validate survey instruments in the assessment of postoperative quality of recovery/satisfaction.

1.2.3 - To compare parameters of immunological responses between TEA and IVPCA groups.

2.0 Background and Rationale

2.1 Introduction

- Postoperative outcomes for surgical resection of cancer involving the liver and pancreas have significantly improved over the last few decades due to improvements in surgical techniques and perioperative care.[1-4] The advent of minimally invasive laparoscopic surgery has led to decreased postoperative pain compared to traditional open surgical procedures.[5, 6] However laparoscopy is not technically feasible and is oncologically inappropriate in the vast majority of these patients. Thus improved methods to limit the morbidity of postoperative pain and its sequelae are in critical need. Inadequate pain control after open abdominal procedures can result in increased complications, length of stay, and delay in overall recovery. This is of particular importance in cancer patients, many of whom require further intensive oncologic therapies after surgical resection. It has been found that a significant proportion of patients who may benefit from adjuvant therapy are unable to proceed due to prolongation of care secondary to surgical complications.[7, 8] An effective regimen of postoperative analgesia based on current evidence-based protocols, may attenuate the detrimental physiologic responses to resection, and contribute to improvement in patient outcomes and lower complications. As an example, uncontrolled postoperative pain may contribute to cardiac morbidity through activation of the sympathetic nervous system, surgical stress response, and coagulation cascade which can increase myocardial oxygen demand by increasing heart rate, contractility, arterial blood pressure, and enhance perioperative hypercoagulability.[9] Despite the availability of pain guidelines, postoperative pain continues to be undertreated.[10] Currently the two major analgesic options after inpatient abdominal surgery in the United States are intravenous patient-controlled analgesia (IVPCA) using narcotics and thoracic epidural analgesia (TEA) using local anesthetics and/or narcotics. There has been considerable debate regarding the advantages and disadvantages between these two

standard of care modalities and how they should be applied in the postoperative setting.

2.2 Intravenous Opioids

- Opioid-based analgesics work by binding to opioid receptors, which are found principally in the central nervous system and the gastrointestinal tract.[11] The analgesic effects of narcotics are due to decreased perception and reaction to pain.[12] By allowing individualization of postoperative analgesic requirements, IVPCA is considered to be the accepted standard by which opioids are delivered to the hospitalized surgical patient. IVPCA provides significantly superior analgesia compared with conventional "as needed" (intravenous, intramuscular, or subcutaneous) opioid administration.[13]

- However, all systemic narcotic-based methods have certain drawbacks. The side effects in postoperative patients include significant nausea, sedation, cough suppression, respiratory depression, constipation, and delayed recovery of bowel function.[14] These effects may lead to increased postoperative complications and delayed recovery, particularly in older, higher-risk patients. Furthermore IVPCA has been found to have a higher incidence of interruptions in analgesic delivery due to system-related events compared to other forms of continuous analgesic delivery.[15]

2.3 Epidural Analgesia

- Unlike that seen with systemic opioids, epidural local anesthetics can block nociceptive (pain) input into the central nervous system and with the addition of a low-dose epidural opioid, may provide an even greater analgesic effect.[16] Due to the potential reduced need for narcotics, post-operative epidural analgesia may decrease postoperative morbidity resulting from excessive narcotic use. A recent systematic review found consistent evidence that TEA reduces risk of cardiovascular and pulmonary complications and hastens return of postoperative gastrointestinal function compared to other forms of intravenous narcotic regimens after abdominal surgery in subsets of high-risk patients.[9] As most adult solid cancers are diagnosed in the elderly, these can be at higher risk of operative complications. Epidural analgesia has been found to provide better pain relief in elderly patients, particularly for dynamic pain, and improves postoperative recovery with a lower incidence of adverse effects compared with IVPCA.[17] Epidural analgesia may provide additional humoral and immunological benefits. In patients receiving regional epidural analgesia, the neuroendocrine response has been found to be attenuated while NK-cell activity is preserved compared to those patients receiving IVPCA.[18, 19] Regional analgesia has been shown to markedly attenuate the neuroendocrine response to surgery, as evidenced by smaller perioperative concentrations of stress-induced plasma catecholamines and cortisol.[20, 21] Similarly, NK and Th1-cell activity is better preserved with epidural techniques.[22, 23]

- Epidural analgesia has its own set of potential drawbacks and can be complicated by pruritus, motor block, hypotension, catheter malfunction, and local infection.[24] Epidural hematoma formation, although very rare, can be a catastrophic complication of epidural catheterization. The risk is theoretically

increased in patients with impaired hemostasis because of coagulopathy or therapeutic anticoagulation. However, the results of several studies looking at over 3000 patients undergoing TEA found the incidence of epidural hematoma to be less than 0.001%. [25-27] Early recognition of these problems can improve outcome and these low-frequency complications need to be balanced against the potentially serious hypoxemia and other postoperative complications associated with intravenous opioids used for postoperative pain relief. [28] Epidural analgesia is labor intensive and needs the support of an Acute Pain Service in order to use this technique safely. Overall, thoracic epidural analgesia has been found to be safe for use on surgical wards. [29]

2.4 Evidence-Based Postoperative Analgesia

- Results of numerous randomized controlled studies comparing these two modalities have shown that TEA results in improved pain scores compared to IVPCA. These studies evaluated analgesic outcomes in a variety of operative procedures: thoracic, spinal, orthopedic, gynecologic, and abdominal surgery. [30-36] A recent meta-analysis found that for all types of surgery and pain assessments, all forms of epidural analgesia (both continuous epidural infusion and patient-controlled epidural analgesia) provided significantly superior postoperative analgesia compared with intravenous patient-controlled analgesia. [13] The authors concluded that almost without exception, epidural analgesia, regardless of analgesic agent, epidural regimen, and type and time of pain assessment, provided superior postoperative analgesia compared to intravenous patient-controlled analgesia (IVPCA). Although none of these studies included patients specifically undergoing liver and/or pancreatic surgery.

