DEFENSE HEALTH AGENCY
NAVAL MEDICAL CENTER
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February 08, 2024

MEMORANDUM

From: DHA IRB Office at Naval Medical Center Portsmouth
To: CDR Michael Lee

Subj: APPROVAL OF NMCCL.2024.0027 "CERVICAL PLEXUS VERSUS INFILTRATION FOR CLAVICULAR OPERATIONS (CERPICO)"

Ref: (a) Code of Federal Regulations, Title 32
(b) DoDI 3216.02 "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research", April 2020, as amended.
(c) Code of Federal Regulations, Title 45, Part 164

1. Submission. A new protocol (EIRB Reference: 966033) was submitted to NMCCL HRPP on 10/03/2023, completed scientific review on 01/17/2024, and was submitted to the NMCP IRB on 01/18/2024.

2. Approval. Naval Medical Center Portsmouth (NMCP) IRB-2 reviewed and approved NMCCL.2024.0027 "Cervical Plexus Versus Infiltration for Clavicular Operations (CERPICO)" at a convened meeting on **01/25/2024** pending changes. Those changes were approved by the Chair via expedited procedures on **02/08/2024**.

3. IRB Determinations. The following determinations were made in accordance with references (a) through (c) as part of this approval:

a. Approval Category(ies). The above referenced study is Full Board.

b. Risk Assessment. The above referenced study has been assigned a risk rating of Greater than Minimal Risk 32 CFR 219 / 21 CFR 56.

c. Enrollment. The above referenced study is approved for 40 subjects.

d. Study Expiration. The above referenced study has been approved for a period of one year minus one day, with an expiration date of **02/07/2025.** Naval Medical Center Portsmouth IRBs are continuing to require continuing reviews for all human subjects research protocols due to the transient nature of base personnel.

e. Informed Consent. An informed consent process encompassing all the required elements of informed consent IAW 32 CFR 219.116 has been approved. Investigators must use the stamped IRB-approved consent form. Federal regulations require that each subject receive a copy of the consent document.

f. HIPAA Authorization. A compound HIPAA Authorization has been approved as part of the stamped, IRB-approved consent form. Federal regulations require that each subject receive a copy of the consent document.

4. Approved Documents. Approval of the above referenced study includes the following documentation:

Submission Components Approved		
Document Type	Version	Date Approved
Submission-Initial Review Submission Form	Version 1.0	02/08/2024
Application-EIRB Protocol Template	Version 1.2	02/08/2024
Consent Form-NMCCL.2024.0027 ICF and HIPAA	Version 1.4	02/08/2024
Document-CERPICO Adverse Event Log	Version 1.0	02/08/2024
Document-CERPICO Con Med Log	Version 1.0	02/08/2024
Document-CERPICO Study ID Log	Version 1.0	02/08/2024
Document-Study Protocol	Version 1.2	02/08/2024
Document-Phone Script	Version 1.1	02/08/2024
Document-Data Collection Tool	Version 1.1	02/08/2024
Document-Patient Pain Diary	Version 1.1	02/08/2024

5. Agreements. It is the Principal Investigator's (PI's) responsibility to obtain necessary approvals from other offices, such as the DHA Privacy Office, Technology Transfer Office, and/or Information Management Control Office, before initiating or continuing research.

6. Protocol Registration. If indicated in the study protocol, it is the PI's responsibility to register the study with Defense Technical Information Center (DTIC) (https://discover.dtic.mil) and/or www.ClinicalTrials.gov as soon as possible.

7. Post-approval Requirements. Post-approval study actions must be submitted in EIRB (https://eirb.csd.disa.mil) by the PI.

a. Continuing Review. The study expiration date is **02/07/2025**. The IRB Office strongly recommends that continuing reviews are submitted at least sixty days prior to study expiration. If the study expires, the IRB Office will notify study investigators that all study activities must be suspended, and the IRB will take steps to administratively close the protocol for non-compliance. A continuing review submission guide can be found on the Clinical Investigation Department (CID) SharePoint (https://esportal.med.navy.mil/nmcp/dir/dpe/ci/Pages/EIRB.aspx).

b. Modifications. Future modifications (including, but not limited to, changes in study personnel, inclusion/exclusion criteria, subject enrollment, or study procedures) must be submitted for IRB review and approval prior to implementation. If a PI deploys or is TDY/TAD for more than 4 weeks, a modification must be submitted naming a replacement PI. A modification submission guide can be found on the CID SharePoint (https://esportal.med.navy.mil/nmcp/dir/dpe/ci/Pages/EIRB.aspx).

