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Reducing perceived pain levels during non-breast lymphoscintigraphy

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Abstract

Purpose—To quantify the reduction of perceived pain levels during lymphoscintigraphy for melanoma, by altering the pH of the Tc-99m SC to near the physiologic value of 7.40.

Materials and Methods—This is an IRB- and FDA-approved randomized, double-blinded, prospective cross-over trial, registered with clinical trials.org. Prior to beginning the procedure and after signing informed consent, 60 serial enrollees presenting for sentinel lymph node imaging of melanoma of the thorax and appendicular structures completed a questionnaire addressing background information, administered by a research support nurse.

An investigator (NH) prepared the injections to be used and labelled them such that no one else could discover which injections contained standard of care solution and which contained the pH-altered solution (buffered to near pH=7.40 using Sodium Bicarbonate).

After each injection, the enrollee was asked, by a research support nurse, to quantify the pain of each injection using a 0–10 scale. The injection site location (head, thorax, appendicular structures, and other) was also recorded.

Results—Sixty subjects were enrolled in the study, of which 57 had complete data. On average, there was a significant decrease of 1.42 points (sd=2.17, 95% CI: 0.85 to 2.00) on the 0–10 pain scale when the buffered injections were used as compared to the standard of care injections ($p<0.0001$). Ordering of injections did not significantly affect perceived pain scores.

Conclusions—The use of sodium bicarbonate to buffer the pH of Tc-99m SC to near the physiologic value of 7.40 significantly reduced perceived pain levels during non-breast lymphoscintigraphy.

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All components of the research were conducted at the University of Arkansas. Additionally, drafting and revising of the manuscript occurred at all 3 sites listed above.

Keywords

pain; sentinel lymph node (SLN); melanoma; and buffering

BACKGROUND

Approximately weekly, patients present to our institution for a melanoma sentinel lymph node (SLN) lymphoscintigraphy. Classically, four injections of Technetium-99m (TC-99m) sulfur colloid (SC) are administered intra-dermally. The injections are in the immediate vicinity of a dermatologic malignancy or biopsy site. This allows for the identification of sentinel lymph nodes in anticipation of surgical removal. The procedure, while well-tolerated in general, is consistently associated with pain and stinging at the injection site.

Pain during breast SLN procedures has been reported to be as high as 8.8/10 (1). The literature suggests that the use of bicarbonate to alkalinize the injected radiopharmaceutical can safely reduce perceived pain from 6.6/10 to 4.7/10 in breast SLN procedures, while not significantly effecting SLN identification (2, 3). Rather than buffering the SC injectate to minimize pain in breast SLN, some institutions consider using lidocaine chloride for local anesthesia. Note, however, that lidocaine chloride in and of itself can be painful on injection, with a reported pain rating of 7.6 / 10. (4). It has been common practice in Emergency Rooms to buffer lidocaine chloride at a ratio of 1:10 with bicarbonate, to reduce the "burning" pain from lidocaine's acidic nature (5). Similarly, Tc-99m SC is normally acidic with a pH of ~6.04 (2). As an alternate to Tc-99m SC, Tc-99m human serum albumin (Tc-99m HSA) may be used for SLN localization. Others have compounded Tc-99m HSA with lidocaine chloride in an effort to minimize pain, but it is known that this process may result in a decline of stability in the mixture (6). Moreover, the time to onset of anesthetic effect of lidocaine chloride has been described to be in the two minute range (7), which necessitates an inconvenient procedural delay. Initial lab work revealed that a similar approach to altering the pH of Tc-99m SC did not significantly reduce the stability of the Tc-99m SC (data not shown).

In the present study, we investigated whether the perceived pain level during SLN techniques could be reduced by raising the pH of Tc-99m SC to near the physiologic level of pH 7.40.

PATIENTS AND METHODS

Patients

Between August 2012 and December 2014, a total of 60 patients with melanoma who presented for SLN evaluation, volunteered to be enrolled in this study. Male and female patients of all races and ethnicities, aged 18 years and older, who presented for SLN imaging for melanoma or who had undergone an excisional biopsy for melanoma of the thorax and/or appendicular structures, and who were scheduled to receive two or more injections of Tc-99m SC, were considered eligible for inclusion. Patients were excluded from enrollment if they were presenting for SLN imaging of lesions involving the breast, ear, nose or

genitourinary regions; if they were scheduled to receive only a single injection of Tc-99m SC; and if pregnant or breast-feeding.

Study Design and Procedures

The study was approved by the local IRB, United States Food and Drug Administration as an investigational new drug, and was registered with clinicaltrials.org as randomized, double-blinded, and prospective cross-over in design.

Prior to beginning the procedure and after signing informed consent, 60 serial subjects were be asked by a blinded research support assistant, to fill out a questionnaire addressing background information (figure 1). Before the first injection and after each subsequent injection, the subject was asked to quantify the pain of every injection using a validated 0 through 10 scale, with 0 being no pain and 10 being severe pain that is disabling (i.e., unable to perform Activities of Daily Living) (figure 2).