2.5 Non-analgesic Benefits

- The advantages of TEA over IVPCA are not only represented by better analgesic scores. Numerous studies have found that there is reduced sedation with less respiratory complications, improved out-of-bed mobilization, faster return of bowel function (ileus) with improved food intake, long-lasting effects on exercise capacity, as well as significant reductions in hospital stay, all of which led to the added benefit of cost effective healthcare with decreased hospital costs. [37-42] Epidural analgesia was found to protect against postoperative pneumonia following abdominal surgery in a recent meta-analysis. [43] One of the more recent measures of postoperative recovery has to do with patient satisfaction and overall perioperative quality of life. Several recent studies found improved impact on overall patient satisfaction and superior perioperative quality of life (QOL) scores in those receiving TEA compared to IVPCA. [31, 39] Additional research is needed to validate these claims in patients undergoing liver and/or pancreatic surgery as well as to develop optimal measures of postoperative recovery and satisfaction in all surgical patients.

2.6 Analgesic Regimens in Cancer

- The use of epidural analgesia versus IVPCA has specifically been studied in the cancer patient population. Epidural analgesia was found to have superior postoperative pain control compared to traditional IVPCA in a large series of patients undergoing surgery for malignancy. Furthermore patients receiving

epidural analgesia experienced faster recovery as judged by shorter mechanical ventilation time and decreased SICU and hospital stays resulting in significantly lower hospitalization costs.[38, 44] There is also recent speculation that opioid narcotics may play a significant role in cancer recurrence with clinical data suggesting that methods of analgesic technique may play a role in tumor dissemination and recurrence.[45-47] In an animal model of surgical-induced tumor seeding and metastasis, researchers found that the addition of regional analgesia (spinal blockade) reduced retention of shed tumor cells by over 70%. A similar benefit was observed when studying the actual development of metastasis.[48] In addition to the clinical observations, there is also evolving basic science literature suggesting that narcotics affect tumor growth.[49] Considerable evidence suggests that narcotics facilitate metastasis both *via* suppression of critical anti-tumor immune functions and by mechanisms independent of immune suppression. Acute and chronic administration of opioids is now known to mediate immune response by a combination of central and peripheral mechanisms. Peripherally exogenous opioids inhibit components of the cellular and humoral immune function such as antibody production, NK-cell activity, cytokine secretion, lymphocyte proliferative responses to mitogens, and phagocytic activity.[50] Signals of central origin may be relayed through 1) the hypothalamic-pituitary-adrenal axis resulting in the production of glucocorticoids, which are immunosuppressive, and 2) the sympathetic nervous system eliciting the release of biologic amines, which in turn, also reduces immunocompetence.[51] Alternative mechanisms by which opioids might promote metastasis are: induction of nitric-oxide (NO) upregulation and angiogenesis by opioids. NO also mediates increased vascular permeability, which could both increase the release of cancer cells into the circulation and increase extravasation of circulating tumor cells and the formation of new metastases. Nitric oxide also regulates endothelial cell proliferation, migration, and protease release – all of which are important for angiogenesis.[52] Vascular Endothelial Growth Factor (VEGF) plays a key role in angiogenesis. Recent evidence indicates that opioids promote VEGF-induced angiogenesis, an effect that is nearly completely blocked by opioid antagonists.[53] A large, multicenter, prospective, randomized trial investigating the influence of type of analgesia (intravenous narcotics versus epidural analgesia) on cancer recurrence is currently underway.[54]

2.7 Analgesia in Liver and Pancreatic Surgery

- Despite the overwhelming evidence supporting its use in a variety of other surgical procedures, postoperative epidural analgesia is universally underutilized in patients undergoing liver and/or pancreatic surgery at most centers. This is due for a variety of reasons such as concerns of longer procedure times, greater initial costs, invasiveness of the procedure, fear of increased complications in this unique subset of patients, and clinical benefits that may in fact be underwhelming. No randomized controlled trials have been performed evaluating the efficacy or safety of epidural analgesia versus IVPCA in this specific patient population.

- There is little data available regarding epidural analgesia in pancreatic surgery. In a retrospective analysis of patients undergoing pancreatic resection epidural analgesia was associated with a modest reduction in postoperative pain scores,

however those patients were more likely to require intensive care unit admissions and required more frequent alterations of analgesics. In that series epidural analgesia was associated with a non-significant increase in blood losses and fluid requirements. The groups (TEA vs. IVPVA) did not differ in bowel function, lengths of stay, morbidities, or mortalities.[55] Others found, also retrospectively, that epidural analgesia after pancreatic resection was associated with hemodynamic instability, which may theoretically compromise enteric anastomoses, gastrointestinal recovery, and respiratory function.[56] In contrast, another analysis in those undergoing pancreatic procedures found that patients treated with epidural analgesia experienced better pain relief, compared with subjects receiving IV analgesia who demonstrated a higher incidence of opioid-related adverse effects such as sedation and respiratory depression.[57]

- The data on epidural analgesia in liver surgery is also sparse and contradictory. In a retrospective analysis of patients comparing epidural analgesia to traditional IVPVA, epidural analgesia was independently associated with increased risk of packed red blood cell transfusion after hepatectomy and did not appear to minimize complications or shorten hospital stay.[58] Data from liver transplantation literature has identified a high prevalence of hemostatic abnormalities in patients undergoing major hepatic resection while receiving epidural analgesia.[59] In contrast, a recent study found that epidural anesthesia does not lead to changes in intravascular volume, but only promotes redistribution of blood, thus decreasing both venous return and portal vein pressure, which in fact may contribute to reduced hepatic congestion and reduced surgical blood loss.[60] None of these studies evaluated effective pain control.

