Title: Sexual Dysfunction in Gynecologic Oncology Patients

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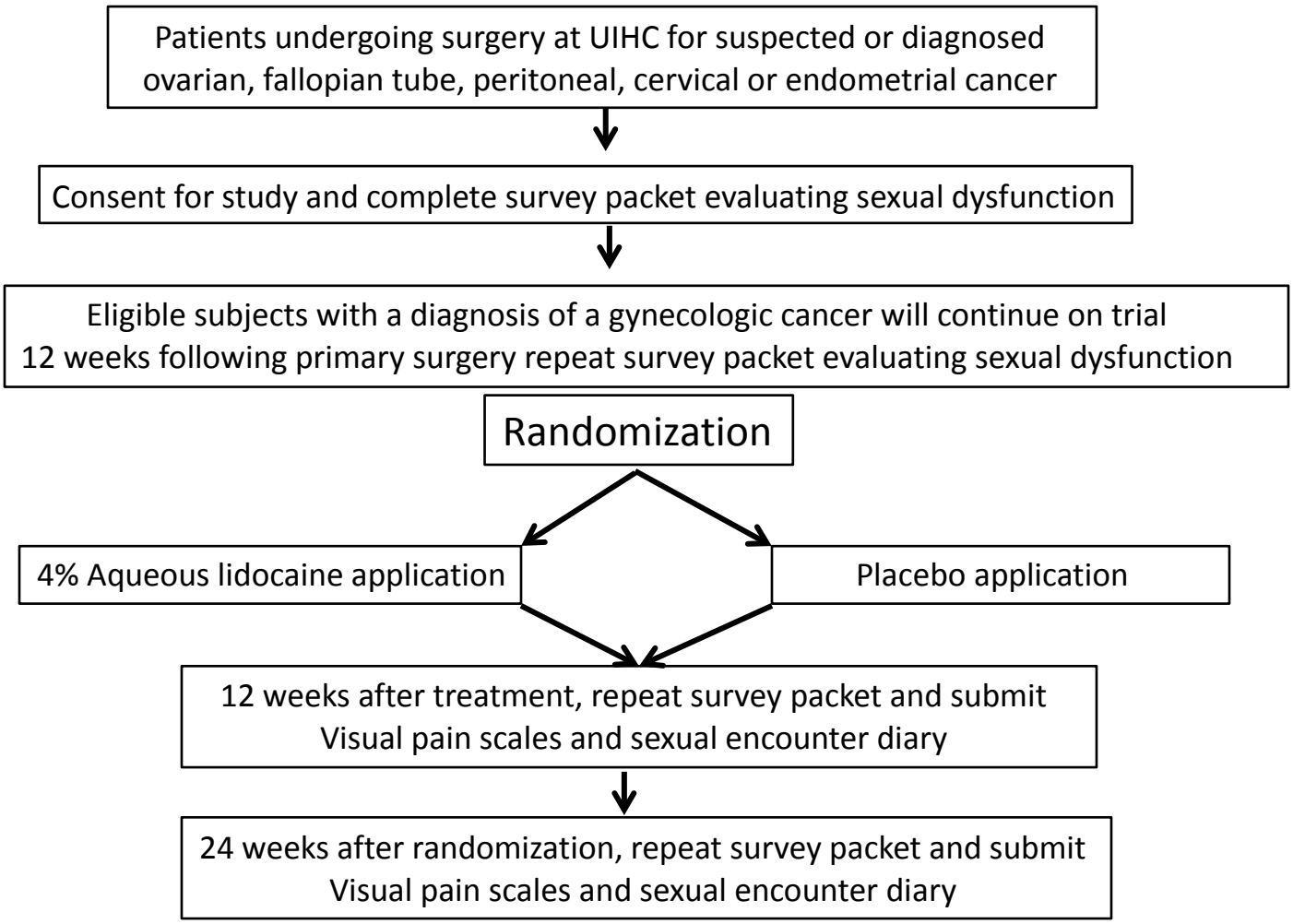
SCHEMA


