THE UNIVERSITY of TENNESSEE
GRADUATE SCHOOL OF MEDICINE

Title: Efficacy of Perioperative Opioid Sparing Techniques on Time to Initiation of Chemotherapy: A Randomized Single Blinded Control Study

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1.0 INTRODUCTION

Enhanced recovery after surgery (ERAS) has become the standard of perioperative care for patients undergoing oncologic surgery[1–4]. Multimodal and regional anesthetic techniques to reduce postoperative pain and opioid requirements are a key component of ERAS[5,6]. Epidural analgesia was considered standard in early ERAS protocols[7,8] however, it is labor-intensive, requires close postoperative follow-up, and may exacerbate hemodynamic instability.

Long-acting intrathecal (IT) opioid use in oncologic surgery has been described as an equianalgesic technique to epidural analgesia with an improved safety profile, although both have the potential for neurological complications and respiratory depression[9–14]. Quadratus lumborum (QL) block is an alternative opioid sparing technique to neuraxial analgesia for abdominal surgery[6,15]. QL blocks can provide similar pain coverage as an epidural with decreased hemodynamic instability. However, it is limited by its relatively short duration of effect, which ranges from 6 to 12 h[16]. Another method employed is the transversus abdominus plane block. One of the advantages of this technique is that it does not depend on a separate service to perform like ITM and QL as it is commonly performed by the surgeon during surgery. However, unlike the QL block which has been shown to spread to the lumbar plexus and even thoracic paravertebral space providing both somatic and visceral analgesia, TAP blocks only provide somatic analgesia coverage[20]. TAP blocks are still frequently performed by oncologic surgeons though the long term success compared to QL and ITM blocks is unclear. Most research looking into the efficacy of these techniques has been aimed at studying their effects on pain scores, opioid requirements, and opioid related adverse drug events.

Time to initiation of adjuvant chemotherapy (AC) following oncologic surgery is an important predictor of survivability[19] that has not yet been considered in QL vs. IT comparison studies. Two meta-analyses demonstrated that postponing the postoperative AC was associated with poor survival in colorectal cancer patients. Results from Biagi et al. showed that every 4 weeks delay result in a 14% decrease of overall survival (OS)[17]. Similarly, Guetz's study indicated that delaying the initiation of AC for > 8 weeks after operation significantly decreased OS[18]. In pancreatic and colorectal cancer, several factors are involved in this metric. One of the more common factors in this patient population is gastrointestinal complications including ileus. Some of these complications can be affected by perioperative opioid consumption.

2.0 RATIONALE

The primary objective is, therefore, to compare time to initiation of chemotherapy between regional blocks specifically quadratus lumborum blocks, surgeon administered Transversus Abdominis Plane (TAP) block, and IT opioid analgesia in oncologic abdominal surgery and whether there is a significant difference between these techniques and standard post operative pain management protocol. Secondary objectives are to compare duration of hospital stay, incidence of postoperative ileus and use of intravenous patient-controlled analgesia. This study aims to establish whether certain opioid sparing techniques are superior

in terms of their ability to decrease time to initiation of chemotherapy following oncologic surgery. Additional sub-aims include evaluating the efficacy of long acting vs. short acting bupivacaine on pain management and time to initiation of chemotherapy. Current clinical practice at UTMC is that some surgeons elect to administer long-acting bupivacaine as TAP blocks. Additionally, the anesthesia team exclusively uses short acting bupivacaine for the QL blocks. Though this study is not designed to compare various products for injection per procedure (i.e. TAP with short acting vs. long-acting bupivacaine), one of the anticipated outcomes is data that will compare pain management between these two techniques. Additional studies may need to be designed to further identify superiority of short acting vs. long-acting bupivacaine.

3.0 TRIAL OBJECTIVES

Hypothesis:

Preoperative intrathecal morphine administration will significantly reduce the time to initiation of post-operative chemotherapy.

3.1 Primary objective

To determine if intrathecal morphine (ITM) administration is superior to quadratus lumborum block or surgeon administered TAP blocks result in decreased time to initiation of chemotherapy following oncologic surgery.

