

CLINICAL STUDY PROTOCOL

Superficial Cervical Plexus Block and Quality of Recovery after Thyroidectomy: A Randomized Controlled Trial

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Confidentiality Statement:

Synopsis

Primary Objective

The primary objective of this study is to investigate whether there are differences in the quality of recovery (as determined by the Quality of Recovery – 40 [QoR-40] survey) after thyroid surgery in patients who receive Superficial Cervical Plexus Block (SCPB) with bupivacaine versus saline within the context of an Enhanced Recovery After Surgery (ERAS) pathway to determine whether the SCPB has an impact on quality of recovery.

Secondary Objective

The secondary objectives of this study are to determine whether there are differences in opioid consumption (in morphine milligram equivalents) in the Post-Anesthesia Care Unit (PACU) and through Post-Operative Day (POD) 1; need for rescue analgesia prior to PACU discharge; presence of nausea and/or vomiting in PACU; need for rescue antiemetics in PACU; PACU length of stay (in minutes); presence of patient reported side effects; and patient reported quantity of other modes of analgesia, if any, through postoperative day 1 in patients who receive SCPB with bupivacaine versus saline.

Study Design

This is a prospective double-blind randomized placebo-controlled trial

Study Date Range and Duration

Each participant's duration on study will be approximately 2 days. The entire study is anticipated to take 2 years to complete

Number of Study Sites

1 location (Yale New Haven Hospital Operating Rooms)

Primary Outcome Variables

- Quality of recovery-40 survey scores on POD 1

Secondary Variables

- Opioid consumption (in morphine milligram equivalents) in PACU and through POD 1
- Need for rescue analgesia prior to PACU discharge
- Presence of nausea and/or vomiting in PACU
- Need for rescue antiemetics in PACU
- PACU length of stay (in minutes)
- Presence of patient reported side effects

• Patient reported quantity of other modes of analgesia, if any in PACU and through POD 1							
Study Population All patients aged 18 years or older with American Society of Anesthesiologists (ASA) grade I–III status scheduled for thyroid surgery in Yale New Haven Hospital Operating Rooms will be considered eligible for the study. Potential participants will be identified by reviewing scheduled thyroid surgery cases of endocrinology surgery co-investigators							
Number of Participants 160 total, 80 participants per group							
Study Schedule <table border="1"> <tr> <td>Week(s) Prior to surgery</td><td>Surgeon co-investigator introduces study to patients at pre-operative visit, patients contacted via telephone to answer any questions, electronic consent obtained, baseline QoR-40 administered</td></tr> <tr> <td>Day of Surgery</td><td>Patients randomized to intervention or control group, receive SCPB, undergo planned surgery, observed during recovery room stay</td></tr> <tr> <td>Postoperative Day 1</td><td>Electronic link to complete QoR-40 survey emailed. Patient called if no survey submitted to complete survey via telephone</td></tr> </table>		Week(s) Prior to surgery	Surgeon co-investigator introduces study to patients at pre-operative visit, patients contacted via telephone to answer any questions, electronic consent obtained, baseline QoR-40 administered	Day of Surgery	Patients randomized to intervention or control group, receive SCPB, undergo planned surgery, observed during recovery room stay	Postoperative Day 1	Electronic link to complete QoR-40 survey emailed. Patient called if no survey submitted to complete survey via telephone
Week(s) Prior to surgery	Surgeon co-investigator introduces study to patients at pre-operative visit, patients contacted via telephone to answer any questions, electronic consent obtained, baseline QoR-40 administered						
Day of Surgery	Patients randomized to intervention or control group, receive SCPB, undergo planned surgery, observed during recovery room stay						
Postoperative Day 1	Electronic link to complete QoR-40 survey emailed. Patient called if no survey submitted to complete survey via telephone						

Protocol Revision History

Version Date	Summary of Substantial Changes
08/10/2023	Initial Submission
10/12/2023	Pre-approval Modifications Required

Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human participants) and other applicable government regulations and Institutional research policies and procedures.