Randomization

Subjects were randomized into one of two sequence groups (A & B)

Sequence group A—The first injection administered was the standard–of-care solution (SOC) followed by the pH-altered solution. The remaining injections were randomly assigned as either standard-of-care or pH-altered.

Sequence group B—The first injection administered was the pH-altered solution followed by the SOC solution. The remaining injections were randomly assigned as either standard of care or pH-altered.

The technique of permuted block randomization was used to assign subjects to sequence groups while ensuring group sizes were similar. The randomization procedure was also stratified according to the following broadly defined sites of injection, to ensure relatively equal distribution of them among the sequence groups:

- Head;
- Thorax, including neck and buttocks;
- Appendicular structures, including shoulder to wrist, including back of hand, and hip to ankle;
- Other (remainder of hand and feet);

Intervention

A board-certified nuclear pharmacist (NH) added a diluted bicarbonate solution in a drop wise manner to raise the pH of the Tc-99m SC to a pH of 7.40 +/- 0.05, using a commercially available micro volume pH meter for confirmation.

then prepared the injections and labeled them, in separate syringes, such that the physician, nuclear medicine technologist, or healthcare professional (not involved in the data assessment) performing the SLN injections was blinded as to which injections contained

SOC solution and which contained the pH-altered solution. Prior to any administration to subjects, all buffered injections were run through a 0.22 micron filter for cold sterilization, as required by the FDA under the IND protocol.

The maximum activity injected was 1.0 mCi with a maximum volume of 1.0 mL. Neither the addition of sodium bicarbonate nor the alteration of the pH resulted in any discernible change in the observable characteristics of the injectate--there was no clouding, color change or precipitate formation.

The procedure for injection of Tc-99m SC was in accordance with the community based standard of care. This study did not change the procedure; it only changed the pH of the solute being injected during a randomized number of injections.

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

Safety Assessments

Injection site pain of 8 out of 10 or less was not considered an adverse event. Injection site pain of 9 or 10 out of 10 was considered an adverse event. All adverse events were appropriately documented and reported to the IRB in accordance with institutional policy. Eleven out of 60 subjects reported significant pain, warranting an adverse event determination. Upon limited breaking of blinding, to investigate the adverse event, all adverse events were found to have the significant pain directly related to the SOC solution and not due to the pH altered solutions. No other adverse events were identified.

Statistical Considerations

The data obtained from the first two injections were used to assess the efficacy of the buffered solution in reducing injection pain. One concern with this design is that since the pain assessments were made within minutes of one another, estimate of the treatment effect may be biased due to the effect of “carry-over”. To evaluate this, we analyzed the data using the two-staged approach proposed by Grizzle (8). The first step in the process was to assess the magnitude of the carry-over effect, which was accomplished by comparing the sequence groups with respect to the mean of the period sums. These mean sums were subsequently compared using a two-sample t-test. We found that the carry-over effect was not significant at the 5% level (mean=1.0.2; 95% CI: -1.20 to 3.25; $p>0.36$). The effect of treatment was estimated by taking the difference of the mean buffered and SOC pain scores and a paired t-test was used to test whether the mean difference was significantly different from 0. An α-level of 5% was used to determine the statistical significance of this test.

RESULTS

Patient Characterization

Fifty-seven of sixty enrolled subjects completed the study with usable data. Subject demographic data is summarized in table 1. As reported in other studies (9), age was not associated with change in perceived pain level (Pearson’s correlation coefficient (r) = 0.026,

95% confidence interval (CI) = −0.28–0.24, and p=>0.85). Histories of nicotine use, regular or recent “pain medication” use, and having had a similar procedure all failed to demonstrate statistical significance (table 2).

Changes in Perceived Pain Levels

Following administration of the standard–of-care injectate, a mean perceived pain of 5.81 (sd=2.24) was observed as compared to 4.39 (sd=2.45) following the pH-altered injectate. Using a paired t-test, the decrease in perceived pain level of 1.42 (sd=2.17) was found to be statistically significant (p<0.0001) (95% confidence interval: 0.85–2.00). There appears to have been a difference between males and females with respect to perceived pain reduction. Males reported a mean pain reduction of 2.1 and females reported a mean pain reduction of only 0.6 (p=0.0117) (table 3).

Moreover, anatomic injection site contributed to changes in perceived pain levels, with appendicular injections having an associated mean pain reduction of 1.9. The remaining anatomic regions of injection sites failed to have an associated significant change in perceived pain level (table 4).

DISCUSSION

Using sodium bicarbonate to alter the pH of Tc-99m SC to near the physiologic value of 7.40 during non-breast lymphoscintigraphy performed for melanoma evaluation resulted in mean perceived pain score decreases from 5.81 to 4.39 (p<0.0001). Males were more likely to perceive reduced pain with buffering than females (p=0.0117), and when injected into appendicular regions, patients were more likely to perceive reduced pain with buffering. Ordering of injections had no significant “order” effect.

