

Title: Does Alkalinization of Technetium-99m Sulfur Colloid reduce perceived pain levels during non-breast sentinel lymphoscintigraphy?

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I. Abbreviations/Definitions

- A. Tc-99m: Technetium 99m
- B. SC: Sulfur Colloid
- C. UAMS: University of Arkansas for Medical Sciences
- D. NM: Nuclear Medicine
- E. DEPT: Department
- F. SLN: Sentinel Lymph Node
- G. SOC: Standard of Care

II. Protocol Summary

- Approximately weekly, a patient presents to the UAMS Nuclear Medicine DEPT for a Sentinel Lymph Node (SLN) lymphoscintigraphy study. Classically, four injections of Technetium-99m (TC-99m) Sulfur Colloid (SC) are injected intra-dermally. The injections are in the immediate vicinity of a dermatologic malignancy or recent biopsy site. This allows identification of sentinel lymph nodes, in anticipation of surgical removal.

** The UAMS Nuclear Medicine DEPT does not do SLN injections of breasts **

- Pain during breast SLN procedures has been reported as high as 8.8/10 (1). Using Bicarbonate to alkalinize the radio-pharmaceutical injection, pain can safely be reduced from 6.6/10 to 4.7/10 during breast SLN procedures (2). There have been no discoverable studies assessing alkalinization to reduce pain during SLN procedures other than in the breast.

- It has been common practice in Emergency Rooms to buffer lidocaine at a ratio of 1:10 with Bicarbonate, to reduce the "chemical" pain from lidocaine's acidic nature. Similarly, Tc-99m SC is normally acidic with a pH of ~6.04 (2). Initial lab work reveals that a similar approach to altering the pH of Tc-99m SC should not significantly reduce the effectiveness of the Tc-99m SC. Alkalinization should significantly reduce the subjective pain.

Study Objectives

1. To quantify the reduction of perceived pain levels during SLN procedures, by altering the pH of the Tc-99m SC to near the physiologic value of 7.40.

Hypothesis

1. The perceived pain level during SLN techniques can be reduced by raising the pH of Tc-99m SC to near the physiologic level of pH 7.40.

Research Methods

1. Design: Randomized and double blinded prospective cross-over study.
2. After signing an informed consent, 60 serial subjects will undergo SLN injections and imaging as per normal routine—genitourinary, breast, and those requiring only a singular injection will be excluded.
3. The Tc-99m SC injections will have been randomized into two groups--- standard of care solution (unaltered) injected first and experimental solution (pH buffered with Sodium Bicarbonate) injected first.
4. A Nuclear Pharmacist will prepare the injections and label them such that the physician (not involved in the data assessment) performing the SLN injections is blinded as to which injections contain standard of care solution and which contain experimental solution.
5. Prior to beginning the procedure and after signing informed consent, the subject will be asked by a blinded research support assistant, to fill out a

questionnaire addressing background information. Prior to beginning and after each injection, the subject will be asked to quantify the pain of each injection using a validated 0 through 10 scale, with 0 being no pain and 10 being severe pain that is disabling; unable to perform Activities of Daily Living.

III. Background and Rationale

- A. Approximately weekly, a patient presents to the UAMS NM DEPT for a SLN lymphoscintigraphy study. Classically, four injections of Tc-99m SC are injected intra-dermally. The injections are in the immediate vicinity of a dermatologic malignancy or recent biopsy site. This allows for identification of SLNs, in anticipation of surgical removal. The UAMS NM DEPT does not do SLN injections of breasts.
- B. Pain during breast SLN procedures has been reported as high as 8.8/10 (1). Using Sodium Bicarbonate to alkalinize the radio-pharmaceutical injection, pain can safely be reduced from 6.6/10 to 4.7/10 during breast SLN procedures (2). There have been no discoverable studies assessing alkalinization to reduce pain during SLN procedures other than in the breast.
- C. It has been common practice in Emergency Rooms to buffer lidocaine at a ratio of 1:10 with Sodium Bicarbonate, to reduce the "chemical" pain from lidocaine's acidic nature. Similarly, Tc-99m SC is normally acidic with a pH of ~6.04 (2). Initial lab work reveals that a similar approach to altering the pH of Tc-99m SC should not significantly reduce the effectiveness of the Tc-99m SC.
- D. Alkalinization should significantly reduce the subjective pain experienced by patients undergoing SLN procedures at UAMS.

IV. Hypothesis and/or Specific Aims

- A. Hypothesis:
 - 1. The perceived pain level during SLN techniques can be reduced by raising the pH of Tc-99m SC to near the physiologic level of pH 7.40.
- B. Specific Aim:
 - 1. To quantify the reduction of perceived pain levels during SLN procedures, by altering the pH of the Tc-99m SC to near the physiologic value of 7.40.