Patients undergoing surgery at UIHC for suspected or diagnosed ovarian, fallopian tube, peritoneal, cervical or endometrial cancer
Consent for study and complete survey packet evaluating sexual dysfunction
Eligible subjects with a diagnosis of a gynecologic cancer will continue on trial
12 weeks following primary surgery repeat survey packet evaluating sexual dysfunction
Randomization
4% Aqueous lidocaine application
Placebo application
12 weeks after treatment, repeat survey packet and submit
Visual pain scales and sexual encounter diary
24 weeks after randomization, repeat survey packet and submit
Visual pain scales and sexual encounter diary

REVISION HISTORY

Version 1, Version Date November 28, 2016

Version 2, Version Date February 20, 2017

Version 3, Version Date March 24, 2017

Summary of Changes:

1. Version number and date updated
2. Questionnaire revisions:
    a. Adverse Childhood Experiences questionnaire replaced by accurate version. Previously included the International version, which is not intended to use.
    b. Revised Subject Diary with pain scale and sexual encounter log
    c. Revised Exit Questionnaire – The term “gel” replaced with “solution” and questions added

Version 4, Version Date May 23, 2017

Summary of Changes: The primary purpose of this amendment is to clarify the unblinding procedure. (Section 5.2.2)

Version 5, Version Date January 2, 2019

Corrected description SPS as Social Provisions Scale (Section 5.2.3)

TABLE OF CONTENTS

1. Abstract

Sexual dysfunction is known to affect women newly diagnosed with cancer. This project will evaluate critical elements contributing to sexual dysfunction in women who have had surgery for gynecologic cancer and potentially provide a simple, easily applicable, and meaningful intervention. The subjects will complete a set of questionnaires about health, daily living, sexual activity, and pain before their surgery and three times following interventions. Each subject will be randomized to receive a perineal application of either lidocaine or a placebo to use immediately prior to any sexual encounters for approximately 6 months while maintaining a journal of sexual encounters and pain. The subjects and healthcare providers will be blinded to the treatment. Total participation will last approximately one year from the date of enrollment. We aim to better characterize elements related to sexual dysfunction in this specific population, and provide a treatment intervention to improve patient's quality of life, measured by changes in their physical, psychological or social functioning.

2. Background / Rationale

Sexual dysfunction in gynecologic cancer survivors has been well-documented [1]. Physical, psychological and social elements contribute to sexual dysfunction in this population. In 2011, over 88,000 women in the United States were diagnosed with gynecologic cancers. The majority of these cases affected women over the age of 60 [2]. Treatment of these cancers, while aimed at preventing death, may cause significant changes in physical, psychological or social functioning. These changes could lead to negative long-term effects on women's sexuality. It is important to recognize the multifactorial nature of this problem. While research exists regarding this topic, few studies include all three domains of sexual functioning. Even fewer studies are aimed at designing a specific intervention to address any aspect of the dysfunction [1]. One previous study from 1989 at the University of Iowa detailed the physical side effects of gynecologic cancer, showing that cancer survivors experienced decreased sexual activity, decreased sexual desire, decreased sexual excitement, less awareness of signs of orgasm, and dyspareunia compared to control groups [3]. In an additional study in the same year by the same group, the psychological effects of treatment are detailed. However, these outcomes were not directly related to feelings regarding sexual activity or the psychological effects of changes in sexuality and were not aimed at interventions [4]. In a study of breast cancer survivors, suffering from dyspareunia, Goetsch, et. al., described the use of 4% lidocaine jelly applied for 3 minutes to areas of pain on a cotton ball. This study found that this preparation reduced pain on exam and insertion when compared to saline placebo [5]. Lack of a full understanding of physical sexual dysfunction following a diagnosis and treatment of gynecologic cancer has been a detriment to developing interventions aimed at these issues.