While topical anesthetic creams should reduce perceived pain level, in theory, they have been found to have mixed results during breast SLN biopsies (10, 11). The use of Tc-99m nanocolloid is a practice in other countries, and it has been reported to have only mild discomfort (12, 13). Moreover, a recently made available commercial compound is reported to have significant pain in only 0.2% of patients (14).

Limitations

A few limitations are identified. We did not assess the time to first lymph node visualization, as this study was concerned primarily with reduction of pain rather than imaging performance. Further study to confirm non-inferiority of buffered injectate may be useful, though it is not anticipated that solution buffering would adversely affect lymph flow and particle trafficking. Though not directly applicable to intradermal injections, the literature on neutral versus buffered solutions in peritoneal lymphatic handling has suggested that neutral solution kinetics are equivalent to those of acidic solutions (15). Additionally, a sample size of 60 may be inadequate to generalize to all practices. We utilized strict inclusion criteria and enrolled only those requiring: >1 injection, for evaluation of melanoma, and not in the following regions: breast, ear, nose, and genitourinary. Future application to a broader patient population may be of benefit.

Future Considerations

A side-by-side cost comparison with new commercially available compounds may be prudent. Further, developing a “thumb-rule” of quantity needed to effect a near physiologic buffering, instead of using a specific pH meter, would be useful. Lastly, evaluation of this technique for patients with other dermatologic malignancies, those requiring only a single injection site, and those with pathology in the breast, ear, nose, and genitourinary regions may prove insightful.

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- Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data were completed by: Johnston, Ntambi, Hilliard, Spencer, Vaughn, Owens, Myrick, Parker, Garner, and Yarbrough.
- Drafting and revising of the manuscript critically for important intellectual content was completed by: Johnston, Ntambi, Hilliard, Spencer, and Yarbrough.
- Final manuscript approval for submission and publication was completed by: Johnston.

ID #: _____ Date: _____

Ethnic Origin: White / Black / Hispanic or Latino / Asian or Pacific Islander

Sex: Female / Male

Age: _____ Weight: _____ lbs.

1. Do you use Nicotine? Yes / No

If Yes, when was your last use: <1 hour / <6 hours / > 6 hours

2. Do you regularly use pain / inflammation relieving medication?
Yes / No

If Yes, when was your last use: <1 hour / <6 hours / > 6 hours

3. Have you used any pain / inflammation relieving medication in the last 12 hours?
Yes / No

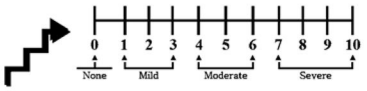
4. Have you had this procedure done before?
Yes / No

If Yes, when was it performed: <1 month / <6 months / > 6 months

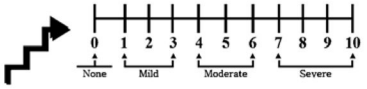
Figure 1.
Background Information

ID #: _____ Date: _____

Level before starting



Injection #1



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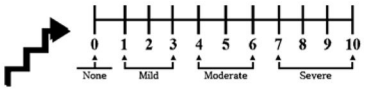

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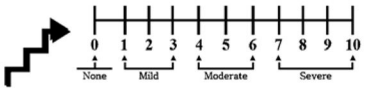

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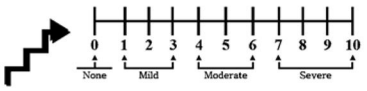

Injection #5

Figure 2.
Pain Quantification tool

Table 1

Subject Demographic Data

Subject Demographic Data			
	n=57	mean	standard deviation (sd)
Age (years)	57		13.6
Sex			
Female	26 (45.6%)		
Male	31 (54.4%)		
Weight (pounds)		159.9	46.1

Table 2

Background Questions

Background Questions	
Nicotine users	15 (26.3%)
Regular “Pain Medication” users	21 (36.8%)
Had used “Pain Medication” in the previous 24 hours	6 (10.5%)
Had a similar procedure previously	1 (1.8%)

Table 3

Gender based differences

Gender based differences					
	n (57)	**mean**	**LCL**	**UCL**	**p**
Female	26	−0.6154	−1.5853	0.3545	**0.0117**
Male	31	**−2.0968**	−2.7275	−1.4660	

- Lower Confidence Level (LCL)
- Upper Confidence Level (UCL)

Table 4

Anatomic Injection Site Based Differences

Anatomic Injection Site Based Differences				
	n (57)	**mean**	**LCL**	**UCL**
Appendicular	28	−1.9286	**−2.6119**	**−1.2452**
Head	5	−0.800	−4.0140	2.4140
Other	6	−0.1667	−2.868	2.3534
Thorax	18	−1.222	−2.4588	0.0143

- Lower Confidence Level (LCL)
- Upper Confidence Level (UCL)