Statistical Analysis Plan

A comparison of pain perception using topical EMLA cream versus lidocaine injection for vulvar biopsy: a randomized controlled trial

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A comparison of pain perception using topical EMLA cream vs. lidocaine injection for vulvar biopsy: a randomized controlled trial

Investigator: Logan Williams

Faculty Mentor: Laura Havrilesky

Statisticians: Jeremy Weber (author), Carl Pieper (faculty)

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Project Summary

The current standard at the Duke Cancer Center Gynecology Oncology Clinic is to use a lidocaine injection as local anesthesia prior to vulvar biopsy. The injection itself is not without pain and awaiting the injection frequently induces anxiety in patients. Other studies have examined the use of a topical anesthetic in addition to or in place of injected anesthesia. A previous study has found that EMLA cream is associated with less pain at the time of anesthesia administration, but injection anesthesia resulted in better biopsy pain control. Pain was measured on a 100 mm visual analog scale at the time of anesthesia administration and immediately following biopsy. The purpose of this study is to compare EMLA cream to lidocaine injection for analgesia for vulvar biopsy using the highest recorded pain score during the procedure.

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Statistical Analysis Plan

Primary Objective

- To compare highest subjective pain score between patients receiving EMLA cream vs. lidocaine for analgesia for vulvar biopsy

Exposure

- Patients were randomly assigned with equal probability to receive either EMLA cream or a lidocaine injection for analgesia for vulvar biopsy

Primary Outcome

- Pain was recorded during the application of EMLA cream or injection of lidocaine, and immediately after the biopsy on a 100 mm visual analog scale. If multiple sites were biopsied and the pain level differed between sites, then the highest pain score was recorded. If the anesthesia was inadequate in either treatment arm prior to biopsy, then an additional lidocaine injection was given and pain was recorded prior to the additional injection. The highest of all these pain measurements will be used as the primary outcome.
    - Continuous variable ranging from 0 to 100

Secondary Objective

- To compare pain scores at vulvar biopsy between treatment arms

Secondary Outcome

- Pain score at vulvar biopsy measured on a 100 mm visual analog scale
    - Continuous variable ranging from 0 to 100

Exploratory Objective

- To compare subjects' and providers' perceptions of acceptability and tolerability of the procedure between EMLA cream and lidocaine

Exploratory Outcomes

- Patient's response to "overall, how acceptable was the procedure performed today" measured on a 100 mm visual analog scale
    - Continuous variable ranging from 0 to 100
- Patient's response to "overall, how would you rate the experience of your biopsy procedure today" measured on a 100 mm visual analog scale
    - Continuous variable ranging from 0 to 100
- Provider's response to "overall, how well did the subject tolerate the procedure today" measured on a 100 mm visual analog scale
    - Continuous variable ranging from 0 to 100
- Provider's response to "overall, how satisfied are you with the procedure performed today" measured on a 100 mm visual analog scale
    - Continuous variable ranging from 0 to 100

Data

- Subjects were recruited from patients visiting the Duke Cancer Center Gynecology Oncology Clinic for a vulvar biopsy. Patients were approached by the provider and asked about interest in participating in the study. If interested, research personnel then discussed the study with the patient. Informed consent was done via an electronic consent form. Enrollment log, study questionnaires, and pain assessment forms were all stored in REDCap. All exported copies are saved on secure Duke password protected servers. Randomization to a treatment arm was done using the randomization tool in REDCap. Data were exported from REDCap on March 13, 2019 by Jeremy Weber and stored on the BERD Method Core's shared drive.

Inclusion Criteria

- Females above 18 years old presenting to Duke Gynecology Oncology Clinic for vulvar biopsy
- Able to provide informed consent in English and agree to the risks of the study

Exclusion Criteria

- Not able to provide informed consent
- Vulvar biopsy on hair bearing surface

Analysis Objectives

1. **Objective:** Describe patient characteristics in the analysis cohort by treatment arm and overall

Analysis: Create a baseline table of patient characteristics by treatment arm and overall. Continuous variables will be summarized with mean (SD), median (25th percentile, 75th percentile), and range. Categorical variables will be reported as frequency and percent. This table can be used to check that randomization approximately distributed confounders equally between the two treatment arms. P values will not be provided.

Conclusions: All pre-procedure data are presented in Table 1.1. There was a total of 37 enrolled patients, with 19 and 18 in the EMLA cream and lidocaine injection group, respectively.