3.2 Secondary objectives

To determine a difference between interventions in time to return of bowel function in days.
To determine a difference between interventions in incidence of opioid related adverse drug events (ORADEs).
To determine a difference between interventions in cumulative and post-operative total morphine milligram equivalents.
To determine a difference between interventions in quality-of-life assessment tool and patient satisfaction (brief pain index short form BPI-sf9).
To determine a difference between interventions in hospital length of stay in days.
To determine the difference between cumulative pain scores between interventions.
To determine the difference between short acting and long-acting bupivacaine in pain management and time to chemotherapy

3.3 Outcomes

The primary outcome is time to initiation of chemotherapy (in days) as deemed by a blinded medical oncologist.

The secondary outcomes are time to return of bowel function, incidence of ORADEs, cumulative and

postoperative morphine milligram equivalents, hospital length of stay, pain scores, and quality of life.

4.0 STUDY PLAN

4.1 Study Design

A prospective, parallel group randomized clinical study in patients undergoing oncologic (foregut, hepatopancreatobiliary (HPB), and colorectal cancer) surgical procedures.

4.2 Study Duration

We plan to enroll ~10 patients per month for 20 months. The total study duration will be approximately 24 month's post IRB approval and study initiation.

4.3 Selection of Study Participants & Informed Consent

Patients at the UT Medical Center who meet the predefined inclusion and exclusion criteria will be enrolled after they provide consent to participate. Consent will take place during the clinical pre-operative visit. The nature and purpose of the study will be explained to the patient by the study member designee and the patient will be given a copy of the informed consent to review. The investigator and/or study coordinator will answer any questions which the patient may have prior to their signing the consent. The signed informed consent will be kept in the patient's research chart and a copy will be given to the patient. No study related interventions will be performed until after the patient signs the informed consent.

4.4.1 Inclusion Criteria

1. 18-80 years of age
2. Patients undergoing open surgery for foregut, HPB, and colorectal cancer
3. Able to read and understand study procedures
4. Willing to participate and sign an ICF
5. If female of childbearing potential, subject must have a negative pregnancy test
6. Recommended for adjuvant chemotherapy
7. Patients scheduled for an AM admit procedure
8. English speaking
9. Patients with a midline incision

4.4.2 Exclusion Criteria

1. Chronic Opioid Use (received an opioid within 90 days preoperatively)
2. Recreational Drug Use
3. Patients with cognitive impairments that can affect their ability to give consent.
4. Patients that are currently taking anti-coagulants <7 days prior to surgery
5. Pregnant or breastfeeding
6. Does not require adjuvant chemotherapy
7. Relative Contradictions for receiving a nerve block*
8. Patients that have been admitted prior to surgery for chief complaint related to complications from malignancy

9. Inability to provide consent

***Absolute Contraindications**

- Lack of patient consent.
- Skin infection at the site of needle insertion.

Relative Contraindications

- Coagulopathy.
- Systemic infection.
- Anatomical distortion.
- Neuropathy.

Drugs/Device usage within 7 Days of Randomization if any:

- Anticoagulants

4.5 Discontinuation of Subjects

An individual patient is to be withdrawn from the trial if any of the following criteria apply:

- The patient withdraws consent, without the need to justify the decision
- The patient is no longer able to participate for medical reasons (e.g., surgery, AEs, or other diseases)
- Decision by the PI to discontinue a specific patient for his/her safety (e.g., in case of SAEs)

Data of patients who discontinue or withdraw prior to enrollment will be entered in the study database and will be listed. Data of patients who discontinue or withdraw after enrollment will be documented and the reason for withdrawal will be recorded in the study record. The data will be included in the study database and will be reported.

5.0 STUDY PROCEDURES

5.1 Screening Assessments

Screening assessments should be completed by delegated study personnel during the patient's pre-operative visit in the surgeon's office. Assessments will be initiated after the Informed Consent Form (ICF) Process. The PI and/or study designee will present the study information to the patient. They will explain the purpose, risk, and benefits to the subject and present them with an IRB approved ICF. The potential participant will be given ample time to read the ICF and all questions and concerns from the subject will be addressed by the PI and/or study team member. No procedures will be initiated prior to the subject signing and dating the ICF. After the subject signs the ICF, a copy will be given to them for their records. Participants will be informed that they can decline participation in the study without

any effect on their health care. They can also withdraw their consent, including the consent to do various screening tests, at any time.

