RESEARCH PROTOCOL

Date	7/31/2023
Title	Evaluating the use of preventive cold saline to decrease bleeding associated with endobronchial biopsy
Principal Investigator	Austin Pittman, BSN, RN
Sub-Investigators	Christine Ture, BSN, RN, CGRN
Research Specialist	Rachel Baker, PhD, RN, CRN-BC
Department	Bethesda North Hospital, Endoscopy Department
Hatton #	23-037

Purpose of Study

Patients undergoing an endobronchial ultrasound and biopsy can experience bleeding during the biopsy. These biopsies are read in real time by pathologists who travel to the endoscopy unit during the procedure. Often, when this happens, the blood contaminates the pathology slides making the slide unreadable. This then requires more biopsies to be performed, thus prolonging the procedure, and increasing anesthesia time. One innovative way to reduce bleeding may be to irrigate the bronchial wall with cold saline, where the biopsy is to be taken, immediately before biopsy, thus causing vasoconstriction and possibly resulting in less blood contamination on the biopsy slides. The current study will evaluate this prophylactic irrigation with saline to control bleeding, thus resulting in a quicker diagnostic result of the biopsies.

Hypothesis or Research Question

- Hypothesis 1: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of unreadable biopsy slides compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

- Hypothesis 2: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of having to reperform biopsies in order to obtain readable slides compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

- Hypothesis 3: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of stopping the procedure without biopsy results compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

- Hypothesis 4: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of requiring epinephrine to control bleeding after the biopsy compared to patients undergoing

endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

Background

Endobronchial ultrasounds are used to investigate lymph nodes and/or lesions within or next to the patient's lungs that are visible on ultrasound. The procedure can be used in the diagnosis or staging of cancer. Fine needle biopsies can be obtained through the endobronchial ultrasound scope, and the tissue obtained is immediately placed on cytology slides and promptly taken outside the room to the mobile cytology cart to be stained. The pathologist will then read the prepared slides in real time, offering feedback as to what cells are seen. However, red blood cells often contaminate the sample, due to bleeding from the biopsy site, and thus potentially cover up and block the obtained specimen. This causes more biopsies to be taken and prolongs the procedure and anesthesia time. During normal bronchoscopies, cold saline is used, and has been studied, to decrease bleeding in the airways. This study evaluates the use of cold saline irrigation BEFORE biopsies are taken to potentially decrease the risk of bleeding. Irrigating with cold saline preventatively BEFORE biopsies are taken is not common practice. Additionally,, there has been no research conducted investigating the use of cold saline prior to bronchial biopsies being taken to decrease bleeding. This study seeks to fill this gap in the literature.

Research Plan

- **Study Design**

  This study will use a randomized, non-blinded, controlled design with two arms:
  - Arm 1: Patient will receive irrigation with 120mL of cold saline 33-39 degrees Fahrenheit), delivered in two 60mL syringes, prior to biopsy
  - Arm 2: Patient will receive standard care which involves biopsy without prior irrigation with cold saline.
- **Setting for the study**

  The study will take place on Bethesda North Hospital's Endoscopy Department. This unit provides care to approximately 2-12 patients undergoing an endobronchial ultrasound and biopsy per week.

- **Participants**

  The study will enroll 120 patients who meet the following inclusion/exclusion criteria:

  Inclusion Criteria:
  - Undergoing an endobronchial ultrasound and biopsy at Bethesda North Hospital

  Exclusion Criteria:
  - Under 18 years old
  - Does not speak English
  - Unable to consent to involvement in the research study

- Is pregnant
- Has a bleeding disorder/diagnosis
- Currently taking anticoagulant medications and not stopped for procedure
- Documented low platelets (<100,000)
- Had a biopsy taken immediately prior to the endobronchial ultrasound

Sample Size Determination: A power analysis was conducted using a small to medium effect size (0.3), power of 0.8, and level of significance 0.05. It was determined that 44 patients would be needed in each group, for a total sample size of 88 patients. To allow for the possibility of removing participants from the final analysis due to missing data, we plan to enroll 120 patients (60 in each group).

- **Data Collection**

  Before the study begins, information about the study will be provided to the providers and endoscopy team members, including information about the study purpose, inclusion/exclusion criteria, and procedures.

