TITLE: The Effect of Pneumatic Tourniquet Use on Upper Extremity Edema Following Axillary Lymph Node Dissection

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1.0 SPECIFIC STUDY AIMS

The purpose of this study is to evaluate the safety of tourniquet use and subsequent resolution of swelling in patients with prior axillary lymph node dissection. We hypothesize that a tourniquet placed for a short period of time at low pressure will cause edema without complication in both arms ipsilateral and contralateral to the side of axillary lymph node dissection in patients status post prior axillary lymph node dissection for cancer.

2.0 BACKGROUND AND RATIONALE

The safety of elective hand surgery in breast cancer patients following ipsilateral axillary lymph node dissection (ALND) is controversial due to concerns of developing upper extremity lymphedema. Prior authors have discussed concern for invasive and non-invasive manipulation of the extremity, including blood pressure measurements, injections, and intravenous access[1-2], although the evidence for these factors in the onset or progression of lymphedema is limited. However, this is controversial in the oncology literature despite being widely accepted in the hand surgery literature[3-5]. Patients are commonly dissuaded from routine elective hand surgery for coexistent pathology[6]. Prior studies have demonstrated no to minimal risk of developing lymphedema acutely or late following hand surgery after prior ALND[6-9]. Furthermore, no evidence is available to demonstrate a relationship between tourniquet use and lymphedema[6-9], and existing literature supports the use of an upper arm tourniquet in patients with prior breast cancer treatment of ALND. The acute effect of swelling in the setting of a tourniquet and the time required for swelling reduction for this population, however, remains unknown.

A pilot study has been completed to evaluate tourniquet use in healthy volunteers and the chosen pressure of 40 mmHg was identified as leading to repeatable swelling without acute or chronic abnormalities. Higher pressures (250, 120, 100 and 80 mmHg) lead to a similar 30-40 mL increase in volume in a healthy volunteer, although transient nerve palsy, pain and petechiae were identified at the higher pressure. No complications were identified in 8 healthy volunteers at 40 mmHg over 25 minutes. The increase in hand volume was less than 30 mL at 30 mmHg or less. Therefore, 40 mmHg most reliably recreates temporary edema formation, while limiting unnecessary or prolonged tourniquet use. Pilot study results further found that both the on head and brace limb postures markedly and significantly decreased swelling greater than the sling posture ($p < .001$).

The purpose of the proposed study is to evaluate the acute impact of swelling caused by low-pressure tourniquet use in the setting of ipsilateral ALND and the change in swelling reduction following tourniquet use in two limb postures, comparing the arms ipsilateral and contralateral to the side of ALND. We hypothesized that tourniquets may be safely applied to patients with prior ALND in either their ipsilateral or contralateral arm. We further hypothesized that patients who have had prior ipsilateral ALND would have an equivalent proportion of upper extremity edema and see improved resolution with increased elevation. Understanding the effect of tourniquet use and its safe practice will aid in the surgical management of patients with prior axillary lymph node dissection.

3.0 STUDY ENROLLMENT AND PARTICIPANT ELIGIBLITY

All patients over the age of 18 who have previously undergone axillary lymph node dissection will be invited to participate in the study. Participants will be identified via chart review of patients with prior ALND.

3.1 Study Enrollment

Recruitment will occur via telephone or in-person encounters based on retrospective review for patients meeting the above inclusion criteria. Advertising for this study is not planned. Participants will be screened based on the above criteria and the exclusion criteria in part 3.2 below. Participants who fail inclusion on screening will be excluded.

The study coordinator or the above study members will consent the patient prior to involvement. In a closed and quiet room, the potential research subject will be able to ask any questions regarding the study and its procedures. No recruitment materials will be provided at the time of consent. Participants may withdraw consent at any time.

3.2 Participant Criteria

All patients over the age of 18 who have previously undergone axillary lymph node dissection will be invited to participate in the study. Patients will serve as their own internal control, using both arms which are ipsilateral and contralateral to the side of ALND. Patients will be excluded who have new-onset lymphedema of the involved limb, infection including cellulitis, or trauma or planned axillary surgery within 6 months of participation.

3.3 Enrollment

Given the variability in our pilot study, we determined by power analysis that we would need to recruit 45 participants (for a total of 90 arms) for the current study for evaluation of relative edema and its reduction following tourniquet use. We expect the study to begin upon approval, 4/2017 and conclude after recruitment in approximately 6-12 months.

4.0 MATERIAL AND METHODS

Study participants will be seated and patients' arms ipsilateral to prior axillary lymph node dissection will be elevated with the hand above the level of the ipsilateral shoulder for 15 minutes. This is to ensure an accurate baseline in all participants. Hand volume will be measured by aqueous volumeter to the level of the proximal wrist crease for a baseline. A tourniquet will then be placed on each study participant's upper arm, again ipsilateral to prior axillary lymph node dissection. This will be inflated to 40 mmHg for 25 minutes, after which hand volume will be again measured as described above. The limb will then be placed in an elevated position at shoulder height or in a sling at the waist, and hand edema will again be measured. The process will be repeated for each limb position after a 15-minute break time. The two limb positions are "sling," with the hand at the level of the waist, and "elevated" with the hand at the level of the shoulder. This will be repeated for the contralateral, healthy arm which will serve as an internal control.