3. Study Goals/Objectives

- The primary objective is to identify changes in sexual function assessments (Female Sexual Function Index survey, frequency of sexual encounters and a visual pain scale assessment with each encounter) after application of an aqueous lidocaine solution to the perineum versus a placebo application.
    - Hypothesis: Subjects surgically treated for ovarian, peritoneal, fallopian tube, cervical or endometrial cancer will have higher sexual functioning and less pain associated with sexual encounters after perineal treatment with aqueous lidocaine.
- Secondary objectives include characterizing the pre and post-treatment functioning of gynecologic cancer survivors with respect to physical, psychological, and social dimensions.
    - Subjects will complete nine short surveys (The Female Sexual Function Index, The PHQ-9, the GAD-7, the SPS, Rosenberg's Body Self-Esteem Index, the Severity of PTS Symptoms Scale, the Adverse Childhood Events Index, the SF-12, and the Dyadic Adjustment Scale) at their initial visit, assessing physical, psychological, and social elements related to sexuality. The same packet of surveys will be completed twelve weeks following surgery, after which, they will be randomized to a blinded perineal intervention. Survey packets will be completed 12 and 24 weeks following randomization to the perineal intervention.
    - A visual pain scale will be completed after each sexual encounter.
    - A diary documenting frequency of sexual encounters will be collected.

4. Study Population

Subjects comprising this study population include women undergoing initial consultation at the University of Iowa Hospitals and Clinics/Holden Comprehensive Cancer Center for a documented or suspected diagnosis of ovarian, fallopian tube, peritoneal, endometrial or cervical cancer. Each subject must be scheduled to undergo surgical treatment for their disease prior to enrollment. Enrollment will be offered and consent obtained by the Investigator or one of the sub-Investigators at the time of initial consultation in the outpatient clinic.

Subjects ultimately diagnosed with one of the previously mentioned gynecologic malignancies will remain eligible to continue on the trial, while those found to have no evidence of cancer will be excluded.

Inclusion/Exclusion Criteria:

4.1 Inclusion criteria

- Female
- Age 18-99

- Planned to undergo primary surgical treatment at the University of Iowa Hospitals and Clinics for a suspected or proven diagnosis of ovarian, fallopian tube, peritoneal, endometrial, or cervical cancer
- Able to give informed consent and follow study procedures
- No previous reactions to lidocaine applications
- GOG Performance Status of 0 or 1
- Reports having engaged in vaginal intercourse at least once in the last 12 months

4.2 Exclusion criteria:

- Failure to confirm invasive ovarian, fallopian tube, peritoneal, endometrial or cervical cancer by pathology from primary biopsy or surgery (subjects will not be eligible to continue the trial beyond the initial completion of the questionnaires)
- Diagnosis of another malignancy within the past five years, excluding basal cell carcinoma of the skin
- Patients undergoing primary or adjuvant external pelvic radiation (excluding adjuvant vaginal brachytherapy)
- Previous reactions to lidocaine applications
- Sexual partners' previous reactions to lidocaine applications

5. Study Design and Methods

5.1 Data Acquisition

Study data will primarily be obtained through questionnaires and self-reported data from a visual pain scale and a diary documenting frequency of sexual encounters.

5.1.1: The questionnaire packet consists of nine short surveys that capture information on psychological, social and physical elements previously cited as potential influences on sexual dysfunction. This survey packet will be completed prior to a surgical intervention with the intent to capture a "baseline" for the subject. Completion of the survey packet will be requested at the three month postoperative check-up visit and then at two more sequential three month follow-up visits. The perineal intervention will be introduced at the first three month postoperative visit.

5.1.2: Subjects will self-report potential discomfort related to each sexual encounter on a visual pain scale. These scales will be collected at each three month follow-up visit.

5.1.3: Subjects will be asked to maintain a diary/calendar documenting the frequency of sexual encounters and the successful or unsuccessful ability to

apply the perineal intervention. The diary/calendar will be collected at each three month visit.

5.2 Procedures

5.2.1: Primary surgical intervention

Subjects will be eligible and plan to undergo a primary surgical procedure for the treatment of their gynecologic cancer (ovarian, fallopian tube, peritoneal, endometrial or cervical) under one of the UIHC gynecologic oncologists. Surgical treatment of these cancers, which includes removing some or all of the gynecologic organs, may cause physical as well as perceived changes in sexual function. Surgical treatment for ovarian, fallopian tube, peritoneal, endometrial, and early stage cervical cancers is often the first option of treatment for appropriately selected patients and critical to a comprehensive treatment approach. It is the goal to systematically evaluate the changes in sexual function prior to and following primary surgery for these subjects.