Abbreviations

Abbreviation	Explanation
ASA	American Society of Anesthesiologists
CMP	Clinical Monitoring Plan
DOS	Day of Surgery
ERAS	Enhanced Recovery After Surgery
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
MME	Morphine Metabolic Equivalent
NSAID	Non-steroidal anti-inflammatory drug
PACU	Post-Anesthesia Care Unit
PHI	Protected Health Information
POD	Post-Operative Day
QoR-40	Quality of Recovery – 40
RCT	Randomized Control Trial
SCPB	Superficial Cervical Plexus Block
YCCI	Yale Center for Clinical Investigation
YNHH	Yale New Haven Hospital

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1 Background/Literature Review

1.1 Background

Thyroid surgery is performed using an anterior midline neck incision and is associated with mild to moderate post-operative pain,¹ with up to 90% of patients requiring opioid analgesia within the first 24 hours of surgery.² Various options have been posited and tested to improve pain management in thyroid surgeries. One of these is using regional anesthesia either in addition to or as an alternative to general anesthesia. Kulkarni et al.³ showed as early as 1996 that bilateral cervical plexus block (in their case both superficial and deep) is an appropriate alternative to general anesthesia in select patients undergoing thyroid and parathyroid surgeries.

Since then, there have been many studies evaluating the SCPB in thyroid surgery. which have been included in a meta-analysis. This metanalysis of fourteen RCTs showed that compared to control, SCPB was associated with less postoperative rescue analgesia in the first 24 hours (OR 0.30; 95% CI 0.18-0.51; P<0.00001).⁴ There was also an improvement in pain scores, time to first analgesic requirement, and hospital length of stay. There was no significant difference in incidence of postoperative nausea and vomiting.

Recent years have seen increased trends in using multimodal non-opioid oral analgesics, often in the context of Enhanced Recovery After Surgery (ERAS) protocols.^{5,6} Regional anesthetics can play an important role in ERAS pathways, however it is currently unclear to what extent the addition of a SCPB can further improve upon pain control and quality of recovery in the context of thyroidectomy surgery using an ERAS protocol. A pre-post study evaluating opioid consumption and pain scores for patients undergoing thyroid or parathyroid surgery before and after implementation of an ERAS protocol, which included multimodal analgesics including acetaminophen and ibuprofen, found no difference when comparing patients who did vs did not receive a block.⁷ This study did not include randomization and SCPB performance was at the discretion of the perioperative team. Nevertheless, this group's experience calls into question the utility of the SCPB in addition to the multimodal analgesic techniques recommended in modern practice.

Recent years have also seen an increase in the number of thyroid surgeries performed on an ambulatory basis. Outpatient thyroidectomy is gaining popularity because of its documented safety, decreased cost of care, and increased patient satisfaction.⁸ As the number of ambulatory surgeries performed each year increases, so does the number of patients who recover at home. Postoperative pain management is one component of postoperative recovery. Understanding the impact of interventions from the patient's perspective is an important part of decision-making regarding patient care, especially when recovery happens at home, and can be better assessed with patient-centered outcome tools such as the "Quality of Recovery-40" (QoR-40).⁹ One prior study has shown that the SCPB can improve quality of recovery after thyroid surgery for patients who are admitted postoperatively.¹⁰ In this study patients also received intravenous flurbiprofen axetil 50mg at the end of surgery and every 12 hours for the next 24 hours.

The proposed study aims to investigate differences in the quality of recovery after thyroid surgery in patients who receive SCPB with bupivacaine versus saline within the context of an ERAS pathway which includes standardized multimodal analgesics (preoperatively administered oral acetaminophen and celecoxib and intraoperatively administered dexamethasone) to determine whether the SCPB has an impact on quality of recovery in this modern context with protocolized multimodal analgesia.

1.2 Prior Experience (if applicable)

A pilot study utilizing the QoR-40 instrument led by the PI will inform design of this RCT.¹¹ Previous studies in ambulatory anesthesia utilizing the QoR-40 survey had been completed by administering the survey over a telephone interview. To improve efficiency and feasibility for future studies, these investigators examined the role of electronic administration of the QoR-40 survey (via emailed survey link) versus traditional telephone interview. In this pilot study, 100 patients were randomized to complete the QoR-40 survey either via telephone interview or electronic (email) administration. This study demonstrated that there were no significant differences in patient response rate or mean QoR-40 scores on post-operative days 1, 2, or 7.