2.8 Current Institutional Practice

- The primary indication for TEA should be pain relief for open abdominal or thoracic surgery as there is sufficient Level 1 evidence that it may provide improved analgesia than intravenous opioids. In our current practice the decision for epidural versus IVPVA is both patient and physician dependent. Based on our institution's extensive experience, the use of perioperative epidural techniques should be considered to expedite recovery of surgical patients and has the added value benefit of being cost effective by reducing hospital stays. Observed advantages of this approach are higher patient postoperative pain satisfaction, increased efficiency, less sedation, lower opioid dosage, and decrease in postoperative complications, particularly in higher-risk patients. We believe as others, that the clinical advantages of TEA outweigh the greater initial cost and invasiveness of this technique.[61] Due to our significant experience with both local-regional anesthetic techniques (>2000 TEA/year) and systemic opioid administration, as well as our established dedicated inpatient Acute Pain Service, patients undergoing liver and/or pancreatic surgery at this institution currently receive either IVPVA or TEA for management of their postoperative pain as standard of care.

- The choice of postoperative analgesic regimens has implications for our current analgesic practice, particularly when considering the use of an indwelling epidural catheter in patients undergoing liver and/or pancreatic resection. We currently understand that disorders of coagulation occur after hepatic resection

even in patients who have normal preoperative coagulation and liver function tests. In our experience, the PT returns to normal within 5 days. Transiently impaired hepatic synthesis after major liver resection may account for this imbalance in hemostatic mechanisms.[62] In addition, due to prolonged biliary obstruction in patients with pancreatic head malignancies, abnormalities in vitamin K dependent coagulation factors are common.[63] The safe conduct of care for liver and/or pancreatic resection patients must take into account the possibility of these phenomena. Until these hemostatic abnormalities are better understood, the anesthesiologist and surgeon caring for patients undergoing liver and/or pancreatic surgery must weigh the theoretical risk of epidural hematoma formation against the benefits of epidural analgesia in this unique population. Further studies to characterize the hemostatic abnormalities after liver and/or pancreatic resection are warranted. Important considerations include discussion with the surgical team, measuring perioperative coagulation, and heightened clinical monitoring in the postoperative period. In our experience we have not had any significant epidural complications and have not had a single epidural hematoma in over 20,000 catheter placements.

- The decrease in the use of TEA for patients undergoing liver and/or pancreatic resection at other institutions may paradoxically result in more complications, as loss of expertise in this technique becomes an issue, thus a critical need for level 1 data to support the use of this modality in these patients. Our hypothesis is that TEA is improves pain control compared to IVPCA in patients undergoing liver and/or pancreatic resection with improved patient satisfaction and perioperative quality of life without significant risk of epidural related complications. In addition the limitation of systemic opioids in the postoperative setting may lead to decreased postoperative complications as well as improved immunological function that may correlate with oncologic outcomes. As a result of the following motivational factors: concerns about the effectiveness of TEA and safety in those patients undergoing liver or pancreatic resection, the lack of randomized controlled data supporting its use in this patient population, the increasing evidence regarding potential immunologic benefits of regional analgesia in cancer patients, the recent national demand for assessment of optimal patient recovery and perioperative satisfaction, our considerable experience and expertise with both modalities of postoperative analgesia, and the appropriate infrastructure and organizational leadership already in place at this institution, we have proposed a novel and much needed clinical postoperative analgesic trial with associated laboratory and patient-directed correlates in this subset of patients. We have designed this study to reflect the current clinical practice standards of postoperative analgesia in patients undergoing liver/and or pancreatic surgery.

3.0 Patient Eligibility

3.1 Inclusion Criteria:

3.1.1 - Patients undergoing liver and/or pancreatic surgical resection for malignancy at MD Anderson Cancer Center.

3.1.2 - Patients 18 years of age and older. There will be no upper age restriction.

3.1.3 - Patients must sign a study-specific consent form.

3.1.4 - Adequate coagulation function within 30 days of surgery:

- Platelets $\geq 100,000/\text{ml}$
- INR ≤ 1.5
- aPTT ≤ 40

3.1.5 - Patients must have no fever or evidence of infection or other coexisting medical condition that would preclude epidural placement.

3.2 Exclusion criteria:

3.2.1 - Evidence of severe uncontrolled systemic disease or other comorbidity that precludes liver or pancreatic surgery.

3.2.2 - History of chronic pain, long-term narcotic use or being considered for chronic pain consultation postoperatively.

3.2.3 - Anaphylaxis to local anesthetics or narcotics.

3.2.4 - Previous or current neurologic disease affecting the lower hemithorax or below.

3.2.5 - Major open abdominal/thoracic surgery in the previous 30 days under general anesthesia, except for TIVA (total intravenous anesthesia).

3.2.6 - Technical contraindications to epidural placement: previous thoracic spinal surgery or local skin or soft tissue infection at proposed site for epidural insertion.

3.2.7 - Ongoing use or planned peri-operative use of anticoagulants (not including DVT prophylaxis).

3.2.8 - Known bleeding diathesis or coagulopathy.

3.2.9 - Educational, psychiatric (untreated or poorly controlled schizophrenia, major depression, or bipolar disorder), or communication (language) barrier that would preclude accurate assessment of postoperative pain and/or ability to answer questionnaires (need to be able to read, comprehend, and answer questions).

3.2.10 - Inability to comply with study and/or follow-up procedures.

3.2.11 - Patient refusal to participate in randomization.

3.2.12 - Pregnant women are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy or who have not been postmenopausal for at least 12

consecutive months) must agree to practice adequate contraception and to refrain from breast-feeding, as specified in the informed consent.

3.2.13 - Patients with obvious unresectable disease prior to signing informed consent.

4. Treatment Plan - Analgesic Regimens

4.1 IVPCA

4.1.1 - Immediately following surgery, the OR Anesthesia team will titrate intravenous narcotics in the PACU for pain down to an acceptable level prior to initiating IVPCA. All patients assigned to IVPCA group will be started on intravenous patient-controlled analgesia protocol according to current institutional policy following surgical procedures. All patients will be given hydromorphone as the opioid of choice per current practice, unless there are contraindications. Fentanyl or Morphine will be secondary alternatives. Initial recommended starting doses are: no basal rate, 0.2mg every 10 minutes demand dosing, and a 0.5mg nursing bolus every 1 hour as needed for additional pain control (Appendix A). Adjunctive use oral, rectal, or intravenous non-narcotic analgesics (acetaminophen, non-steroidals, etc.) will be utilized at the discretion of the Primary Surgical Team.