Table 1.1. Patient demographics and characteristics

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)
Generalized Anxiety Disorder 7-Item Scale: Over the last 2 weeks, how often have you been bothered by the following problems?			
1. Feeling nervous, anxious, or on edge			
Not at all sure	8 (42.1%)	10 (55.6%)	18 (48.6%)
Several days	7 (36.8%)	5 (27.8%)	12 (32.4%)
Over half the days	2 (10.5%)	1 (5.6%)	3 (8.1%)
Nearly every day	2 (10.5%)	2 (11.1%)	4 (10.8%)
2. Not being able to stop or control worrying			
Not at all sure	13 (68.4%)	13 (72.2%)	26 (70.3%)
Several days	5 (26.3%)	3 (16.7%)	8 (21.6%)
Nearly every day	1 (5.3%)	2 (11.1%)	3 (8.1%)

Table 1.1. Patient demographics and characteristics

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)
3. Worrying too much about different things			
Not at all sure	13 (68.4%)	7 (38.9%)	20 (54.1%)
Several days	3 (15.8%)	7 (38.9%)	10 (27.0%)
Over half the days	1 (5.3%)	2 (11.1%)	3 (8.1%)
Nearly every day	2 (10.5%)	2 (11.1%)	4 (10.8%)
4. Trouble relaxing			
Not at all sure	13 (68.4%)	6 (33.3%)	19 (51.4%)
Several days	4 (21.1%)	8 (44.4%)	12 (32.4%)
Over half the days	1 (5.3%)	1 (5.6%)	2 (5.4%)
Nearly every day	1 (5.3%)	3 (16.7%)	4 (10.8%)
5. Being so restless that it's hard to sit still			
Not at all sure	16 (84.2%)	12 (66.7%)	28 (75.7%)
Several days	1 (5.3%)	4 (22.2%)	5 (13.5%)
Over half the days	1 (5.3%)	1 (5.6%)	2 (5.4%)
Nearly every day	1 (5.3%)	1 (5.6%)	2 (5.4%)
6. Becoming easily annoyed or irritable			
Not at all sure	14 (73.7%)	9 (50.0%)	23 (62.2%)
Several days	5 (26.3%)	8 (44.4%)	13 (35.1%)
Nearly every day	0 (0.0%)	1 (5.6%)	1 (2.7%)
7. Feeling afraid as if something awful might happen			
Missing	1 (.%)	0 (.%)	1
Not at all sure	14 (77.8%)	14 (77.8%)	28 (77.8%)
Several days	3 (16.7%)	4 (22.2%)	7 (19.4%)
Nearly every day	1 (5.6%)	0 (0.0%)	1 (2.8%)
Total scores			
Total - Not at all sure			
N	19	18	37
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Range	(0.0-0.0)	(0.0-0.0)	(0.0-0.0)
Total - Several days			
N	19	18	37
Mean (SD)	1.5 (1.5)	2.2 (1.5)	1.8 (1.5)
Median	1.0	2.0	2.0
Q1, Q3	0.0, 3.0	1.0, 3.0	1.0, 3.0
Range	(0.0-5.0)	(0.0-5.0)	(0.0-5.0)

Table 1.1. Patient demographics and characteristics

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)
Total - Over half the days			
N	19	18	37
Mean (SD)	0.5 (1.5)	0.6 (1.3)	0.5 (1.4)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Range	(0.0-6.0)	(0.0-4.0)	(0.0-6.0)
Total - Nearly every day			
N	19	18	37
Mean (SD)	1.3 (3.5)	1.8 (3.6)	1.5 (3.5)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 3.0	0.0, 0.0
Range	(0.0-15.0)	(0.0-12.0)	(0.0-15.0)
Total Score			
N	19	18	37
Mean (SD)	3.3 (4.0)	4.6 (4.2)	3.9 (4.1)
Median	1.0	3.5	2.0
Q1, Q3	0.0, 5.0	2.0, 8.0	1.0, 7.0
Range	(0.0-15.0)	(0.0-15.0)	(0.0-15.0)
If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?			
Missing	1 (.%)	0 (.%)	1
Not difficult at all	14 (77.8%)	14 (77.8%)	28 (77.8%)
Somewhat difficult	4 (22.2%)	3 (16.7%)	7 (19.4%)
Extremely difficult	0 (0.0%)	1 (5.6%)	1 (2.8%)
Age			
N	19	18	37
Mean (SD)	57.9 (16.3)	58.7 (10.8)	58.3 (13.7)
Median	60.0	58.5	60.0
Q1, Q3	46.0, 74.0	51.0, 65.0	51.0, 66.0
Range	(27.0-81.0)	(40.0-78.0)	(27.0-81.0)
Race			
Black or African American	7 (36.8%)	9 (50.0%)	16 (43.2%)
White or Caucasian	12 (63.2%)	9 (50.0%)	21 (56.8%)
Ethnicity			
Not Hispanic	18 (94.7%)	18 (100.0%)	36 (97.3%)