Additionally, a retrospective pre-post ERAS implementation study conducted by this study team found that average pain scores were 2-3 on an 11-point numerical rating scale following thyroid and parathyroid surgery (N = 675), the majority of which were ambulatory (N = 521 (77%)). However, ERAS patients undergoing thyroidectomy demonstrated a significant reduction in opioid consumption post- compared to pre- ERAS implementation: mean (SD) 26.3 (23.6) MMEs vs 16.8 (16.6); $p = 0.007$. Opioid consumption for parathyroidectomy was not significantly different: mean (SD) 21.3 (23.2) post vs 17.6 (12.4); $p = 0.32$ pre-ERAS implementation. Therefore, we speculate that due to the fact that the majority of parathyroid surgeries were minimally-invasive, there is greater opportunity for improvement in the quality of recovery for thyroidectomy patients. We have decided to focus on this surgical population for this RCT. (Project accepted for oral abstract presentation at American Association of Endocrine Surgeons 2023 annual meeting and manuscript submitted for review).

2 Rationale/Significance

2.1 Rationale and Study Significance

The proportion of thyroid surgeries performed on an outpatient basis continues to grow each year, resulting in early recovery after surgery occurring in the home. Therefore, interventions that improve the early quality of recovery can benefit both patients and their caregivers, as poor recovery can be distressing to both without the immediate availability of healthcare workers to assist. Prior studies have demonstrated that the SCPB is an opioid-sparing analgesic modality that reduces pain scores after thyroidectomy.⁴ However these studies preceded the modern context of ERAS pathways and protocolized multimodal analgesia. This study seeks to identify if the addition of a SCPB improves early quality of recovery after thyroid surgery when included as part of an ERAS protocol with multimodal analgesics.

2.2 Purpose of Study/Potential Impact

Thyroid surgery is associated with mild to moderate post-operative pain, with most patients requiring opioid analgesia postoperatively. Regional anesthesia interventions, such as SCPB, are an important component of multi-modal non-opioid analgesia plans. The evidence base for SCPB in thyroid surgery has been generated prior to the current practice of ERAS protocols and standardized multimodal analgesia with acetaminophen, NSAIDs, and steroids. Whether the SCPB improves analgesia and quality of recovery in this context is unknown. Most prior studies of SCPB for thyroid surgery have focused on pain scores and opioid consumption, while patient-centered outcomes such as quality of recovery measured by the QoR-40 survey provide a more global picture of recovery. This study aims to determine whether the SCPB has an impact on quality of recovery in this modern context with protocolized multimodal analgesia.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks associated with this study relate to the administration of the SCPB.

Systemic Toxicity from the local anesthetic agent is possible. This issue will be addressed through placement of the block by an experienced anesthesiologist co-investigator so as to avoid intravascular injection. This anesthesiologist will also have familiarity with treating local anesthetic systemic toxicities in the event any were to occur. The dose of bupivacaine used in this study is low and therefore local anesthetic systemic toxicity from delayed systemic absorption is exceedingly unlikely and has not been seen with this block in the past.

A potential risk very rarely associated with administration of bupivacaine is increased risk of methemoglobinemia. This risk is greatly minimized by the very low dose of bupivacaine used for this study. The participant's oxygen saturation is continuously monitored as part of their routine anesthesia care. This will allow the clinical team to monitor for any signs of methemoglobinemia as it is known that methemoglobinemia alters SpO₂ readings to around

84-86% due to structural differences in oxyhemoglobin and methemoglobin that affect their absorbance spectrum ¹². If methemoglobinemia is detected, it will be treated with supplemental oxygen. **Any event including methemoglobinemia will be reported to the IRB immediately, as part of the Adverse Event reporting obligations.**

SCPB may also rarely affect or damage surrounding structures such as the recurrent laryngeal nerve, deep cervical plexus, brachial plexus, accessory nerve, internal jugular vein, and carotid artery. If the brachial plexus is affected, this may cause temporary shoulder weakness until the local anesthetic wears off. These risks will be minimized through meticulous technique, attention to detail, and superficial plane of injection. The block is performed in the subcutaneous plane so does not impact the respiratory function (i.e. by reaching the phrenic nerve or pleural space).