4.1.2 - Patients whose IVPCA's are not functioning or not providing adequate analgesia will be considered for possible postoperative placement of TEA (coagulation studies permitting) as an alternative analgesic regimen (patient crossover).

4.1.3 - Further drug information can be found in the MDACC formulary and the FDA approved package inserts of the medications as they are all commercially available.

4.2 TEA

4.2.1 - All patients assigned to TEA will have thoracic epidurals placed preoperatively in either the holding area or in the operating room according to current institutional protocol. Epidural catheters will be placed between the Thoracic 5th-Thoracic 10th interspinous levels using standard technique according to institutional practices. All epidural catheters will be tested for correct placement and level of block documented and secured as is currently practiced. The epidural will be initially dosed according to current practices with hydromorphone (10 mcg/kg for pts 65 yrs or younger and 5 mcg/kg for pts > 65yrs) after induction of anesthesia. Standard epidural solutions are: Hydromorphone (10 mcg/ml for pts 65yrs or younger and 5 mcg/ml for pts > 65yrs) and Bupivacaine (0.075%) at 10 ml/hr continuous infusion and a 3ml every 10 minutes demand dosing, and a 5ml every 3 hours clinician bolus as needed for additional pain control (Appendix B). Fentanyl with Bupivacaine

will be secondary alternatives. Adjunctive use of oral, rectal, or intravenous non-narcotic analgesics (acetaminophen, non-steriodals, etc.) will be utilized at the discretion of Acute Pain Service and/or Primary Surgical Team. Epidural catheters will remain in place a maximum of 7 days postoperatively. Epidural catheters will be removed once patients are successfully tolerating a full diet or tube feeds and are transitioned to oral/enteral analgesics. Indwelling urinary catheters will be removed after TEA removal per current policy.

4.2.2 - Patients whose TEA's are not functioning or not providing adequate analgesia will be considered for IVPCA as an alternative analgesic regimen (patient crossover).

4.2.3 - Further drug information can be found in the MDACC formulary and the FDA approved package inserts of the medications as they are all commercially available.

5. Treatment Plan – Perioperative Monitoring

5.1 Intraoperative Monitoring

5.1.1 - Patient in both groups will have arterial lines placed per current procedural policy. As is currently practiced hemodynamic and physiologic parameters will be monitored. If available, LiDCO-Rapid technology will be used to track other hemodynamic parameters during the duration of the procedure. Perioperative fluids, vasoactive medication administration, urine output, and blood product transfusions will be documented as per current guidelines. Central venous pressure will be recorded in those patients that have central venous catheters.

5.2 Postoperative Monitoring

5.2.1 - After surgery, patients in both groups will be initially admitted to the PACU and subsequent disposition to either intensive care unit, overnight recovery suite, or general surgical floor dictated by patient status and the anesthesia and primary surgical team discretion. Patient monitoring in ICU, overnight recovery, or floor will be per current practice.

5.2.2 - 15cc of blood will be drawn intraoperatively prior to anesthesia induction and daily every other day (POD# 1, 3, 5) postoperatively with other standard postoperative tests, for laboratory correlates of analgesic mediated immune function. 5cc of blood will be drawn into purple top (ETDA) tubes and 5cc will be drawn into 2 green top (Heparinized) tubes. All blood samples will be kept on ice for transport (up to 8hrs). After blood draw (performed at same time as routine daily postoperative labs) samples will be sent to laboratory Y6.25 (pager -713-404-2911). Laboratory personnel involved include Javier Valenzuela and Juan Cata. For cell separation a Ficoll gradient technique will be used and for plasma collection, we will spin each EDTA sample for 10 min at

2000 rpm at 4 degrees C. Samples will be stored until processing at -80 degrees C in laboratory freezer with samples de-identified for confidentiality. These correlative studies are optional however will not require additional blood draws to the patient as they are being drawn simultaneously to the routine perioperative blood draws.

6. Postoperative Assessments

6.1 Postoperative Epidural Assessment (TEA only)

6.1.1 - The Acute Pain Service will monitor epidural site daily for evidence of hematoma, cellulitis, abscess, CSF leak, and malfunction as is current practice.

6.2 Postoperative Motor Block Assessment (TEA only)

6.2.1 - Motor status will be assessed approximately every nursing shift and before ambulation as is current practice (Appendix C).

6.3 Postoperative Sensory Block Assessment (TEA only)

6.3.1 - Sensory status will be assessed approximately every nursing shift to ensure adequate epidural function and that block is within expected dermatome levels as is current practice (Appendix D).

6.4 Postoperative Sedation Assessment (TEA and IVPCA)

6.4.1 - Sedation will be assessed using Richmond Agitation Sedation Scale (RASS) approximately every nursing shift per current practice (Appendix E).

6.5 Postoperative Pain Assessment (Both TEA and IVPCA Groups)

6.5.1 - Pain scores will be assessed in both groups with a Numeric/Visual Pain Scale (0-10) at various time points in the clinical record per current inpatient policies (Appendix F). Beginning in the PACU after surgery, pain will be assessed by nursing staff approximately every hour per current practice until disposition to inpatient care units. In the overnight recovery suite and general floor pain will be assessed by nursing staff approximately every 4 hours per current practice. In the SICU pain will be assessed by nursing staff approximately every hour per current practice. The pain assessments that are being used for analysis are average pain scores within first 6hrs postop, the next 18hrs, and each 24hr period thereafter. The pain scores for each 24 hour period after this will be averaged (as many as are collected). Pain will re-assessed by nursing staff approximately 1 hour after every analgesic intervention per current practice on all nursing floors. All dosing alterations, changes, and total narcotic/analgesic use will be documented in the clinical record per current practice.