c. Event Reporting. Any deviation to the protocol that may affect the safety or rights to study subjects or the integrity of the study, Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSOs), and all Serious Adverse Events (SAEs) must be promptly reported to the IRB and local HRPP via telephone (757) 953-5939 or via email (usn.hampton-roads.navhospporsva.list.nmcp-irboffice@health.mil) within ONE business day of discovery. A Reportable Event form must be submitted within THREE business days of discovery. An Adverse Event (AE) that is neither serious, nor unexpected, nor related to research, should be reported to the IRB and local HRPP at the time of

continuing review. If investigators are unsure of the classification of an event, they should contact the IRB or local HRPP. A Reportable Event submission guide can be found on the CID SharePoint (https://esportal.med.navy.mil/nmcp/dir/dpe/ci/Pages/EIRB.aspx).

d. Closure. When the project has been completed, a Closure Report and a manuscript, abstract, or summary of study results must be submitted. If research cannot be completed, a Closure Report must be submitted along with an explanation of why the project will not continue. It is the PI’s responsibility to ensure that Closure Reports are uploaded to DTIC (https://discover.dtic.mil) within 90 days of closure. A DTIC submission guide can be found on the CID SharePoint https://esportal.med.navy.mil/nmcp/dir/dpe/ci/Pages/IRB Submission Guidance.aspx).

8. Publication. All abstracts, presentations, manuscripts, and review articles must be approved by the local command prior to submission for publication. At NMCP, approval request forms may be obtained from the CID SharePoint (https://esportal.med.navy.mil/nmcp/dir/dpe/ci/Pages/Publication Approval.aspx). Investigators from other commands should contact their local Public Affairs Office.

9. Funding. Approval of this study does not guarantee that funds are available to support it. If funding for supplies, equipment, or personnel is required, contact the NMCP Department of Professional Education or the PI’s local command.

10. Contacts. The local HRPP contact at Naval Medical Center Camp Lejeune is Ms. Chemely Walker (chemely.m.walker.civ@health.mil, (910) 450-3460). The NMCP IRB Office may be contacted at (757) 953-5939 or via email at usn.hampton-roads.navhospporsva.list.nmcp-irboffice@health.mil. SOPs, policies, and guidance can be found on the CID SharePoint (https://esportal.med.navy.mil/nmcp/dir/dpe/ci/).

Kersten Wheeler

Signature applied by Kersten N Wheeler on 02/08/2024 02:05:40 PM CST

NMCP IRB OFFICE

STUDY ROLES

PRIMARY RESEARCHERS

Drs. Lee and Willett

The Primary Researchers will:

- Explain study details to interested participants
- Obtain consent from patients
- Be unblinded to patient study allocation
- Prepare and distribute the study medications to the study physicians
- Be available to provide information on study protocol, such as reminding non-research providers to not give alternative opioids or adjunct analgesics
- Collect treatment and assessment data gathered by other providers
- NOT perform any procedure, injection, or patient assessment

STUDY PHYSICIANS

Surgeons: Drs. Lewandowski, Richards, and Nappo

The Study Physicians will:

- Gauge patient interest at pre-operative appointments
- Explain study details to interested participants
- Be blinded to patient study allocation
- Administer study injections to patients during the procedure

RESEARCH COORDINATOR

Ms. Shannon Kelly

The Study Coordinator will:

- Perform study-related administrative duties
- Be blinded to patient study allocation
- Call the patient to assess Post-Operative Day 1 pain

STUDY PROCEDURES

RECRUITMENT & CONSENT

To gauge patients' interest, those undergoing scheduled clavicle surgeries will be told about the study during the preoperative visit, which takes place approximately 3-14 days before surgery. The Study Physicians will explain the study to interested patients in detail, answering any questions, and then provide a hard copy of the informed consent to take home, so potential participants have time to properly review it.

Patients who expressed interest will be approached in their private room on the day of surgery, during the preoperative preparation period. The Primary Researcher or Study Physician will ask if the patient is still interested in participating and ensure no exclusion criteria apply. If so, the Primary Researcher will review the study methodology and its objectives. The study candidate will be given another opportunity to discuss and ask any questions. If the study candidate is amenable to participation, the study candidate will be provided with another hard copy informed consent and contact information for Dr. Lee will be provided. Informed consent and enrollment will be completed prior to the administration of any sedating medications.