Infection is also a possible risk. This will be minimized through proper aseptic techniques.

Another potential risk is the risk of extended time of anesthesia from the administration of the block which is around three minutes.

Currently a SCPB is performed for some patients for thyroid and parathyroid surgeries at the discretion of the surgical team when one of five anesthesiologists are assigned to the case. These five anesthesiologists are very experienced with the block and do it routinely for these cases. The block is always done in combination with general anesthesia. Other anesthesiologists do not do the block as part of their routine practice and the block is not considered a standard of care. Risks associated with being randomized to the saline group include possible increased need for alternative methods of pain control which will be readily available to the patient on an as needed basis.

Another potential risk is breach of confidentiality which can occur with any research study collecting PHI. Utmost consideration will be taken when handling PHI and patient data, as detailed in Section 6 of the study protocol.

2.3.2 Potential Benefits

This study has the potential benefit of demonstrating an intervention that improves overall quality of recovery after thyroid surgery, which would benefit society and science. Participants in this trial who receive SCPB with bupivacaine may have the benefit of decreased pain and improved quality of recovery after surgery.

3 Study Purpose and Objectives

3.1 Hypothesis

We hypothesize that pre-incisional administration of a Superficial Cervical Plexus Block (SCPB) with bupivacaine will result in superior quality of recovery when compared to a saline injection control for patients 18 years or older undergoing thyroid surgery with general anesthesia.

3.2 Primary Objective

The primary objective of this study is to investigate whether there are differences in the quality of recovery (as determined by the QoR-40 survey) after thyroid surgery in patients who receive SCPB with bupivacaine versus saline within the context of an ERAS pathway which includes standardized multimodal analgesics (preoperatively administered oral acetaminophen and celecoxib and intraoperatively administered dexamethasone) to determine whether the SCPB has an impact on quality of recovery in this modern context with protocolized multimodal analgesia.

3.3 Secondary Objective

The secondary objectives of this study are to determine whether there are differences in opioid consumption (in morphine milligram equivalents) in PACU and through POD 1; need for rescue analgesia prior to PACU discharge; presence of nausea and/or vomiting in PACU; need for rescue antiemetics in PACU; PACU length of stay (in minutes); presence of patient reported side effects; and patient reported quantity of other modes of analgesia, if any, in PACU and through POD 1 in patients who receive SCPB with bupivacaine versus saline.

4 Study Design

4.1.1 General Design Description

This proposed study is a double-blinded randomized saline-controlled trial comparing QoR-40 scores after bilateral superficial cervical plexus block with either bupivacaine or saline in patients undergoing thyroidectomy within an ERAS pathway.

4.1.2 Study Date Range and Duration

Each participant's duration in the study will be approximately 2 days.

The entire study is anticipated to take 2 years to complete.

4.1.3 Number of Study Sites

This study will take place in the operating rooms of Yale New Haven Hospital. This is the only study site.

4.2 Outcome Variables

4.2.1 Primary Outcome Variables

- Quality of recovery-40 survey scores on postoperative day (POD) 1

4.2.2 Secondary Outcome Variables

- Opioid consumption (in morphine milligram equivalents) in PACU and through POD 1
- Need for rescue analgesia prior to PACU discharge
- Presence of nausea and/or vomiting in PACU
- Need for rescue antiemetics in PACU
- PACU length of stay (in minutes)
- Presence of patient reported side effects
- Patient reported quantity of other modes of analgesia, if any through POD 1

4.3 Study Population

This study aims to enroll patients aged 18 years or older undergoing thyroid surgery in the Operating Rooms of Yale New Haven Hospital. Potential participants will be identified by reviewing scheduled thyroid surgery cases of endocrinology surgeon co-investigators performing the surgeries.

Patients undergoing thyroid surgery are most likely to benefit from this intervention due to the ability of the SCPB to target the mild to moderate pain associated with the anterior midline neck incision performed in thyroid surgeries.

4.3.1 Number of Participants

Anticipated enrollment for this study is 160 patients – 80 participants in each group. Patients will be screened sequentially in the week(s) prior to surgery at Yale New Haven Hospital. For patients who do not have any exclusion criteria, based on electronic medical record review, their treating surgeon will introduce the study to the patient at the preoperative visit. If the patient expresses interest in participating, they will then be contacted by a study investigator by telephone. If, after review, they meet all inclusion criteria and informed consent is obtained, they will be enrolled in the study. We anticipate needing to screen 320 patients for our enrollment goal.