6.5.2 - The Acute Pain Service team/nurse will assess all patients in both groups (TEA and IVPKA). Therapeutic analgesic interventions in the TEA group will be per discretion of the Acute Pain Service per current practice. Therapeutic interventions in the IVPKA group will be per discretion of the primary surgical team per current practice and the primary surgical team will be blinded to the Acute Pain Service assessment of patients in IVPKA group.

6.6 Postoperative Quality of Life and Recovery Questionnaires

- Several postoperative Quality of Life and Surgical Recovery instruments will be filled out by participating patients in both groups. Please refer to 7.2.2 for details.

7. Measured Outcomes (TEA and IVPKA)

7.1 Primary Endpoints

7.1.1 - Pain scores (Numeric/Visual Pain Scale)

Pain score AUC within the first 48 hours will be used as the primary endpoint. The AUC for each patient will be computed using the trapezoidal method using the pain score versus time curve. The mean AUC pain scores within the first 48 hours will be compared between TEA and IVPKA groups for the primary analysis.

7.1.2 - Quality of Life

- Patients will complete a validated SF-8, Acute Recall QOL survey (preoperatively and then at approximately 24hrs after surgery) (Appendix G)
- Patients will complete a validated SF-36v2, Acute Recall QOL survey (preoperatively and then prior to discharge or at approximately 1 week after surgery – whichever is first) (Appendix H).

7.2 Secondary Endpoints

7.2.1 - Postoperative complications

- Hospital stay
- ICU admissions
- Postoperative bleeding
- Infection
- Anastomotic leak
- Respiratory complications
- Cardiac complications
- DVT/VTE
- Recovery of bowel function

- Time to ambulation
- Epidural complications

7.2.2 - Quality of Recovery/Patient Satisfaction

- Several short (5-10 minute), simple survey instruments will be utilized in this study to assess patient-centered perioperative pain control, and overall recovery, satisfaction. Although all of these survey instruments have been validated in other studies, none have been applied in the evaluation of patients undergoing liver and/or pancreatic surgery. The use of multiple instruments with some overlap in measures allows for redundancy in assessments and the determination of the accuracy of patient reporting. Such data will assist in comparing the efficacy of these various instruments in capturing the “true” quality of recovery in this subset of patients. Any variations and discrepancies in the reported redundant measures will assist in the formulation of a subsequent improved instrument for validation on a greater scale.

- The Health Outcomes Recovery Questionnaire (HORQ), a validated postoperative recovery instrument, will be administered daily for the first 5 postoperative days and includes questions regarding patient satisfaction, daily activities, and opioid-related symptoms (Appendix I).[64]
- The Postoperative Pain Survey (PPS), an outcome-oriented validated survey to assess quality improvement in postoperative pain management, will be administered daily for the first 5 postoperative days (Appendix J).[65]
- The Opioid-related Symptom Distress Scale (SDS), a validated and reliable measurement tool that measures twelve opioid-related symptoms, will be administered daily for the first 5 postoperative days (Appendix K).[66]
- The Quality of Recovery Survey (QoR), a useful and validated summary measure of recovery after anesthesia and surgery, will be administered daily for the first 5 postoperative days (Appendix L).[67]

7.2.3 - Immunologic correlates

-Cytotoxicity assays will be performed to detect NK and NKT killing activity. These assays will be done by flow cytometry. These assays will be from optional blood collected as described in 5.2.2.

-Cytokine determination will be done by ELISA technique using commercially available kits for each cytokine. These

assays will be from optional blood collected as described in 5.2.2.

7.2.4 - Pain score at each time point

- Mean pain scores at various time points will be compared between groups (TEA vs. IVPCA). There will be 6 specific timepoints that will be used for secondary analysis as each timepoint will be an independent measure and may differ between groups dependent on duration from surgery as was found in previous studies: 1). mean pain scores compared between groups at 6 hrs postop; 2). mean pain scores compared between groups for subsequent 18hrs postop; 3). mean pain scores compared between groups over 24hrs on postop day #2; 4). mean pain scores compared between groups over 24hrs on postop day #3; 5). mean pain scores compared between groups over 24hrs on postop day #4; and 6). mean pain scores compared between groups over 24hrs on postop day #5.

8.0 Statistical Considerations

8.1 Methodology

- This is a two-arm randomized non-blinded study whose primary objectives are to compare postoperative pain scores and quality of life (QOL) scores in patients undergoing liver and/or pancreatic resection between those receiving TEA versus IVPCA. Eligible patients will be randomized in a 3:1 allocation ratio to the treatment group of TEA or IVPCA group (to represent our current institutional practice as well as to allow a more accurate determination of overall TEA failures and complications). Randomization will be stratified by the resection type (liver or pancreatic - 1:1). The randomization will be conducted by the CORE prior to surgery and after consent and registration. Pain will be assessed using a numeric/visual pain score at various timepoints. The pain scores will be averaged for each patient and be compared between TEA and IVPCA groups at specific time points as follows: pain scores for the first 6 hours after surgery, pain scores for the next 18hrs after surgery, pain scores for each subsequent 24hr period after surgery until postoperative day #5 or epidural removed, whichever occurs first. QOL will be assessed pre- and postoperatively using SF-8 and SF-36v2. These validated instruments will score 8 domains that will be reduced to two summary measures scales, Physical Component Summary (PCS) and the Mental Health Component Summary (MCS). Scoring will be performed utilizing proprietary certified scoring software from the vendor. QOL scores will be calculated and compared between the two groups of patients.
- Categorical data will be tabulated with frequency and percentages, and continuous variables will be summarized using descriptive statistics mean, standard deviation, median and range. The primary

endpoint for pain scores is mean pain scores within the first 48 hours, computed as the AUC the pain score vs. time curve for each individual. In case there is missing data, we will compute the AUC while using last value carried forward to fill in the missing data. For primary analysis, 2-sample t-tests or Wilcoxon rank sum test will be used to compare mean pain scores within 48 hours post operation between TEA and IVPCA arms. The same methods will also be applied to compare mean pain scores at each time point between TEA and IVPCA. Linear mixed models including treatment, evaluation time, and interaction of treatment and evaluation time will be fit to determine the treatment effect on pain scale. Each pain score in PPS form will be analyzed for the primary analysis. Chi-square test or Fisher's exact test will be used to compare the binary outcomes between the two arms, which are related to effects of pain on patients' movement or mood, such as pain's influence on mobility or movement, cough or breath deeply, sleep and mood. Generalized estimating equation (GEE) regression models will be fit to estimate the treatment effects on the listed binary outcomes. Chi-square test will be used to compare the categorical items of QOL pre and post surgery between the two treatment arms, the same method will also be used to compare the changes pre-postoperative in items of QOL between the two arms as well.