ALLOCATION & BLINDING

After informed consent and enrollment, the study candidate will be assigned a subject ID number and then proceed to the operating room. Subject IDs will have been previously assigned a study intervention, either the UGICPB Arm or LIA Arm, by computer-generated randomization, and placed into an opaque manilla envelope.

The Primary Researcher will open the allocation envelope after the patient has been brought to the OR to begin their procedure. They will collect the necessary amounts/dosages of both bupivacaine and saline from their standard storage location (typically the Pyxis or med cart). The OR bay is designed such that an area is out of sight of other providers. In this area, the Primary Researcher will draw the solutions into the syringes as dictated by the study allocation and then verify the syringes are correct for the study allocation. Once prepared, the Primary Researcher will pass the syringes to the Study Physicians, or their respective nursing staff as applicable.

Both anesthetics are clear and visually indistinguishable, so the Study Physicians will be blinded. The patient will be under general anesthesia at the time of both blocks, so they will also be blinded. Though in different dosages, the total amount of bupivacaine administered is the same regardless of study arm. This total amount, not the dosages or location of administration, will be recorded in the patient's chart.

Furthermore, both the post-op PACU nurse (who will assess pain and pain medication needs) and the Study Coordinator (who will assess pain levels on post-operative day one) will be blinded to the study allocation.

CLAVICLE OPERATION

ALL PATIENTS (STANDARD CARE)

Patients will be administered a standardized anesthetic plan of preoperative anxiolysis (midazolam 2mg) and induction of anesthesia (lidocaine 1-1.5mg/kg, fentanyl 0.5-1.5mcg/kg, propofol 1-3mg/kg, and rocuronium 0.6-1.2mg/kg). Airway management will be at the discretion of the staff anesthesia provider.

Following endotracheal intubation, the anesthesia provider will perform an ultrasound-guided intermediate cervical plexus block. Ultrasound imaging will be used to identify the sternocleidomastoid muscle at its midpoint between origin and insertion. An echogenic needle will be advanced under live ultrasound guidance just deep to the posterior aspect of the sternocleidomastoid muscle.

UGICPB ARM (RESEARCH PROCEDURE)	LIA ARM (RESEARCH PROCEDURE)
10ml of bupivacaine 5mg/ml will be injected in 2ml aliquots with intermittent aspiration under direct visualization to confirm appropriate solution propagation and to avoid intravascular injection.	10ml normal saline will be injected in 2ml aliquots with intermittent aspiration under direct visualization to confirm appropriate solution propagation and to avoid intravascular injection.

ALL PATIENTS (STANDARD CARE)

Patients will then be administered a standardized anesthetic maintenance plan consisting of sevoflurane to age-adjusted MAC of >0.5, acetaminophen 1000mg IV, dexamethasone 10mg IV, ketorolac 30mg IV, tranexamic acid 1000mg IV, and rocuronium for neuromuscular blockade as indicated. The antibiotic regimen will be at the discretion of the orthopedic surgeon. For intraoperative pain control, the anesthesia provider will administer fentanyl 25-100mcg q5 min for HR and/or BP >20% baseline attributable to pain in the judgment of the anesthesia provider. No alternative opioids or adjuncts, such as nitrous oxide, ketamine, or dexmedetomidine, will be administered.

UGICPB ARM (RESEARCH PROCEDURE)	LIA ARM (RESEARCH PROCEDURE)
Prior to wound closure, the orthopedic surgeon will infiltrate the anticipated surgical site with 20ml of normal saline using a landmark-based technique.	Prior to wound closure, the orthopedic surgeon will infiltrate the anticipated surgical site with 20ml of bupivacaine 2.5mg/ml using a landmark-based technique.

ALL PATIENTS (STANDARD CARE)

Intermittent aspiration will be performed to avoid intravascular injection. The injectate will be evenly distributed along the skin, subcutaneous plane, musculature, and periosteum.

All patients will receive sugammadex 2-4mg/kg for reversal of neuromuscular blockade prior to emergence. Ondansetron 4mg may be given at the discretion of the staff anesthesia provider. Airway management for extubation will be at the discretion of the staff anesthesia provider; however, patients will not be transported to the PACU until emerged from general anesthesia.

On arrival to the PACU, the PACU nurse will perform their normal duties, including recording the times of PACU admission and discharge, initial and maximum pain score during phase 1 recovery, pain score at time of discharge, presence of nausea, administration of anti-emetic medication, emetic events, and incidence of Horner's syndrome in the patient's chart.