4.3.2 Eligibility Criteria/Vulnerable Populations

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Aged 18 years or older
- ASA classification I-III
- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Scheduled for thyroid surgery in YNHH Operating Rooms
- Access to smartphone device or computer with internet connection and has an email address

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-English speaking
- ASA classification > III
- Have an intolerance or contraindication to the medications involved in the study
- Undergoing repeat thyroid surgery
- Undergoing surgery with planned neck dissection
- Plan for admission post-operatively
- Diagnosis of any of the following: Glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise
- Pregnant by patient report, or positive pregnancy test on day of surgery (for participants with child-bearing potential)
- Refusal to participate

5 Study Methods/Procedures

5.1 Study Procedures

All patients enrolled in this study will receive general anesthesia according to the local standard practice for thyroid surgery and in compliance with the YNHHS ERAS pathway for thyroid surgery. Specifically, acetaminophen 1000mg and celecoxib 200mg will be administered orally in holding prior to entering the operating room. Anesthesia will be induced with propofol and maintained with a total intravenous technique with propofol and remifentanyl. All patients will receive dexamethasone 10mg intravenously after induction. Additional prophylactic antiemetics will be based on the risk-based guideline recommendations that are standardized in the ERAS pathway.

Randomization will occur using the randomization tool in REDcap on the day of surgery. One unblinded anesthesiologist investigator will perform the randomization and prepare the study drug (Two 10mL syringes of 0.25% bupivacaine vs two 10mL syringes of saline, one for each side of the bilateral block). The study drugs are readily used in clinical practice and are stored in the operating room Pyxis™ which is maintained by the perioperative pharmacy team. The unblinded anesthesiologist investigator will label the syringes with the following: "0.25% bupivacaine vs. saline" as well as the date and time and their initials.

After induction and patient positioning, and prior to surgical prepping and draping, the SCPB will be performed according to standard protocol by a blinded anesthesiologist investigator. This will be the only intervention administered for purposes of this study and will add approximately three minutes to the time the patient is under anesthesia. For this research study, the block will always be performed after intubation and prior to surgical incision, prior to extubation, and under general anesthesia. Patients will then have their scheduled surgery.

Post-operatively, information about their PACU stay will be collected from the electronic medical record by blinded investigators. Upon discharge, the patients will be instructed, per ERAS protocol, to take, for pain, acetaminophen 650mg and ibuprofen 600mg every 6 hours, alternating the medications every 3 hours (ex. 6am acetaminophen, 9am ibuprofen, 12pm acetaminophen, 3pm ibuprofen, etc.) Patients will also receive a prescription for 5 tablets of oxycodone 5mg with instruction that the oxycodone is to be used only for pain not controlled by the acetaminophen and ibuprofen. Information regarding the participant's post-discharge analgesic use will be solicited via questions included in the POD 1 survey.

After discharge, patients will be emailed surveys to electronically complete on POD1. If a patient does not complete their survey by the evening of POD1, a blinded member of the research team will contact the patient via telephone to complete the survey. The electronic medical record will also be reviewed to record intraoperative and postoperative data into the study database.

5.1.1 Study Schedule

Week(s) Prior to surgery	Screening of electronic health records to identify potential participants, surgeon co-investigator will introduce study to patients, patients contacted via telephone to answer any questions, electronic consent obtained, baseline QoR-40 administered
Day of Surgery	Patients randomized to intervention or control group, receive SCPB, undergo planned surgery, observed during recovery room stay
Postoperative Day 1	Electronic link to complete QoR-40 survey emailed. Patient called if no survey is submitted to complete survey via telephone

5.1.2 Screening

Patient's electronic medical records will be reviewed prior to surgery to assess eligibility for enrollment. If any exclusion criteria are identified as detailed in section 4.3.2, patients will not be contacted for enrollment. If a patient meets all inclusion criteria, then the surgeon co-investigator performing the surgery will introduce the study to the patient during a routine clinic visit. At this visit, the patients will receive an infographic briefly explaining the study. Then, potentially interested patients will be contacted by telephone phone call within a week of their surgery to answer any questions. Patients who are screened out of the study will not be re-screened at a later time.