When a patient who meets the inclusion/exclusion criteria arrives for an appointment, a nurse from the study team will describe the study, answer any questions the patient has, and if the patient wants to enroll in the study, the study team nurse will review the information consent form. After the patient provides written informed consent, the nurse will remove the next envelope out of a box of prefilled and sealed opaque envelopes. The envelope will provide the Subject ID number to be used on all study-related documentation and the study Arm that the patient has been randomized to, either:

1. Cold saline group
2. Standard care group

These envelopes will be filled using a computerized simple random number generator (1:1 randomization) prior to the start of the study.

In addition to the group assignment, the envelope will include a data collection form. Data will be recorded directly on this form during the patient's visit. The form will collect the following information:

- Whether patient was assigned to the cold saline group or the standard care group
- Patient demographics including age, gender, current anticoagulant medications, current cancer diagnoses
- Temperature of cold saline (cold saline group only)
- Time cold saline placed (cold saline group only)
- Volume of cold saline used for irrigation
- Time each biopsy was obtained
- Number of biopsies
- Gauge of needle used to perform biopsy
- Type of suction used (i.e. slow-pull or 5mL, 10mL)

- Number of slides prepared
- Number of slides that were successfully read
- Number of slides unable to be read due to blood on slide
- Whether another biopsy was attempted
- Whether the procedure was stopped without successful slide reading
- Whether patient needed epinephrine post-biopsy to stop bleeding
- Name of MD performing biopsy
- Start and end time of procedure

After the procedure, the RN will complete the data collection form and place the signed informed consent form and data collection form in the locked resource nurse's office in an area designated for study materials.

On the data collection forms, RNs are instructed to call a member of the study team immediately if there are any safety concerns related to the cold saline. If the study team receives a call about a safety concern, recruitment and enrollment of new participants will stop until the study team meets and reviews the incident with the pulmonologist involved and determines it is safe to continue. The study team includes nurses with clinical experience and expertise in endobronchial biopsy procedures. They will consult with the medical team if any adverse events arise. Any adverse events and serious adverse events will be reported to the IRB in compliance with IRB safety policies.

- **Intervention or experimental aspect of the study**
  In patients randomized to Arm 1, the clinician will scan the cold saline using the infrared temperature scanner and confirm saline is between 33-39 degrees Fahrenheit. Then after identifying the lymph node or lesion to be biopsied on ultrasound, using the endobronchial ultrasound scope, two 60mL syringes of cold saline will be inserted, through the biopsy channel of the endobronchial ultrasound scope, directly onto the bronchial wall where the biopsies are to be performed. The saline will then be sucked out of the airway using the endobronchial ultrasound scope. The FNA needle or biopsy forceps will then be passed down the biopsy channel of the endobronchial ultrasound scope, and the biopsy will be obtained. Cold saline irrigation is part of the normal procedure and may cause coughing. The study may benefit these patients if the preventive cold saline irrigation prevents bleeding.

  Patients randomized to Arm 2 will receive standard care that includes no irrigation with cold saline prior to the biopsy. After identifying the lymph node or lesion to be biopsied on ultrasound, the FNA needle or biopsy forceps will then be passed down the biopsy channel of the endobronchial ultrasound scope, and the biopsy will be obtained.

In both Arm 1 and Arm 2, TriHealth pulmonologists will conduct the endobronchial ultrasound and biopsy according to standard clinical practice. Patients will receive the same care procedure and biopsy that they would receive if they were not enrolled in the study. The only research procedure is that patients in Arm 1 will receive irrigation of the biopsy site with cold saline before the biopsy is performed. The rest of the procedure will follow standard clinical practice.

Data recorded on paper data collection forms will be entered into a password protected database. Only study team members will have access to the database. No personal information will be entered into the electronic database. Data will undergo range checks when entered in the database, and quality control procedures will be performed to ensure accuracy of the data in the electronic database.