- Informed Consent
- Medical History Review for Exclusion Criteria
- Concurrent Medication Review
- Review of Inclusion / Exclusion Criteria
- Confirmation of Subject eligibility by PI and/or study designee representative on eligibility form.

5.2 Enrollment/Baseline Assessments

Enrollment/Baseline assessments will be completed on the scheduled day of surgery. This will be after the screening/enrollment visit after the patient has signed the informed consent form if all enrollment criteria have been confirmed.

- Concurrent Medication Monitoring (gabapentin, NSAIDs, topicals, muscle relaxers, opioids, and SNRIs)
- Medical History Review for Eligibility
- Confirm Inclusion & Exclusion Criteria
- Enrollment
- Intervention Assignment
- Study Intervention Administration

6.0 Randomization

Randomization will be completed by a selected study team member. When a patient is qualified for entry into the randomized interventional period, intervention assignment will be made by means of a randomization table prepared by a third-party biostatistician or applicable team member. Randomization will be done in a 1-1-1 fashion. Using allocation software, patients will be allocated randomly into 1 of 3 groups: the intrathecal morphine group (ITM), the quadratus lumborum group (QL), or the TAP block group (TAP).

7.0 INTERVENTIONS/GROUPS

Intervention 1:

The ITM group will receive an intrathecal morphine block performed by the Anesthesiologist. This will be accomplished by placing the patient in a preoperative holding room with standard ASA monitors 150 mcg of morphine will be administered intrathecally.

Intervention 2:

The QL group will receive a bilateral quadratus lumborum block containing 30 mL of 0.25% bupivacaine and 4mg of dexamethasone. This will be accomplished by placing the patient in a preoperative holding

room with standard ASA monitors where the bilateral quadratus lumborum block will be performed by the Anesthesiologist.

Intervention 3:

In the TAP block group, patients will undergo a bilateral transverse abdominis plane block performed by the surgical team using an exparel-based solution mixed with 50mL of saline. This block will be performed intraoperatively before the incisions are closed.

8.0 Follow Visit/Collection Time Points (90-post discharge)

Perioperative data will be extracted from the patient's chart. The first follow-up visit will take place 14 days following the baseline visit when intervention was administered. Three additional follow-up visit assessments will be completed once per month. The study coordinator and/or investigator will review the subject's concurrent medication and medical history. They will question the subjects for any possible adverse events. If adverse events are reported, the PI will assess for causality, severity, intervention, and outcomes. The following procedures will be completed:

- Concurrent Medication Monitoring (gabapentin, NSAIDs, topicals, muscle relaxers, opioids, and SNRIs) (intra-operative, PACU, inpatient, and up-to 90 days post discharge refills and number of pills remaining)
- Time to bowel function return documented during first follow-up visit
- Time to initiation of first chemotherapy. (Decision made by investigators only)
- Visual Analog Scale (post-op 1h, 2h, 6h, 24h, 48h, 7, 30, 60, and 90 days), The Face, Legs, Activity, Cry and Consolability (FLACC) scale 30 minutes and 1h, height, weight, BMI, gender, date of surgery, duration of operation, estimated blood loss, PACU length of stay, and hospital length of stay.
- Patient satisfaction scores (BPI-sf9) post-op 14, 30, 60, and 90 days.
- Adverse Event Monitoring
- Record criteria for decision to start chemotherapy off pain medication, return to bowel function, no uncontrolled infection, no continued post-operative drains, and nutritional intake.