5.1.3 Informed Consent

To obtain informed consent:

1. Research staff will assess participant eligibility via screen of operating room schedule(s) of surgical co-investigators. Only PHI regarding participant inclusion/exclusion criteria will be reviewed prior to contacting patients.
2. If eligible, the surgeon co-investigator performing the surgery will introduce the study to the patient during a routine clinic visit. At this visit, the patients will receive an infographic briefly explaining the study. Potential participants will then be contacted by a member of the study team via telephone within a week prior to their surgery to obtain informed consent.
3. During the telephone consent process, a study investigator will call potential participants and answer any questions that they may have regarding the study. Those who are interested will have the opportunity to carefully review the consent form electronically and ask questions.
4. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

5. If a patient chooses to participate in the study, the study investigator will confirm understanding and obtain electronic informed consent. Participants will receive a copy of the informed consent form via email.
6. For all potential participants, a physician co-investigator will be available for any questions the potential participant has. If participants consent to be in the study, their treating surgical physician will be informed of their consent prior to the procedure.

The following consent documents are attached to this protocol:

- Informed Consent Form

5.1.4 Enrollment

Patients will initially be approached by their treating surgeon during the routine pre-operative visit prior to undergoing thyroid surgery in the operating rooms at YNHH. Patients who express interest in the study will receive an infographic handout that briefly introduces the study. A member of the research team will then call the patient within a week of the day of surgery to obtain informed consent and the baseline QoR-40 survey. No other study procedures will occur until the day of surgery.

After electronic informed consent is obtained, patients will be enrolled into the study on the day of surgery. The participant's attending anesthesiologist (who is a study investigator) will meet the participant in the preoperative area prior to surgery as part of the routine preoperative care, during which the anesthesiologist can answer any additional questions the participant may have. Randomization will occur at the time of enrollment and will be executed in 1:1 fashion through the REDCap randomization tool.

The following recruitment document is attached to this protocol:

- Patient-facing infographic describing the study that surgeon co-investigators will give to patients when introducing the study

5.1.5 Blinding

This is a double-blind study. The intervention drug (bupivacaine 0.25% 10 mL on each side) and saline (10mL on each side) will be prepared by an unblinded co-investigator in a sterile, non-patient facing setting to ensure identical appearance and blinding. All study investigators will remain blinded with the exception of one unblinded co-investigator who will not be involved in data collection. If the blind must be broken in an emergency, the unblinded co-investigator will provide the identification of drug.

5.1.6 Study Visits

Week Prior to surgery	- Patient screened for enrollment - If eligible, informed of study by their surgeon during routine clinic visit and given infographic. Then, contacted via telephone by study team member to answer any questions
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	- Electronic consent obtained - Baseline QoR-40 survey administered
Day of Surgery	- Arrive in pre-surgical holding - Reconfirm eligibility - o Negative pregnancy test for participants with child-bearing potential - Enrollment & Randomization - Receive SCPB with bupivacaine or saline after anesthesia start but before surgery start - Undergo surgery, recovery room stay, and discharge home
Postoperative Day 1	- Receive email with link to postoperative day 1 survey - If survey not complete by the evening of POD 1, a study investigator will call to complete it by telephone

5.1.7 End of Study and Follow-up

Participants will be followed for one day following their surgery. Once they have submitted their survey on post-op day 1, no further patient follow-up is planned.

Participants who withdraw from the study will be contacted to ascertain the reason for withdrawal.

All participants will be given contact information for the study team and will be instructed to call with any concerns regarding the study.

5.1.8 Removal of participants

Patients may withdraw themselves voluntarily from the study at any time. Patients who voluntarily withdraw will be contacted to ascertain the reason for withdrawal.

There are no anticipated adverse events that would require removing participants from this study.

If patients withdraw from the study, their previously collected survey data will be utilized in the final statistical analysis (intention-to-treat analysis).

5.2 Statistical Method

5.2.1 Statistical Design

This is a randomized, double-blinded, placebo-controlled, trial. The hypothesis is that the administration of SCPB with bupivacaine pre-operatively will result in improved quality of recovery for patients undergoing thyroid surgery.