Table 1.1. Patient demographics and characteristics

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)
Hispanic	1 (5.3%)	0 (0.0%)	1 (2.7%)
Highest level of education			
Less than a high school diploma	0 (0.0%)	2 (11.1%)	2 (5.4%)
High school degree or equivalent (GED)	5 (26.3%)	4 (22.2%)	9 (24.3%)
Some college	9 (47.4%)	7 (38.9%)	16 (43.2%)
Graduated college	3 (15.8%)	5 (27.8%)	8 (21.6%)
Post graduate degree	2 (10.5%)	0 (0.0%)	2 (5.4%)
Prior vulvar biopsy	16 (84.2%)	17 (94.4%)	33 (89.2%)
Number of prior vulvar biopsies			
N	16	17	33
Mean (SD)	3.2 (4.6)	1.8 (1.0)	2.5 (3.3)
Median	2.0	1.0	2.0
Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 3.0
Range	(1.0-20.0)	(1.0-4.0)	(1.0-20.0)
Takes any prescription medication for pain	5 (26.3%)	3 (16.7%)	8 (21.6%)
Takes any prescription medication for nerves or anxiety	2 (10.5%)	5 (29.4%)	7 (19.4%)
Missing	0	1	1
Baseline vulva pain (mm)			
N	19	18	37
Mean (SD)	7.7 (21.4)	2.4 (4.5)	5.1 (15.7)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 5.0	0.0, 3.0	0.0, 3.0
Range	(0.0-92.0)	(0.0-17.0)	(0.0-92.0)
Baseline anxiety level (mm)			
N	19	18	37
Mean (SD)	21.8 (21.5)	38.1 (29.3)	29.7 (26.5)
Median	19.0	31.5	21.0
Q1, Q3	0.0, 31.0	12.0, 61.0	8.0, 48.0
Range	(0.0-65.0)	(0.0-91.0)	(0.0-91.0)

2. **Objective:** Compare highest subjective pain score between patients receiving EMLA cream vs. lidocaine

Analysis: Linear regression will be used to test if the highest pain score differs between treatment arms, controlling for baseline pain.[1] The regression coefficient, 95% confidence interval, and p value will be reported for the treatment effect. A significant p value would indicate that the highest pain score, on average, differed between the two treatment arms. If there is not a significant difference between treatment arms with regards to the highest pain score, then the mean and variance estimates from these patients will be used to recalculate the sample size needed (objective 3).

Conclusions: The highest pain score was created as the maximum between pain during application of anesthesia and pain immediately following biopsy. The median highest pain score in the EMLA cream group was 20.0 mm vs. 56.5 mm in the lidocaine injection group.

Table 2.1. Highest pain score by treatment arm

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)
Highest pain score (mm)			
N	19	18	37
Mean (SD)	26.7 (29.0)	52.5 (32.0)	39.2 (32.8)
Median	20.0	56.5	27.0
Q1, Q3	5.0, 50.0	26.0, 80.0	12.0, 61.0
Range	(0.0-100.0)	(5.0-100.0)	(0.0-100.0)

All patients in the lidocaine injection group reported having the same as or more pain during the injection than the biopsy. Four out of nineteen patients in the EMLA cream group reported more pain from the application of the cream than the biopsy, and three reported the same amount of pain.

Frequency **Row Percent**	**More pain from biopsy**	**Same amount of pain**	**More pain from application of anesthesia**	**Total**
Lidocaine injection only	0 0.00	1 5.56	17 94.44	18
EMLA cream	12 63.16	3 15.79	4 21.05	19
Total	12	4	21	37

From the linear regression model, patients that received EMLA cream were expected to report their highest pain score 25.7 mm lower than the lidocaine injection group (95% CI = [-45.1, -6.3], $p < 0.01$). In other words, the highest pain score in the EMLA cream group was significantly lower than in the lidocaine injection group.