5.2.2 Randomization

Patients will be randomized to receive either the lidocaine solution or a placebo using permuted block technique based on cancer origin. Patients and investigators are blinded to assignment. Only the Investigational Drug Service will maintain the blinded codes. Patient and investigator will be unblinded at the conclusion of the study. Patients are randomized 1:1 to each arm.

Randomization will be stratified by pathological category of cancer type.
Thirty subjects will be randomized within each of three groups:
1. Ovarian, fallopian tube, primary peritoneal cancer
2. Endometrial cancer
3. Cervical cancer

5.2.3 Evaluation of sexual dysfunction

The survey packet evaluates physical, psychological, and social elements related to sexuality. Each packet will be assembled into a large envelope and handed to the subject by the healthcare provider in the UIHC Gynecologic Oncology outpatient clinic. The surveys will be completed by the subject in the clinic (in a private area) on the day of the visit and then collected by the research data managers.

Each survey packet will contain:

1. Female Sexual Function Index: A self-report measure of sexual functioning

2. Patient Health Questionnaire 9 (PHQ-9): Instrument for screening, diagnosing, monitoring, and measuring the severity of depression.

3. Generalized Anxiety Disorder 7-item scale (GAD-7): A brief measure for assessing generalized anxiety disorder.

4. Social Provisions Scale (SPS): Instrument to assess provisions of social relationships.

5. Rosenberg's Body Self-Esteem Index: Scale that measures global self-worth by measuring both positive and negative feelings about the self.

6. Severity of Posttraumatic Stress Symptoms-Adult: Assesses the severity of posttraumatic stress disorder following a particular event or experience.

7. Adverse Childhood Events Index: A scale measuring types of physical, verbal, and emotional childhood trauma

8. SF-12: A generic measure of health status

9. Dyadic Adjustment Scale: A relationship adjustment self-report measure.

5.2.4 Diary of Sexual Encounters

A diary of sexual encounters during the 24 weeks of observation will be kept by participating subjects. On the calendar, subjects will be asked to document date of sexual encounter and an accompanying successful or unsuccessful perineal application of the intervention. For each encounter, subjects will also be asked to mark a visual pain scale.

5.2.5 Adverse Events

Study participants will be asked if there have been any reactions to the solution supplied for perineal application at each clinic visit. They will be encouraged to contact their primary gynecologic oncologist or the study chair immediately should any adverse reactions be experienced with the perineal application.

Each questionnaire packet will be reviewed immediately following collection for an immediate assessment to positive responses to the depression and suicidal ideation items of the PHQ-9. If the PHQ-9 score reflects severe depression, the clinician overseeing the patient's care for their gynecologic malignancy will be notified and asked to use their clinical discretion for intervention and appropriate referrals within the UIHC health system.

6. Study Procedures

6.1 Self-reported measures of physical, psychological and social stressors influencing sexual function

Patient-completed surveys, measuring the different elements of sexual dysfunction, will be completed at their initial visit, following their assessment by a UIHC

gynecologic oncologist, and their decision to pursue a surgical intervention for their gynecologic cancer. At the twelve week postoperative visit, and if a pathologic diagnosis of cancer is confirmed, subjects will be asked to complete the same survey packet. At subsequent 3 and 6 month follow-up visits, subjects will be asked to complete the survey packet following the visit with their gynecologic oncology healthcare provider.

6.2 Aqueous Lidocaine and Placebo Perineal Application

Once subjects have a confirmed diagnosis of their gynecologic cancer, and they complete the survey packet at their 12-week follow-up visit, they will be randomized to receive a solution containing either aqueous lidocaine or a placebo. They will also be given a package of cotton balls with instructions to put the solution on three cotton balls and apply them to the perineum/vaginal introitus for one minute prior to sexual intercourse. Subjects will be asked to document in their diary successful or unsuccessful application of the perineal solution. They will also be asked to complete a visual pain scale for each sexual encounter. Subjects will be reminded to bring the calendars to the return visit with a phone call.