5.0 STATISTICAL CONSIDERATIONS

We will evaluate the data per recommendations of our statistician by categorical and continuous statistical testing, as applicable. For the primary outcomes of percentage change in hand volume from baseline after tourniquet application, and secondary outcome of residual volume as a percentage of baseline following limb positioning, we will compare the healthy contralateral arm versus the arm status post ALND. Paired t-tests will be used to compare measures averaged to produce a single pre-tourniquet hand volume and a single post-tourniquet hand volume. The differences will again be compared between patients' arms ipsilateral and contralateral to the side of ALND. Linear mixed effects model will also be fitted to account for the correlations between measurements on the same subject and history of ALND, arm position after tourniquet use, and patient-specific risk factors. This specific issue power analysis is further discussed below (5.3).

5.1 Outcome Measurements

Study participants will be evaluated prior to and following the above process.
Data collection:
A. Demographic will be recorded: Age, sex, height, weight, BMI, comorbidities, number of lymph nodes excised in ALND, and presence of lymphedema
B. Procedural measures: hand volume and percent change

Primary outcome: percentage change in hand volume from baseline after tourniquet application

Secondary outcome: residual volume as a percentage of baseline following limb positioning after tourniquet use

C. Tourniquet complications: unresolved edema (i.e. persistent swelling lasting greater than the 30 minute evaluation period), petechiae (i.e. pinpoint skin redness or purple color caused by a minor bleed from broken capillary blood vessels), pain, paresthesias (tingling sensation), palsy (neurologic change related to peripheral nerve compression), by direct visualation and neurologic evaluation by a medical provider at the time of tourniquet use

Acute or delayed symptoms related to tourniquet use will be assessed and managed with routine care. Participants may contact the study staff at any time regarding delayed complication.

5.2 Analysis plan

Data will be analyzed as above. To reiterate the methods (Section 4.0), a baseline volume will be measured in all participants prior to tourniquet use. The absolute change in hand volume, percentage change from baseline, and residual volume as a percentage of baseline immediately following tourniquet use will then be measured in all patients. The mean will be compared between the arms ipsilateral and contralateral to the side of ALND by paired t-tests. The parameters listed above are the primary outcomes. Each participant will then be monitored in two limb positions (elevated and sling as described above), with measurements taken on both arms ipsilateral and contralateral to the side of

ALND. Volume is measured after each position. The change in limb edema as a factor of time will be analyzed by a linear mixed effects model. This is the secondary outcome.

5.3 Sample size

We analyzed preliminary data on percent change in hand volume in normal controls as a response to the application of a tourniquet. Similar data is not available in the literature for patients following ALND. In the pilot, the median change was 9.1%, with a standard deviation of 1.6% assuming each subject contributed one baseline hand volume and one volume following the application of the tourniquet.

Our scientific hypothesis is that the difference in change of mean hand volume among women who have had lymph node dissection, between the arms ipsilateral and contralateral to the side of ALND is zero or negligible. We therefore seek a sample size that expresses non-inferiority between ipsilateral and contralateral arms. In the absence of clinical norms for the margin of non-inferiority, we made the sample size calculation on the basis of margin of non-inferiority of 1% (in units of percent change in hand volume).

We plan to accrue 45 extremities in each group, with two arms per patient. We have 90% power that the upper 95% confidence interval of the difference will be at or below the stipulated margin of 1%. A confidence bound above the stipulated margin will be taken as evidence of some difference between ipsilateral and contralateral arms, indicating an effect of the prior axillary lymph node dissection over and above the effect of the tourniquet.

The above calculation assumed a standard deviation of 1.6 percentage point, and 45 patients with two arms each (ipsilateral and contralateral to ALND) to provide 90% power for a margin of equivalence of one percentage point using a two-sided significance level of 5%, with a primary endpoint of percentage change from baseline following tourniquet use. If 10% of patients are uninformative (N=40 for ipsilateral and contralateral arms), we expect have 87% power for the same margin of equivalence. If 20% are uninformative (N=35 for ipsilateral and contralateral arms), we would have 82% power. The secondary outcome of residual limb volume following elevation in the two limb positions (elevated and sling) are not included in this power analysis and are not primary outcomes.

We expect the study to begin upon approval, and conclude after recruitment in approximately 6-12 months.

6.0 DATA MANAGEMENT CONSIDERATIONS

6.1 Data management

The study members will be present at all times during the procedures, and will adhere to the standard methods of care and safety of the participating subjects. Patient information will subsequently be accessed by only those investigators involved in the study who have been named on this protocol. Data will be recorded electronically. Research data resulting from the analysis of will be safeguarded in password-secured laboratory computers where

careful records will be maintained, and data-backup will be performed routinely. Medical information acquired from subjects directly will be de-identified and stored in a secure location in the research office.

6.2 Confidentiality

The privacy of the participants and data collection will be maintained in strict accordance to HIPAA standards. Records will be deidentified following data collection and stored securely as described above.

6. Protocol Review and Amendments

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Center Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

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APPENDIX A**: Participant Eligibility Checklist**

Protocol Title:	**The Effect of Pneumatic Tourniquet Use on Upper Extremity Edema Following Axillary Lymph Node Dissection**
Protocol Number:	**BRS0075**
Principal Investigator:	**Dr. Jeffrey Yao**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☒ IRB Approved ☒ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. 18 years of age or earlier	☐	☐	
2. Presence of prior axillary lymph node dissection (group A)	☐	☐	
3. Absence of prior axillary lymph node dissection (group B)	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. New-onset lymphedema of the involved limb	☐	☐	
2. Infection including cellulitis	☐	☐	
3. Trauma or planned axillary surgery within 6 months of participation.	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	