V. Study Design and Procedures

- A. Design:
 - 1. Randomized, double blinded, and prospective cross-over design.
 - 2. Prior to beginning the procedure and after signing informed consent, 60 serial

- subjects will be asked by a blinded research support assistant, to fill out a questionnaire addressing background information. Before the first injection and after each injection, the subject will be asked to quantify the pain of each injection using a validated 0 through 10 scale, with 0 being no pain and 10 being severe pain that is disabling; unable to perform Activities of Daily Living.
3. Subjects will be randomized into one of two sequence groups (A & B):
 - a. Sequence group A. The first injection administered will be the standard of care solution (SOC). The second injection will be the pH altered solution. The remaining injections will be randomly assigned as either standard of care or pH altered.
 - b. Sequence group B. The first injection administered be the pH altered solution. The second injection will be the standard of care solution (opposite order). The remaining injections will be randomly assigned as either standard of care or pH altered.

Injection order for the two groupings which enrollees will be randomly assigned:

- Sequence group A: SOC, pH altered, random, random, random, etc.
 - Sequence group B: pH altered, SOC, random, random, random, etc.
4. A Nuclear Pharmacist will prepare the injections and label them such that the physician (not involved in the data assessment) performing the SLN injections is blinded as to which injections contain standard of care solution and which contain the pH altered solution. A planned dose range of 0.1 to 1.0 mCi will be used. The maximum activity injected will be 1.0 mCi with a maximum volume of 1.0 mL. Neither the addition of Sodium Bicarbonate nor the alteration of the pH result in any discernible change in the observable characteristics of the injectate---there is no clouding, there is no color change, there is no precipitate formation, etc.
 5. As per normal routine—genitourinary, breast, and those requiring only a singular injection will be excluded.

* The procedure for injection of Tc99m SC is currently being used as a diagnostic procedure and is in accordance with the community based standard of care. This study does not change the procedure; it only changes the pH of the solute being injected during a randomized number of injections.

* For the purposes of this study, the protocol is ended for each subject upon completion of the final pain assessment. The subjects will then continue on to the standard of care imaging and continued clinical management.

B. Survey instrument:

1. A questionnaire addressing pain quantity will be used. A validated 0 through 10 scale, with 0 being no pain and 10 being severe pain that is disabling; unable to perform Activities of Daily Living. Additionally, background

information will be collected for subset analysis.

VI. Study Population

- A. Recruitment: Serial voluntary enrollment of 60 subjects.
- B. Study population: All patients, age 18 years and older, who present to UAMS NM DEPT for SLN evaluation.
- C. Inclusion criteria:
 - 1. Male and female patients of all races and ethnicities, age 18 years and older, presenting for SLN imaging for melanoma or who have had an excisional biopsy for melanoma of the thorax and appendicular structures;
 - 2. Patients scheduled to receive two or more injections of Tc-99m SC for the purpose of clinical management of melanoma or who have had an excisional biopsy for melanoma of the thorax and appendicular structures.
- D. Exclusion criteria:
 - 1. All patients presenting for SLN imaging of lesions involving the breast, ear, nose, and genitourinary regions;
 - 2. Patients scheduled to receive only a single injection of Tc-99m SC;
 - 3. All pregnant or breast feeding women. Women will be screened according to UAMS NM DEPT routine operating procedures prior to being considered for enrollment. Subsequently, only women who are found to be non-pregnant AND non-breast feeding will be invited for enrollment.

VII. Risks and Benefits

- A. Risks:
 - 1. Loss of patient personally identifiable information: In order to mitigate this, investigators shall maintain all personally identifiable information in accordance with UAMS policies. Moreover, only the primary investigator will have access to the code that identifies the subjects.
 - 2. Listed potential adverse reactions include:
 - a. For Tc-99m: Cardiopulmonary arrest, seizures, anaphylactic shock, hypotension, dyspnea, abdominal pain, fever, chills, bronchospasm, nausea, vomiting, perspiration, redness, urticaria, numbness, dizziness and burning at the injection site. Several deaths and cases of lung and soft tissue uptake other than RES have been reported in association with the use of Technetium Tc 99m Sulfur Colloid Injection.
 - b. For Sodium Bicarbonate: Chemical cellulitis.
- B. Benefits: Significantly less pain and suffering could potentially be experienced by future patients.

VIII. Efficacy Assessments

- A. Prior to beginning and after each injection, subjects will be asked, by a blinded clinical assistant, to quantify the pain of each injection. Prior to beginning the injections, subjects will provide relevant background information by filling out a questionnaire.

IX. Safety Assessments

- A. Injection site pain of 8 out of 10 or less will not be considered an adverse event. Any adverse events will be appropriately documented and reported to the IRB in accordance with institutional policy.
- B. The principal investigator will assess the relationship of the adverse event to the investigational compound. The relationship will be assessed using the following categories:
 - 1. Definitely Related: A direct cause and effect relationship between the investigational compound and the adverse event exists.
 - 2. Possibly Related: A direct cause and effect relationship between the investigational compound and the adverse event has not been clearly demonstrated, but is likely or very likely.
 - 3. Unlikely Related: A direct cause and effect relationship between the investigational compound and the adverse event is improbable, but not impossible.
 - 4. Unrelated: The adverse event is definitely not associated with the investigational compound.