9.0 Study Schematic

	Screen Visit/ Enrollment (in clinic)	Baseline (at day of surgery)	Post-op to discharge (See times above)	Study Day 14 (±3 days)	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)
Informed Consent	x						
Demographics	x						
Inclusion/Exclusion	x	x					
Randomization		x					
Medical History	x	x		x	x	x	x
Study Intervention Administration		x					
The Face, Legs, Activity, Cry and Consolability (FLACC) scale			x				
Visual Analog Scale			x	X	X	X	X
Perioperative Details(date of surgery, blood loss, hospital LOS, duration of operation)			x				
CC Opiate Med (pre-operative, intra-operative, PACU, inpatient, 90-day MMESs)	x	x	x	x	x	x	x
Patient satisfaction scores (BPI-sf9)				x	x	x	x
Time to bowel function return			x				
Time to initiation of first chemotherapy					x	x	x
Report opioid related adverse events		x	x	x	x	x	x

10.0 RISKS

10.1 Physical Risks

Although the intervention being used in this protocol have been well tested for efficacy and safety, there may be potential risks associated with participation. Any medical treatment can have temporary and permanent side effects and can cause unforeseen adverse reactions, intolerance, or worsening of co–morbidities (including, revealing unknown allergies), which could lead to acute adverse event such as itching, prolonged length of stay. Any subject with known medical conditions, or on a concurrent medication in which the study intervention is not recommended, will be excluded from participation.

The intervention used in this study are currently in common use and will be administered in accordance with current standards. Patients will be carefully screened for contraindications to participation prior to study enrollment. We will monitor for adverse events in enrolled patients, refer to section 11.0.

10.2 Intervention Risk

There is the potential risk of an interventional failure for study participants. The study results may not support the primary hypothesis that in patients undergoing a foregut, HPB, or colorectal cancer surgery, ITM intervention is a superior analgesic. It is possible that the intervention will prove to be less effective than QL or TAP blocks. Patients receiving neuraxial or regional blocks will be comprehensively informed of potential risks during the informed consent process, including failed block, respiratory depression, post-dural puncture headache, bleeding, infection, neurologic injury, allergic reactions, and local anesthetic systemic toxicity). Moreover, they will be made aware of potential side effects, such as nausea, pruritis.

Throughout the regional/block placement procedure, patients will be continuously monitored with pulse oximetry, electrocardiography, and blood pressure monitoring. Additionally, an equipped regional cart containing emergency medications (such as lipid emulsion, ACLS medications) and airway management supplies will be readily accessible. Postoperatively, anesthesia personnel will conduct evaluations to detect any regional/block-related adverse events. All identified adverse events will be meticulously monitored, documented, and reported to the Institutional Review Board in accordance with regulatory requirements.

10.3 Psychological Risks:

A potential psychological risk could occur if patients feel a sense of coercion to participate in the study. The likelihood is small, because patients will be assured in the informed consent document and face-to-face discussion that participation is purely voluntary, and they can withdraw their participation at any time.

10.4 Research Risk

No identifiable patient information will be linked to patient assessments during the study. For this

specific project, all information related to patients will be identified only by patient initials and study number. However, for research purposes, it may be required to collect PHI such as age, DOB, Medical Record Number, and dates of diagnoses. Only the study team will have access to this data, and it will not be shared with anyone outside of the study team. The greatest research risk, although rare, is the loss of confidentiality caused by unauthorized release or misuse of information from research records.

10.5 BENEFITS

Although there may be immediate clinical benefits for some patients in this study who are assigned to the study intervention, the anticipated primary benefit is the future potential to decrease the total MME utilization and improve the quality of life for patients undergoing oncologic (foregut, hepatopancreatobiliary (HPB), and colorectal cancer) surgical procedures.Information obtained from this research may help patients in the future achieve better health outcomes and provide clinicians with pertinent information about post-operative opioid induced dependency.

11.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs that are considered possibly, probably, or definitely related to the study procedure will be recorded in the CRFs. AEs will be assessed starting with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the patient's condition is stable.