- **Statistical Analysis**
  Statistical analyses will be performed using Intellectus Statistics statistical software. The following analyses will be performed to address each hypothesis:

  - Hypothesis 1: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of unreadable biopsy slides compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

    To compare the effects of the intervention, a Chi Square test will be used to compare frequency of unreadable biopsy slides among patients who received the cold saline irrigation compared to patients who did not receive the cold saline irrigation. A level of significance of $\alpha=0.05$ will be used.

  - Hypothesis 2: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of having to reperform biopsies in order to obtain readable slides compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

    To compare the effects of the intervention, a Chi Square test will be used to compare frequency of having to reperform biopsies among patients who received the cold saline irrigation compared to patients who did not receive the cold saline irrigation. A level of significance of $\alpha=0.05$ will be used.

  - Hypothesis 3: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of stopping the procedure without biopsy results compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

To compare the effects of the intervention, a Chi Square test will be used to compare frequency of stopping the procedure without biopsy results among patients who received the cold saline irrigation compared to patients who did not receive the cold saline irrigation. A level of significance of α=0.05 will be used.

- Hypothesis 4: Patients undergoing endobronchial ultrasound and biopsy who receive irrigation with cold saline prior to biopsy will experience a lower incidence of requiring epinephrine to control bleeding after the biopsy compared to patients undergoing endobronchial ultrasound and biopsy who do not receive irrigation with cold saline prior to biopsy.

  To compare the effects of the intervention, a Chi Square test will be used to compare frequency of epinephrine administration to control bleeding after the biopsy among patients who received the cold saline irrigation compared to patients who did not receive the cold saline irrigation. A level of significance of α=0.05 will be used.

Interim data analysis will occur (1) once approximately 1/3 of the participants have been enrolled in each group and (2) once approximately 2/3 of the participants have been enrolled in each group. If interim calculations at time (1) or time (2) note a significant difference in outcomes between groups, data collection will be completed at that time and final analysis will be completed.

Ethical Considerations

- **Informed consent**

  All study staff will complete CITI training. A study staff member will meet with potentially eligible patients and describe the study and answer any questions. If the patient is interested and meets all the inclusion/exclusion criteria, the study staff will review the *Informed Consent Form* and obtain written informed consent. Patients will receive a copy of their signed Informed Consent form.

  Informed Consent forms will be stored in a locked room that only staff will have access to. After the study closes, the signed Informed Consent forms will be boxed and sent to off-site storage and securely stored for 10 years after the close of the study. At that time, the hard copy forms will be shredded.

- **Privacy information**

  Personal identifiers will not be entered into the electronic database. Hard copy data collection forms and Informed Consent forms will be stored in a locked room that only staff will have access to. Electronic data will be stored on a password-protected folder on the U drive. Only study staff will have access to the electronic study documents. After data analysis and dissemination is completed, hard copy forms will be boxed and sent to off-site storage and securely stored for 10 years after the close of the study. At that time, the hard copy forms will be shredded.

Cost/Budget

There will be no costs to conduct this study and no additional charges to patients.

Estimated Period of Time to Complete Study	
When will study begin?	5/26/2023
Protocol Development Completed	2 weeks
IRB Approval	6 weeks
Data collection	6 months
Data analysis	2 weeks
Presentation development (if applicable)	2 weeks
Manuscript Development (if applicable)	1 month
Journal submission process (if applicable)	4 months
Study closure	2 weeks

- **When and how will results be disseminated?**
  Results will be disseminated internally to the TriHealth endoscopy team and system-wide through the TriHealth Research Council. Results will be disseminated nationally through presentation at a professional organization conference. Finally, results will be disseminated nationally and internationally by publication in a relevant peer-reviewed journal.

References

- Sehgal, I.S., Gupta, N., Dhooria, S., Aggarwal, A.N., Madan, K., Jain, D., et al. (2020). Processing and reporting of cytology specimens from mediastinal lymph nodes collected using endobronchial ultrasound guided transbronchial needle aspiration: a state-of-the-art review. *J Cytol, 37*, 72-81.
- Yao, X., Gomes, M. M., Tsao, M. S., Allen, C. J., Geddie, W., & Sekhon, H. (2012). Fine-needle SSPIRATION biopsy versus core-needle biopsy in diagnosing lung cancer: A systematic review. *Current Oncology, 19*(1), 16–27. https://doi.org/10.3747/co.19.871