8.2 Sample Size

- A total of 200 liver and pancreatic resection patients will be enrolled in order to achieve 140 evaluable patients. As these surgical procedures are for resection of malignancy, a proportion of patients will be identified with unresectable or metastatic disease at the time of planned resection either during initial laparoscopy or after open exploration. Those patients deemed unresectable at laparoscopy will not undergo open exploration, and thus, will be inevaluable for postoperative pain due to differences in incision type. Furthermore those patients that do undergo an open exploration but are deemed unresectable due to local or metastatic disease found intraoperatively will have markedly different prognoses compared to those that have a successful resection, which may bias their response to pain and quality of recovery and bias the questionnaire responses. Based on previous work at our and other institutions, it is expected that up to 30% of patients will not be evaluable due to various reasons, including ineligibility, patient withdrawal from the study, unresectable disease, and failure to complete or inaccurate completion of questionnaires. Based on historical information, if the difference in mean pain score between the two evaluable treatment groups of patients is 1 and the common standard deviation is 1.5, with a total of 140 evaluable patients (105 in TEA group and 35 in IVPCA group), the study will yield a 92% power to detect the difference, using a two-sample t-test at a two-sided significance level of 0.05. Furthermore, the study will have a 99% power to detect a difference of 10 in QOL score with a corresponding standard deviation of 9 using a two-sided Student's t-test with a type I error of 0.05. All statistical analyses will be performed with an intent to

treat methodology, including those patients who cross over between treatment groups.

- Patients undergoing major hepatectomy are a subset population of interest, since they are at higher risk of perioperative complications. Major hepatectomy is defined as resection of 3 or more segments of the liver, while minor hepatectomy is resection of 1 or 2 segments. With a target accrual to 200 patients and 140 evaluable patients, we anticipate enrolling 70 patients undergoing major hepatectomy. Based on our previous work it is expected that half of the 140 patients will undergo major hepatectomy. With 70 patients who undergo major hepatectomy and assuming a 3:1 randomization to the experimental arm and control arm (51 in TEA group and 17 in IVPCA group), this sample size will have 80% power to detect an effect size of 0.796 (i.e. 0.796-SD) in the mean pain scores between the two treatment arms, using a two-sample t-test at a two-sided significance level of 0.05. Two-sample t-tests or Wilcoxon rank sum test will be used to compare mean pain scores within 48 hours postoperatively between TEA and IVPCA arms.

9. Data and Protocol Management

After obtaining informed consent, patients will be registered by an Anesthesia/Surgery Research Nurse, who will register them on the MDACC computerized Protocol System. The PI, Dr. Vauthey, and Dr. Mark Truty at Mayo Clinic College of Medicine will analyze the data once the study is closed. Only Limited Data Sets (LDS) will be sent to Dr. Truty at Mayo Clinic College of Medicine, however, Mayo Clinic will not participate in the analysis or in any part of the study. LDS is Protected Health Information that excludes the sixteen (16) direct identifiers listed in the U.S. Department of Health and Human Services Health Insurance Portability and Accountability Act (HIPAA). A Data Use Agreement will be used to send the data to Dr. Truty. All data obtained will be de-identified after the conclusion of the study.

10. Data Safety and Monitoring Board

This study will be monitored by The Data Safety and Monitoring Board (DSMB), through routine reviews and/or institutional audits. The DSMB reports to the President, or his designee, as the on-campus representative of The University of Texas Board of Regents. It oversees the data and patient safety issues for randomized Phase III clinical trials that originate at UTMDACC; that are coordinated or analyzed by UTMDACC and are not being monitored by any other DSMB; or has been designated as the DSMB for any trial at the request of the IRB, the CRC, or institution. The primary objectives of the DSMB are to ensure that patients' rights pertaining to participation in a research study are protected, and that patients' interests are prioritized over the interests of the scientific investigation. Responsibilities include:

- (a) **Review interim analyses of outcome data after 60 evaluable patients are enrolled (prepared by the study statistician or other responsible person at the time points defined in the study) approved by the IRB and additional time points as determined by the DSMB, and to**

recommend, if necessary, whether the study needs to be changed or terminated based on these analyses;

- (b) Determine whether, and to whom, outcome results should be released prior to the reporting of study results;**
- (c) Review interim toxicity data and efficacy of treatment;**
- (d) Review major research modifications proposed by the investigator or appropriate study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results from the study or results of other studies, increasing target sample size).**

The DSMB consists of not more than 15 members (including the Chair) as recommended by the President, or his designee, for each fiscal year. The committee includes physicians, statisticians and lay member(s), and will be selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of the same), and knowledge of good clinical trial methodology. The committee meets 5 times per year, and may schedule additional meetings if needed.

11. Confidentiality

- This study will be conducted in accordance with all applicable privacy laws, rules and regulations. The Principal Investigator will take steps to guard against any loss of confidentiality. Only the Principal Investigator, Study Co-Chairs, and the authorized research team will have access to the identifiable information from this study.

- Identifiers (such as name and medical record number) will be collected but will be replaced by study numbers in the analytic file. The key linking to these numbers will be retained in a secure computer file. Access to this file will be limited to the Principal Investigator, Study Co-Chairs, and the authorized research team. All computer files are password-protected and stored on institution computers behind the institution firewall to further ensure database security and all records are kept confidential. Any reports or publications resulting from this study will not include any personal identifiers.