All AEs will be characterized by the following:

- AE name
- Start and Stop dates
- Relationship to study procedure
- Severity
- Action taken
- Outcome

Relationship

The investigators will assess the AEs and using their clinical judgment will assign an attribution to the AE using the following categories:

- **Unrelated** – The AE *is clearly NOT related* to the study procedure
- **Unlikely** – The AE *is doubtfully related* to the intervention
- **Possibly** – The AE *may be related* to the study procedure
- **Probably** – The AE *is likely related* to the study procedure
- **Definitely** – The AE *is clearly related* to the study procedure

Severity

The severity of the AEs should be graded by the investigator as follows:

- **Mild** – Transient discomfort; no prescribed medical intervention/therapy required and does not interfere with daily activities.
- **Moderate** – Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; medical intervention/therapy required.
- **Severe** – Discomfort and limitation in daily activities, assistance required; medical intervention/therapy required.

Action Taken

The action taken in response to the AE should be reported using the following categories:

- None
- Procedure or physical therapy
- Withdrawn from study due to AE
- Hospitalization
- Prescription drug therapy
- Non-prescription drug therapy
- Other (specify)

Outcome

The clinical outcome of an AE should be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death
- Unknown/lost to follow-up
- Other

SAE Reporting

All SAEs will be documented in the CRFs. SAEs will be reported to the local IRB per the following guidelines:

Adverse event reports will only be submitted to the local IRB if they are determined by the principal investigator to be: unanticipated, serious, and possibly, probably or definitely related to a research study procedure.

SAEs meeting these criteria (except for deaths) must be reported to the IRB *within 5 working days* of the study team's notification of occurrence. Deaths that are unanticipated and are possibly, probably or definitely related to a research study procedure must be reported to the IRB *within 24 hours* of notification of occurrence. Any relevant follow-up information regarding the SAE should be submitted to the IRB as soon as it becomes available and/or upon request. SAE reports to the IRB must include

the following: subject identifier, adverse event or problem description, the event relationship to the test article or underlying condition, seriousness assessment, whether the event was anticipated or unanticipated, type of report (initial or follow-up), date of injury, whether the intervention was stopped, and, if so, whether it was re-started, and whether the event provides new risk information that alters the risk-benefit assessment and/or should be added to the informed consent disclosure.

12.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The researchers hypothesized a moderate effect size of f = 0.25 associated with the treatment. With 1:1:1 allocation across the three groups (Arm 1: Arm 2: Arm 3), an alpha value of 0.05, a beta value of 0.20, the aforementioned moderate effect size of f = 0.25, and an attrition rate of 20%, a total of n = 201 participants (n = 67 in each active treatment arm and n = 67 in the TAP arm) for adequate statistical power. The power analysis was performed G*Power Version 3.1.

Descriptive and frequency statistics will be used to describe the demographic characteristics of the sample. The inferential analyses for the trial will be performed in an “intention-to-treat” fashion. MCAR (missing completely at random) analysis will be performed to assess missingness of trial data. If the missingness is random (as per Little’s chi-square statistic), then imputation of missing data will be performed using multiple imputation with expectation-maximization. A “per-protocol” analysis will also be performed on the data. The primary outcome of time to chemotherapy (days) will be assessed between the three treatment arms using either a one-way ANOVA (if normality and homogeneity of variance assumptions are met), or a Kruskal-Wallis test (if either or both assumptions are violated). Means, standard deviations, mean differences, and 95% confidence intervals (95% CI) of the mean differences for each group will be reported for ANOVA analyses, medians and interquartile ranges for a Kruskal-Wallis test. If a significant main effect is detected for either test, post hoc analyses will be performed using either Student-Newman-Keuls tests (ANOVA) or Dunn’s test (Kruskal-Wallis). The same statistical methods will be performed for the continuous outcomes measured in days (time to return of bowel function, MMEs, number of ORADEs, quality of life assessments, and hospital LOS). The incidence of AEs and SAEs will be compared amongst the groups using either chi-square or Fisher’s Exact test. All analyses will be performed using SPSS Version 29 and statistical significance will be assumed at an O’Brien-Fleming adjusted alpha value of 0.0492.

The researchers plan an interim analysis of the primary and secondary outcomes at 50% enrollment for the three treatment arms. A decision will be made regarding early termination due to efficacy or futility, or the trial will continue to full enrollment. Statistical significance for the interim analysis will be assumed at an O’Brien-Fleming adjusted alpha value of 0.0054 for the primary and secondary outcomes, and an adjusted alpha value of 0.0492 for the final analysis at full enrollment. Statistical power calculations will be performed based on effect sizes yielded from the interim analysis.