X. Data Handling and Recordkeeping

- A. Data form: A paper questionnaire to quantify the pain will be used. Additionally, it will collect background demographics---Appendix 1.
- B. The PI will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the principal investigator's office. Only Dr. Mickaila Johnston or designated study staff will have access to the code and information that identifies the subject in this study.
- C. Upon completion of the study, all hard copy and electronic study records containing PHI will be destroyed or cleansed.

XI. Statistical Considerations

- A. Planned Data Analysis: Reported pain responses to SOC and pH altered injections will be assessed using a basic cross-over design. Specifically, the two treatments will be studied within each subject; however, the sequence in which subjects will receive treatment will be randomized. Subjects randomized to one sequence group will receive the SOC injection first followed by the pH altered, while the other sequence group will receive pH altered then SOC injections. The following table succinctly presents this design.

Period	Sequence Group	
	A	B
1	SOC	pH altered
2	pH altered	SOC

In addition to the effect of treatment, the statistical model used to analyze this data must account for the effect of the sequence group, as well as the effect of *period*; therefore, the following mixed-effect analysis of variance model is proposed:

$$Y_{ijk} = \mu + \text{SEQ}_i + \text{sub}_{ij} + \text{PER}_k + \text{TRT}_h + e_{ijk}, \text{ where}$$

Y_{ijk} is the pain assessment for the j th subject during the k th period in the i th sequence group ($i = 1, 2; j = 1, 2, \dots, n_i; k = 1, 2$), SEQ_i is the effect of the i th sequence group, sub_{ij} is the effect of the j th subject in the i th sequence, PER_k is the effect of the k th period, TRT_h is the effect of the h th treatment ($h=1, 2$), and e_{ijk} is the error. The sequence, period and treatment effects will be modeled as fixed effects, while the subject effect and the error will be modeled random effects. An α -level of 5% will be used to determine the statistical significance of the treatment effect, as well as the other fixed effects.

One potential shortcoming of the proposed cross-over design is that the pain assessments will be made within minutes of one another; thus, a period or “carry-over” effect may be present. The proposed model will be able to detect such effects and, if present, only data from the first period will be used to evaluate the effect of treatment. In this case, the model reduces to a simple two-sample t-test.

- B. Sample Size Justification: We wish the study to be sufficiently powered in the event that a significant “carry-over” or period effect is detected and only the first period data is used to evaluate the effect of treatment. To this end, the following sample size calculation is based on a two-sample t-test. A recent study by Stojadinovic et al. reported a pain scale standard deviation of 2.65 for a SOC group. We anticipate that the pH adjusted group will reduce pain, on average, by 2 points. Given this information, a two-sample t-test will have over 80% power to detect this difference assuming 30 subjects per group (60 in total) are enrolled. (It should be noted that if no carry-over effect is detected and both periods are

used in the analysis, the proposed sample size will provide the test of the treatment effect with over 98% power to detect a 2 point difference and with over 80% power to detect a 1 point difference).

C. Randomization: To ensure the number of subjects randomly assigned to each sequence group is equal, the technique of permuted block randomization will be employed. The randomization procedure will also be stratified according to the following, broadly defined sites of injection:

1. Thorax, including neck and buttocks;
2. Head;
3. Appendicular structures, including shoulder to wrist, including back of hand, and hip to ankle;
4. Other (remainder of hand and feet).

Randomization will be applied independently within each stratum. That is, a separate randomization “schedule” will be applied within each stratum. This will ensure that the injection site distribution of the sequence groups will be similar.

XII. Ethical Considerations

- A. This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.
- B. The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits and alternate treatment(s). The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their trial participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject’s research record.

- C. At any time during the clinical encounter, any participant may opt out of the study by providing written direction or by simply verbally communicating to any staff member that the participant no longer wishes to be enrolled in the study. At that time, the participant would be no longer enrolled in the study, and the remainder of their care would only be that of the routine standard of care, without bias.
- D. In the event that a participant reports pain associated with the procedure and requests analgesia, no analgesia will be provided by the UAMS NM DEPT. None is provided as the standard of care in day-to-day routine.

XIII. Quality Control and Quality Assurance

- A. Industry standard quality control tests have already been run on initial bench work versions---all tests passed quality control appropriately.
- B. Prior to beginning administration of controls and experimental interventions to subjects, the buffering procedure will be validated in vitro with more sensitive pH metering. Quality control will again be assessed on the pH altered samples. After the buffering procedure is proven to be reliable and reproducible, administration with subjects will begin according to the verified buffering procedure.

XIV. Study Registration and Publication

- A. Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a subject. The study will be registered with www.clinicaltrials.gov.

XV. References

- (1) Relieving the pain of sentinel lymph node biopsy tracer injection. S Fetzer and S Holmes, Clin J Oncol Nurs. 2008 Aug;12(4):668-70.
- (2) Standard versus pH-adjusted and lidocaine supplemented radiocolloid for patients undergoing sentinel-lymph-node mapping and biopsy for early breast cancer (PASSION-P trial): a double-blind, randomized controlled trial. A Stojadinovic, et al. Lancet Oncol. 2009 Sep;10(9):849-54. Epub 2009 Aug 5.

XVI. Appendices

Attached as separate documents.