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Appendix A: Inpatient IVPCA Orders

This is a printed copy of the Order Set. Please refer to the official Order Set version in ClinicStation.

Inpatient Physician Orders
PCA IV Medications - Adult

Date Printed: **11/22/2010** MRN: **282273**
Pt Name: **TEST, PATIENT Q**
DOB: **02/03/1979** Sex: **F**

Order Status: New Order Change in Order Transfer Order Page 1 of 1

Attending Physician: _____

Ordering Service: Primary Team Supportive Care Cancer Pain Management Acute Pain Medicine

Height: **167** cm Weight: **72** kg Adjusted Body Weight: _____ kg BMI: _____

Allergies: Benadryl, Lisinopril, ADR: Betadine

Vital Signs 1. Respiratory rate and level of sedation every 2 hours for 12 hours, then every 4 hours while on PCA.
2. Check as indicated: continuous pulse oximetry ETCO₂ except during ambulation or toileting.

Interventions 1. Please obtain ordering service approval prior to administering these medications. Any previous orders for these medications should be clarified.

- Opioids in any route (e.g., HYDROmorphine, MORPHine)
- Sedation-causing medications (e.g., DiphenhydRAMINE, Promethazine, LORazepam, PROchlorperazine, ZolpiDEM, Haloperidol, DIAZepam)

2. If patient meets one or more of the following:

- Sedation scale equals -3 (RAAS scale)
- O₂ saturation less than 90% for 2 minutes
- Respiratory rate (RR) 8 or less

STOP PCA infusion, place patient on 2 liters O₂ per nasal cannula, and notify ordering service.

Medications

Medication via IV PCA: (Choose only one)	PCA Dose	Lockout Interval	Continuous Dose	Nurse Bolus prn pain
<input checked="" type="checkbox"/> HydroMORphone (Recommended dose ranges)	0.2 mg (0.1 – 0.5 mg)	10 minutes	_____ mg/hour	0.5 mg every 1 hours (0.5 – 1 mg)
<input type="checkbox"/> FENTanyl (Recommended dose ranges)	_____ mcg (5 – 25 mcg)	minutes	_____ mcg/hour	_____ mcg every _____ hours (25 mcg)
<input type="checkbox"/> MORPHine (Recommended dose ranges)	_____ mg (0.5 – 2 mg)	minutes	_____ mg/hour	_____ mg every _____ hours (2 – 4 mg)

Medications as needed (prn)

1. Administer **Naloxone (Narcan®)** as follows if patient does not respond to stimuli or continues to deteriorate as indicated under Interventions:
 - a. Dilute an ampule of **Naloxone 0.4 mg** in 9 mL NS for injection. (Final concentration: 0.04 mg/mL.)
 - b. Inject **0.5 mL of diluted Naloxone** IV Push every 2 minutes until respiratory rate is greater than 8 per minute and/or drowsiness abates.
 - c. Only push entire dose of **Naloxone 0.4 mg** for respiratory arrest or continued hypoxia.
2. **Ondansetron 4 mg** IV every **6** hours prn nausea/vomiting. Notify ordering service if patient has no relief.
3. **Nalbuphine 5 mg** subcutaneous every **4** hours **2.5 mg** IV every **4** hours prn pruitus. Notify ordering service if patient has no relief.

Instructions/Education _____

Signature/Credentials/ID Code: _____

Pager: _____ Date: **11/22/2010** Time: **10:40 AM**

File under: Physician Orders

Page 1 of 1

INS 00004 V21 11/10/2010

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Appendix B: Inpatient TEA Orders

This is a printed copy of the Order Set. Please refer to the official Order Set version in ClinicStation.

Inpatient Physician Orders Date Printed: 11/22/2010 MRN: 282273

Pt Name: TEST, PATIENT Q Date Printed: 11/22/2010 MRN: 282273

DOB: 02/03/1979 Sex: F

Epidural Orders

Acute Pain Medicine (APM) Pager 713-404-2264

Order Status: New Order Change in Epidural Orders Transfer Order

Allergies: Benadryl, Lisinopril, ADR: Betadine

Vital Signs

1. Respiratory rate and level of sedation every 1 hour for the first 12 hours, then every 2 hours for the next 12 hours, then every 4 hours while receiving epidural infusion.
2. Continuous pulse oximeter for first 24 hours of therapy, then every 4 hours until epidural discontinued.
3. Check as indicated: ETCO₂ except during ambulation or toileting.

Interventions

1. **Please obtain Acute Pain Medicine (APM) approval prior to ordering or administering these medications:**
 - Sedatives: (e.g., Diphenhydramine, Promethazine, Lorazepam, Prochlorperazine, Zolpidem, Haloperidol)
 - Opioids in any route (e.g., HydroMorphone, Morphine)
 - Anticoagulants (e.g., IV heparin, Enoxaparin, Dalteparin, Fondaparinux, Warfarin) *Note: only subcutaneous heparin and enoxaparin up to 40 mg single dose every 24 hours are allowed.*
 - Antiplatelet agents (e.g., Clopidogrel)
 - Hypotension and Bradycardia-causing medications (beta blockers such as metoprolol)
2. If patient meets one or more of the following:
 - Sedation scale equals -3 (RASS scale)
 - Respiratory rate (RR) 8 or less
 - O₂ saturation less than 90% for 2 minutes**STOP** epidural infusion, place patient on 2 liters O₂ per nasal cannula and notify APM.
3. **DO NOT** change epidural dressing.

IV Fluids If IV fluids discontinued, maintain IV access until epidural infusion discontinued.

Epidural Medications

1. Formulation as indicated below prepared in preservative free (PF) NS 250 mL and administered via epidural pump.
 Standard: **HydroMorphone 10 mcg/mL with Bupivacaine 0.075%**
 Other: _____

Pump Settings Units: mL Admin Rt: Epidural Load Dose: 0 mL	Basal Rate (Basal Rate)	Patient Bolus (Pt. Bolus)	Bolus Interval (Bolus Int)	Number Bolus/Hour (Number Bolus/hr)	Clinician Dose* (ClinDose)
	10 mL/hour	3 mL	10 min (5-15 min)	_____	5 mL every hour(s) prn

*Clinician dose for breakthrough pain if BP stable and patient is alert and oriented. Recheck BP again in 15 minutes.