13.0 STUDY MANAGEMENT

The PI and study team has the site resources, time availability, and the patient population needed to complete this protocol under GCP guidelines. The PI is ultimately responsible for the conduct of the

trial; however, he will delegate authority to appropriate members of the research team. The PI will ensure the following:

- Study team complies with be GCP and other regulatory requirements.
- The study team allows monitoring and auditing of regulating institutions.
- Ensures person delegated trial responsibilities are qualified and trained appropriately.
- Ensure that study team members have sufficient time to properly conduct and complete the trial.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the treatments being administered, and their study-related duties and functions.
- Ensures compliance with GCP guidelines regulatory requirements.
- Will maintain a list of research team members and delegated duties.
- Assures protocol compliance.
- Reports protocol non-compliance appropriately.
- Obtains IRB approval.
- Followings regulations and guidelines to protect subject rights, safety, and welfare.
- Assures compliance by all research team members of GCP regulations

14.0 DATA MANAGEMENT

Data will be collected and managed by trained study team members. Data will be backed up with OneDrive and access will be limited to study personnel. Data collected during the study will be retained in patients' research records for at least 6 years after the study is completed. At that time, the research information not already in the patients' medical records will be destroyed, per institutional guidelines.

14.1 Data Protection

Throughout the study, measures to ensure the privacy of information on study subjects will be maintained. All project investigators and staff have been trained in the use of human subjects in research and have received training in the new HIPAA regulations. Subjects and staff will be informed of the confidentiality of information and assured that data will be used only for statistical purposes in which the individual cannot be identified. Conversely, no identifiable information on any individual will be released to anyone other than project personnel without a signed medical release from the subject, or where appropriate, the next of kin or a physician in case of a life-threatening emergency to the subject. All project personnel will be instructed not to discuss any cases with persons other than project personnel.

For this specific project, all information related to patients will be identified only by patient initials and study number. However, for research purposes, it may be required to collect PHI such as age, DOB, Medical Record Number and dates of diagnoses. Only the study team will have access to this data, and it will not be shared with anyone outside of the study team. Data will be collected on paper source documents and transcribed into the GSM REDCap system. Only study team members will have access to the database. The database will utilize the study number assigned and will not include the subjects name or MRN. All subjects will have an assigned number. All completed paper

forms will be kept in locked files in locked rooms to which only project personnel have access.

14.2 Data and Safety Monitoring

Monitoring will be completed by the GSM Office of Research Support and/or The Office of Clinical Trials and include a review of original case records. It will include monitoring to assess patient safety, the consent process, record-keeping, protocol adherence, and data collection. The Investigator will record all protocol deviations. Unexpected clinically significant adverse events will be reported to the IRB. In general, the investigators will monitor any adverse reaction to the questionnaires and assessments conducted during the study. Any missing data will be omitted from the final statistical analysis.

14.3 Protocol Deviations

A protocol deviation is failure to follow procedures specified in the approved research protocol, which include (but are not limited to), deviations from study inclusion/exclusion criteria, or failure to follow criteria for subject follow-up, withdrawal, or timely monitoring procedures. Protocol deviations will be reported per the UTGSM IRB SOPs.

14.4 Records

14.5.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents will be stored and maintained by the study team in a secure location. Data entered in the database that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. All electronic data must be derived from source documents.

14.5.2 Direct Access to Source Data and Documents

The PI will permit trial-related monitoring, audits, and regulatory inspection, providing direct access to source data/documents.

14.5.3 Storage of Records

The PI will retain the source documents and essential documents for a period of at least 6 years after the research is completed and the study is closed with the IRB. Records will be kept longer if other requirements apply.

15.0 COMPLETION OF TRIAL

When the trial is completed, the PI will inform the IRB and sponsor of the completion in writing.

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APPENDIX

I. Opioid related adverse events with ICD-10 codes