The PACU nurse will also, as a part of their normal duties, administer fentanyl per the standard institutional order set (25mcg fentanyl every 5 minutes as needed for pain score 1-4, 50mcg fentanyl every 10 minutes as needed for pain score 5-6, and 50mcg fentanyl every 5 minutes as needed for pain score 7-10) in the event rescue analgesia is indicated, up to a maximum of 250 mcg while in recovery phase 1. If the subject's pain continues to be uncontrolled after the administration of 250 mcg of fentanyl, or if the risk of continued opioid administration outweighs the benefit (in the opinion of the PACU anesthesia provider), alternative analgesics may then be utilized at the discretion of said PACU anesthesia provider.

Patients will be discharged with 800mg ibuprofen every 8 hours as needed, 1000mg acetaminophen every 8 hours as needed, and 5mg oxycodone every 6 hours as needed (15 tablets) for post-discharge analgesia, as is standard.

ALL PATIENTS (RESEARCH PROCEDURE)

After the patient has been discharged from the PACU, the Primary Investigators will retroactively collect the data from the OR and PACU that has been recorded in the patient's chart by their treatment providers. Note that the Primary Investigators will not make any treatment decisions or patient assessments, only record the existing information that other healthcare providers have collected.

Before discharge, the patient will receive a one-page pain diary on which to record answers regarding their pain level for the first 24-36 hours, to aid them in recalling their pain details for the post-op phone call.

POST-OPERATIVE DAY 2-3

ALL PATIENTS (RESEARCH PROCEDURE)

On the first business day 24 hours after the participants discharge, which should be about 24 to 72 hours post-discharge, the Study Coordinator will contact the research subject by phone to obtain the following information: lowest pain score following discharge, average pain score following discharge, maximum pain score following discharge, duration of perceived block effectiveness (i.e. when the block wore off), number of 5mg oxycodone tablets taken, need to return to hospital for pain control, and satisfaction with postoperative pain control on a 1-5 satisfaction scale. The patient will be informed that their participation in the research study is now complete.

The Study Coordinator will make 3 attempts to contact the participant via telephone.

POST-OPERATIVE 2 WEEK FOLLOW UP

ALL PATIENTS (RESEARCH PROCEDURE)

All patients are schedule for a post-operative follow up visit approximately two weeks after surgery. If the participant was unable to contacted by phone, the Study Physician will attempt to ask the participant about their post-operative pain 24 hours after discharge at this visit. This will be the final attempt to collect the post-discharge data. Participants who are not able to be contacted by phone and do not attend their 2-week follow up appointment will be considered lost to follow up.

STUDY TIMELINE

	Timing	Tasks
Initial Injury Visit	3-21 Days Before Surgery	Identify potential participants
Pre-Operative Visit	3-14 Days Before Surgery	Assess interest of potential participants Review Informed Consent Document (ICD) with interested patients Send ICD home with interested patients for their review
Day of Surgery	Day 0; Preoperative Room	Review research study with interested patients Confirm no exclusion criteria apply Participants sign ICD
	Day 0; Operating Room	Participant is randomized Primary researcher prepares injections Participant receives general anesthesia
	Day 0; Operating Room	Participant is given a Cervical Plexus Block (CPB) • Participants in the **CPB arm** will have **bupivacaine** in their injection • Participants in the **LIA arm** will have **saline** in their injection
	Day 0; Operating Room	Clavicle open reduction and internal fixation performed
	Day 0; Operating Room	Participant is given a Local Infiltration Analgesic (LIA) • Participants in the **CPB arm** will have **saline** in their injection • Participants in the **LIA arm** will have **bupivacaine** in their injection
	Day 0; Operating Room	Participant emerges from general anesthesia
	Day 0; PACU	Participant remains in PACU at the discretion of the PACU anesthesia provider Assessments are made by PACU nurse as part of their normal duties
	Day 0; PACU	Participant is given a pain diary Participant is discharged
Post-Op Day 1	0-24 hours post discharge	Primary Investigators will collect OR and PACU data from the patient chart Participant is asked to complete pain diary
Post-Op Day 2-3	24-72 hours post discharge	Research staff collects pain diary data via telephone interview (3 attempts)
Post-Op Follow-Up	~14 days post discharge	Final attempt to reach participants; if no data available, participant will be considered lost to follow-up