Medications as needed (prn) Notify ordering service if patient has no relief.

1. Administer **Naloxone (Narcan®)** as follows if patient does not respond to stimuli or continues to deteriorate as indicated under Interventions.
 - a. Dilute an ampule of **Naloxone 0.4 mg** in 9 mL NS for injection. Final Concentration: 0.04 mg/mL.
 - b. Inject **0.5 mL of diluted Naloxone** IV Push of diluted Naloxone every 2 minutes until respiratory rate is greater than 8 per minute and/or drowsiness abates.
 - c. Only push entire dose of **Naloxone 0.4 mg** for respiratory arrest or continued hypoxia.
2. **Ondansetron 4 mg** IV every 6 hours prn for nausea/vomiting.
3. **Nalbuphine 5 mg subcutaneously** every 4 hours prn pruritis.

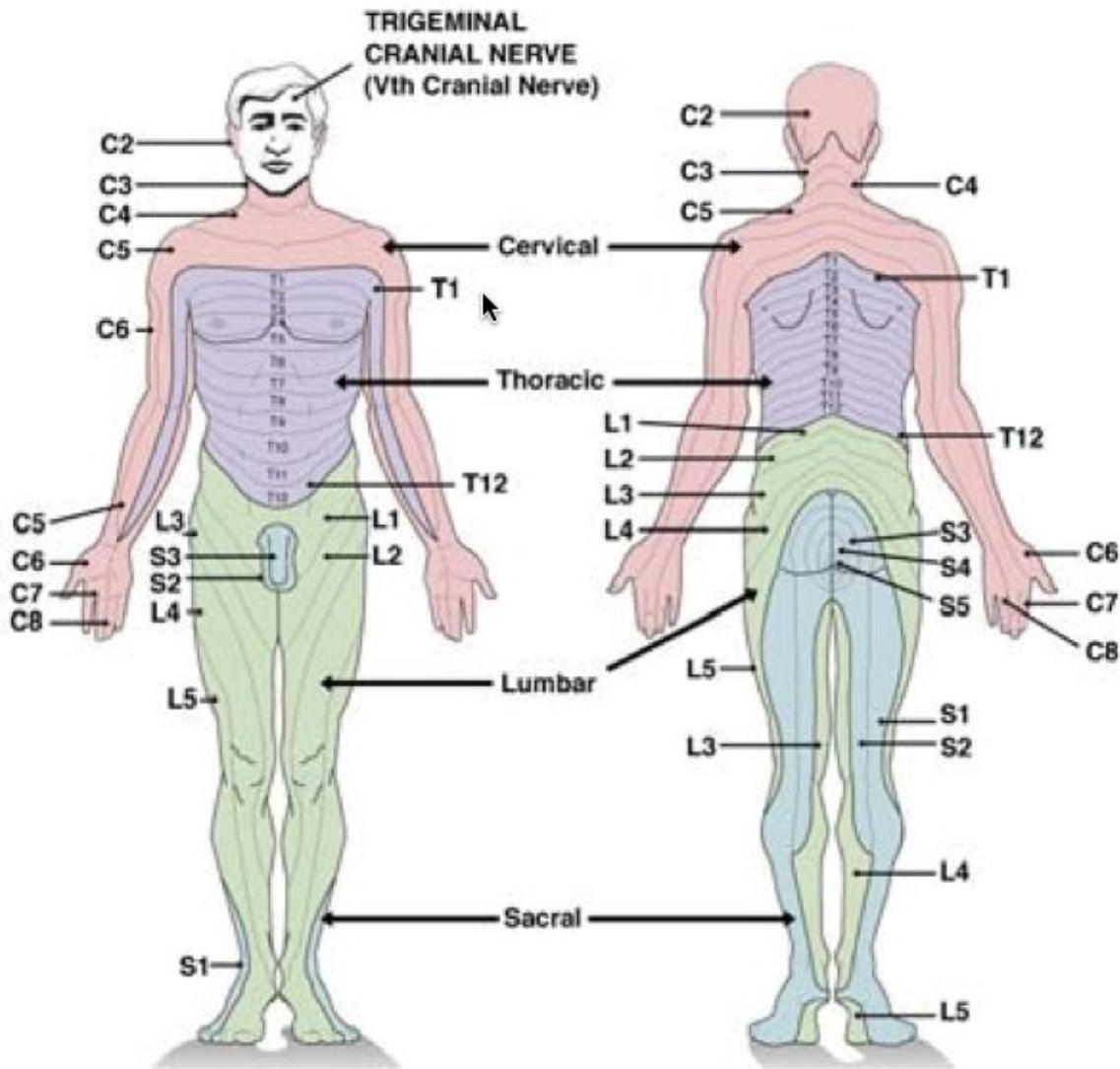
HYDROMorphone _____ mg IV every 2 hours prn breakthrough pain. (Only administer if box checked by prescriber.)

Signature/Credentials/ID Code: _____
Pager: _____ Date: 11/22/2010 Time: 10:40 AM

Appendix C: Motor Block Scale

Bromage Motor Block Scale (0/5 complete motor block; 5/5 no motor block)	Right Leg	Left Leg
Hip Flexion	0 - 5	0 - 5
Knee Extension	0 - 5	0 - 5
Ankle Dorsiflexion	0 - 5	0 - 5
Ankle Plantar Flexion	0 - 5	0 - 5
Great Toe Dorsiflexion	0 - 5	0 - 5

Appendix D: Dermatome Sensory Block Map



Appendix E: Richmond Agitation Symptom Scale

+4	Combative	Violent, immediate danger to self or staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive behavior
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact > sec)
-2	Light Sedation	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	Moderate Sedation	Movement or eye-opening to voice (but no eye contact)
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Appendix F: Numeric/Visual Analog Pain Scale