3. **Objective:** Calculate the new sample size needed using effect estimates from the interim analysis

Analysis: Using the difference in means between groups and the estimate of the standard deviation, the sample size needed to detect the observed difference in pain scores between the two treatment arms at 90% power with an alpha level of 0.05 using a two-sample t-test will be calculated. This will be the number of patients that will need to be NEWLY accrued. The current patients do not count towards this sample size.

Conclusions: Since the highest pain score was significantly lower in the EMLA cream group compared to the lidocaine group, the trial does not need to continue.

4. **Objective:** Compare secondary and exploratory outcomes between treatment arms

Analysis: The secondary objective, pain at vulvar biopsy, will be compared between treatment arms using linear regression, controlling for baseline pain, similar to the primary objective. The exploratory objectives, excluding provider's response to "overall, how satisfied were you with the procedure," will be compared between treatment arms using Wilcoxon rank sum test. A significant p value would mean that one of the treatment arms tended to have higher scores on the VAS than the other. Since the same providers are rating their satisfaction with the procedure multiple times, the responses will be correlated. To take this into account, provider procedure satisfaction scores will be compared between treatment arms with a marginal model using generalized estimating equations (GEE) assuming a normal distribution. The working correlation matrix will be chosen using QIC and the robust variance estimator will be used.

Conclusions: There was not a significant difference between treatment arms with regards to pain at biopsy (EMLA cream β = 6.9; 95% confidence interval [-12.0, 25.9]; p = 0.47). Patients that were randomized to EMLA cream had a significantly better experience with the procedure than those that received lidocaine (p = 0.02). There was not a significant difference between treatment arms for patient acceptability or provider's perception of subject tolerance (p = 0.06 for both). A compound symmetric working correlation structure was used for the marginal model comparing provider satisfaction scores between treatment groups. There was not a significant difference between treatment arms for provider satisfaction scores (p = 0.35). As a note, do not place too much emphasis on the insignificant results as this is still a small sample size and the trial was not powered for these objectives. A lack of statistical significance does not prove that there is no difference. Summary statistics for the secondary and exploratory objectives are shown in table 4.1. A lower score indicates better results for all outcomes.

Table 4.1. Secondary and exploratory outcomes

	EMLA cream (N=19)	Lidocaine injection only (N=18)	Total (N=37)	P value
Pain at vulvar biopsy (mm)				0.47
N	19	18	37	
Mean (SD)	24.1 (30.3)	17.4 (29.1)	20.8 (29.5)	
Median	6.0	3.0	5.0	
Q1, Q3	1.0, 50.0	0.0, 15.0	0.0, 26.0	
Range	(0.0-100.0)	(0.0-100.0)	(0.0-100.0)	
Patient's experience with the procedure (lower is better)				0.02
N	19	18	37	
Mean (SD)	11.2 (23.1)	27.1 (29.7)	18.9 (27.3)	
Median	2.0	17.0	6.0	
Q1, Q3	0.0, 17.0	5.0, 38.0	0.0, 25.0	
Range	(0.0-99.0)	(0.0-100.0)	(0.0-100.0)	
Patient's acceptability of the procedure (lower is better)				0.06
N	19	18	37	
Mean (SD)	10.8 (21.1)	17.9 (19.8)	14.2 (20.5)	
Median	0.0	10.5	5.0	
Q1, Q3	0.0, 18.0	1.0, 33.0	0.0, 21.0	
Range	(0.0-86.0)	(0.0-67.0)	(0.0-86.0)	
Provider's perception of patient tolerance (lower is better)				0.06
N	19	18	37	
Mean (SD)	16.6 (28.7)	20.4 (18.0)	18.5 (23.8)	
Median	3.0	15.0	13.0	
Q1, Q3	0.0, 19.0	9.0, 27.0	0.0, 20.0	
Range	(0.0-99.0)	(0.0-62.0)	(0.0-99.0)	
Provider's satisfaction with the procedure (lower is better)				0.35
N	19	18	37	
Mean (SD)	21.2 (35.8)	13.1 (13.5)	17.2 (27.3)	
Median	3.0	9.5	7.0	
Q1, Q3	0.0, 18.0	3.0, 18.0	0.0, 18.0	
Range	(0.0-99.0)	(0.0-51.0)	(0.0-99.0)	

References

1. Committee for Proprietary Medicinal Products (CPMP). Points to Consider on Adjustment for Baseline Covariates. Stat Med 2004;23(5):701-9.