The aqueous lidocaine/placebo solution will be supplied by the Investigational Drug Service. It will be labeled in a manner that does not identify the presence of active ingredient.

CALENDAR/SCHEDULE OF EVENTS

Procedures	Visit 1 Pre-surgery	Visit 2 (12 weeks post-surgery)	Visit 3 (24 weeks post-surgery)	Visit 4 (32 weeks post-surgery)
Informed Consent	x			
Inclusion / Exclusion Criteria	x			
Performance Status	x	x	x	x
Physical Exam	x	x	x	x
Questionnaires	x	x	x	x
Diary of Sexual encounters and lidocaine/placebo usage		x	x	x
Randomization		x		

7. Safety

7.1 Possible Adverse events of lidocaine include:

- Rare allergic reactions: Itching; hives; edema of the face or hands; tingling in the mouth or throat or chest tightness (which can cause trouble breathing).
- Other uncommon reactions: Blurred or double vision; confusion; dizziness; lightheadedness; or drowsiness; chest pain or an uneven heartbeat; skin rash; swelling in the area where this medicine is applied; and trembling (shaking).

7.2 Other risks of the study procedures include:

- Embarrassment: discomfort answering some of the questions of the surveys (subjects may skip any questions they choose).

7.3 Stopping Rules:

- Subject may stop participating at any time
- Subject not following instructions
- Gel becomes unavailable
- Attending physician decision to withdraw subject
- Breach of confidentiality

8. Statistical Evaluation/Considerations

The primary objective of this double-blinded, randomized, placebo-controlled study is to assess the relative efficacy of aqueous lidocaine solution in improving sexual functioning within the population of females undergoing a primary surgical procedure for the treatment of ovarian, endometrial, and cervical cancer. Sexual functioning will be assessed using the self-reported Female Sexual Function Index (FSFI; full scale score ranges from 2 to 36 where scores <26 are indicative of sexual dysfunction). Given the lack of existing literature pertaining to sexual functioning immediately following surgical intervention, this will be a pilot study aimed at obtaining estimates of relative efficacy as well as assessing feasibility. Existing literature on sexual functioning in gynecologic cancer survivors, assessed a year or more post-surgery, provide median and mean estimates ranging between 16.6-17.2 and 19.75-19.9 (SD 7.0-9.8), respectively, on the FSFI full scale [6, 7, 8, 9]. We anticipate sexual functioning will be even lower in the 24 weeks immediately following surgery. A sample size of 15 patients per treatment group achieves 80% power to detect an increase of 9.3 between the null hypothesis that both group means are 17.0 and the alternative hypothesis that the mean of the aqueous lidocaine solution treatment group is 26.3 with estimated group standard deviations of 10.0 and a significance level of 0.05. Power calculations were based on using a one-sided two-sample t-test for a single point in time while assuming the actual distribution of the FSFI full scale is normal. Accordingly, 30 patients from each cancer type—ovarian, endometrial, and cervical—will be recruited for a total of 90 subjects.

To assess changes in sexual, physical, psychological, and social domains, linear mixed effects regressions models will be utilized. Random effects will be employed to account for the longitudinally correlated nature of repeated questionnaire measurements.

9. Data Collection and Record Keeping

9.1 Data will be collected primarily by paper forms that include reported information from each study participant. Information will be transferred to electronic database collection documents for use by the statisticians without any identifiable information.

9.2 In order to protect confidentiality the subject will be assigned an identification number. This number will be used on all specimens from the subject and will be used for documentation purposes. Data management for the entry, processing, storage, and retrieval for this protocol's data will be managed by the principal investigator. The database will be located on a computer or in a locked cabinet in a locked office. This computer will be secured using UIHC standard protections and accessible only by the research team. For quality control, auditing, and data integrity, there will be a regular review of data performed periodically throughout the data collection phase.

9.3 Study data will be maintained according to University of Iowa policies. Since this project includes protected health information, copies of all research records will be stored for at least six years following study closure. Study documents will be stored in a secure storage room of the department for the required amount of time. The space is only accessible to relevant study staff.

10. References

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