The two study groups are patients receiving SCPB with bupivacaine and patients receiving SCPB with saline. The baseline and intraoperative characteristics of the groups will be compared using descriptive summaries (means, medians, frequencies, standard deviations, interquartile ranges).

The primary outcome for this study is the QoR-40 score on POD1.

Secondary outcome variables include:

- Opioid consumption (in morphine milligram equivalents) in PACU and through POD1
- Need for rescue analgesia prior to PACU discharge
- Presence of nausea and/or vomiting in PACU
- Need for rescue antiemetics in PACU
- PACU length of stay (in minutes)
- Presence of patient reported side effects
- Patient reported quantity of other modes of analgesia, if any through POD1

5.2.2 Sample Size Considerations

Hu¹³ et al. observed a 13 point reduction in the total QoR-40 score on POD 1 between the bilateral SCPB group (149.0 [IQR 144.0 to 153.5]) and the control group (162.0 [157.5 to 166.5]) among uremia patients who had parathyroidectomy. For the proposed study, we expect a higher overall QoR-40 score and a smaller group difference in our institution because patients are cared for using multimodal analgesia. In our pilot study of patients who underwent either thyroidectomy or parathyroidectomy, the average QoR-40 score was 170 (SD 10). For the sample size calculation, we consider an improvement of QoR-40 score on POD1 by 6 points as clinically significant, and we assume the SD is 12. With a significance level of 0.05 using a two-sided two-sample equal-variance t-test, a sample size of 64 per group will achieve 80% power to reject the null hypothesis of equal QoR-40 scores. Anticipating a 20% dropout rate, the final group size is 80 subjects per group.

5.3 Planned Analyses

Interpretation of the study findings will be mainly based on the results from the intention-to-treat analyses. The primary outcome for this study is the QoR-40 score on post-operative day 1. Comparisons of this score will be performed in a repeated measures mixed model analysis. The model will include fixed effects for treatment, time and their interaction as well as baseline QoR-40 scores. An unstructured covariance pattern will be used to accommodate repeated measures. Linear contrasts and 95% confidence intervals will be used to estimate the difference between study groups on POD 1.

Comparisons of secondary outcomes that are repeated in PACU and through POD 1 will be performed using the generalized estimating equations (GEE) models with log link for opioid

consumption and logit link for nausea and vomiting. The models will include the same covariates as specified for the primary analysis, and empirical standard errors will be used to test the hypotheses.

Comparisons of other secondary outcomes such as length of PACU stay and need for rescue analgesia will be compared between study groups using Wilcoxon Rank Sum tests.

5.3.1 Analysis of Participant Characteristics (if applicable)

As this is a randomized study, we expect the distribution of possible baseline and intraoperative confounders to be similar between treatment groups. These variables will be compared between groups with descriptive summaries (means, medians, frequencies, standard deviations, interquartile ranges). If differences are observed, we will include these factors in all analyses.

5.3.2 Handling of Missing Data

Comparisons of treatment assignment and baseline characteristics will be performed between those who had follow-up data and those who did not to investigate the potential missing data mechanism. Appropriate actions will be addressed, for example, if the proportion of dropouts is significantly higher in one study arm than the other, we will perform inverse probability weighting analysis to account for potential non-ignorable missing data.

5.4 Adverse Events Definition and Reporting

5.4.1 Definitions

An adverse event (AE) can be any untoward or unfavorable medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

5.4.2 Adverse Event Characteristics

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples

of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

5.4.3 Severity of Adverse Events

Adverse events will be graded in severity according the following guidelines:

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.]

5.4.4 Relationship to Study Intervention

All AEs must have their relationship to study intervention assessed by the clinician who evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or

underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

5.4.5 Recording of Adverse Events

All adverse events will be recorded in a participant specific AE log. The AE log will be maintained by the research staff and kept in the participant's research chart on REDCap.

5.4.6 Reporting of Adverse Events to Yale IRB

All AEs occurring during this study will be reported to the IRB according to the IRB policy.

6 Trial Administration

6.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

A member of the study team will obtain documented consent according to ICH GCP and local regulations, as applicable, from each potential participant or each participant's legally authorized representative prior to participating in the research study. Participants who agree to participate will sign the IRB approved informed consent form (ICF) and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

To obtain informed consent:

1. Research staff will assess participant eligibility via screen of operating room schedule(s) of surgical co-investigators. Only PHI regarding participant inclusion/exclusion criteria will be reviewed prior to contacting patients.
2. If eligible, the surgeon co-investigator performing the surgery will introduce the study to the patient during a routine clinic visit. Potential participants will then be contacted by a member of the study team via telephone within a week prior to obtain informed consent.
3. During the telephone consent process, a study investigator will explain the research study to the potential participant by phone and answer any questions that may arise. Those who are interested will have the opportunity to carefully review the consent form electronically and ask questions.
4. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.
5. If a patient chooses to participate in the study, the study investigator will confirm understanding and obtain electronic informed consent. Participants will receive a copy of the informed consent form via email, or via physical copy on their day of surgery.
6. For all potential participants, a physician co-investigator will be available for any questions the potential participant has. If participants consent to be in the study, their treating surgical physician will be informed of their consent prior to the procedure.

The following consent documents are attached to this protocol:

- Informed Consent Form

6.2 Institutional Review Board (IRB) Review

As required by local regulations, the PI will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will promptly report to the IRB any new information that may adversely affect the safety of the participants or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, a study closure report will be submitted to the IRB.

All protocol amendments will be submitted to the IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale University's IRB's policies.

6.3 Participant Confidentiality

Participant confidentiality is held in strict trust by the research team. Participant medical record review will be limited to only the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into the study-specific REDCap database. Surveys will also be administered via REDCap and directly transmitted to the REDCap database for storage.

6.4 Deviations/Unanticipated Problems

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by email notification.

6.5 Data Collection

The data collected for this study include baseline and surgical characteristics, QoR-40 survey responses, and any adverse event data for all enrolled participants. Surveys will be administered electronically via an email link. The survey will be built in a REDCap database and results will be collected within this same database. Only study team members will have access to the data.

The QoR-40 survey is included as an appendix.

6.6 Data Quality Assurance

All study investigators will complete REDCap training prior to study enrollment. All survey information will be entered directly by patients via emailed link or, for non-responders, via telephone call and manual entry by a study investigator. Completed surveys will be stored within the REDCap environment.

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

6.7 Study Records

The following items are considered "Study Records":

- All study protocols
- Regulatory documents related to clinical trial administration
- Consent forms
- Demographic information and completed surveys (stored in REDCap database)

6.8 Access to Source

Patients will complete the study survey (appendix) directly into the REDCap database. Only IRB approved study investigators, who have completed required REDCap training, will have access to this database.

6.9 Data or Specimen Storage/Security

Data will be collected digitally in the REDCap environment. Participant data will be stored within this database only.

6.10 Retention of Records

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all essential documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure REDCap environment. Essential documents will be retained for a minimum of 2 years. These documents will be retained for a longer period, however, if required by local regulations.

6.11 Study Monitoring

Clinical site monitoring will be regularly performed by the principal investigator and will include a site initiation visit as well as on-site interim monitoring of study data. Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, that the facilities and staffing are adequate for continued study conduct, and that the conduct of the trial is in

compliance with the currently approved protocol/amendment(s), with International Council for Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s) including federal, state and local regulations and institutional policies and procedures.

6.12 Study Modification

Study modifications, if required, will be reviewed by the Yale University IRB. If a modification is deemed necessary, this protocol will be updated, and following IRB approval, will be implemented into the study.

6.13 Study Completion

Once 160 patients have been enrolled, with all surveys completed, patient enrollment will stop. After data analysis and manuscript preparation, the study will have been deemed to have been completed. The IRB will be notified at the conclusion of patient enrollment.

6.14 Funding Source

This study is supported by the Department of Anesthesiology and a one year medical student research fellowship supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health and the Yale School of Medicine.

6.15 Conflict of Interest Policy

All investigators will follow the applicable conflict of interest policies.

6.16 Publication Plan

The principal investigator holds primary responsibility for publishing the study results.

7 Appendices

Appendix #	Title	Section	Topic
1	QoR-40 Survey		
2	Patient infographic handout		

8 References

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