

Version #4, 4/11/16

TITLE: The effects of timing of administration of belladonna and opium suppositories on post-operative bladder spasms and urinary discomfort in patients undergoing lithotripsy.

## RESEARCH PLAN

### A. Specific Aims

List the broad, long-term objectives and describe concisely and realistically what the specific research described in your proposal is intended to accomplish, and the hypothesis to be tested.

The long-term objectives of the study are to determine whether earlier administration of Belladonna and opium (B and O) suppositories ameliorates the discomfort associated with bladder spasms and reduces the need for oral narcotics and antimuscarinics in the post-operative setting.

Most patients who receive B and O suppositories in the post-operative period receive them in the PACU after expressing discomfort. The administration of B and O suppositories in these cases can often be hours from surgery end time. The hypothesis to be tested is that giving patients B and O suppositories prior to surgery or post-operatively while still in the operating room will reduce the amount of pain medications that people will need post-operatively, reduce the amount of discomfort that patients experience from bladder spasms, and possibly reduce the length of hospital stay.

### B. Background and Significance

Briefly give the background to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps which the project is intended to fill. Cite literature and include a list of references.

Bladder Spasms are a frequent cause of discomfort in the post-operative setting after lithotripsy, and while B and O suppositories are occasionally used post-operatively to relieve bladder spasms, there are no studies that show how effective they are. There are two studies that evaluated the use of B and O suppositories in a perioperative setting after robotic prostatectomies:

Lukasewycz S, Holman M, Kozlowski P, Porter CR, Odom E, Bernards C, Neil N, Corman JM. Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy?

Results of a single institution randomized study. Can J Urol. 2010 Oct;17(5):5377-82. PubMed PMID: 20974030

Scavonetto F, Lamborn DR, McCaffrey JM, Schroeder DR, Gettman MT, Sprung J, Weingarten TN. Prophylactic belladonna suppositories on anesthetic recovery after robotic assisted laparoscopic prostatectomy. Can J Urol. 2013 Jun;20(3):6799-804. PubMed PMID: 23783051.

These two studies show a possible benefit to perioperative belladonna and opium suppositories. However, these studies have never evaluated the use of the suppositories in lithotripsy procedures where the bladder is dilated and drained multiple times during a procedure. The constant distension leads to bladder spasms in the post-operative setting, which require narcotics and anti-muscarinics. There are also no studies to evaluate the effect of timing of administration of these suppositories in lithotripsy cases on postoperative pain, the use of narcotics in the post-operative period, and length of hospital stay.

### C. Preliminary Studies

Provide an account of the PI/IS's preliminary studies pertinent to the protocol and/or any other information that will help to establish the experience and competence of the PI/IS to pursue the proposed project. The titles and complete references to appropriate publications and manuscripts submitted or accepted for publication may be listed.

There have not been any preliminary studies done by the PI on this subject. However Dr. Mufarrij has several years experience dealing with lithotripsy patients in the post-operative setting. All attending physicians participating in this study have years of experience dealing with lithotripsy patients.

### D. Research Design and Methods

Describe the research design and the procedures to be used to accomplish the specific aims of the project. Include the means by which the data will be collected, analyzed, and interpreted.

-1. Subjects will be identified as meeting inclusion criteria for this study during an office visit at the MFA urology clinic. Opportunity to participate in the study will be offered to the subject and informed consent obtained as appropriate. As noted above, patients will be informed of their right to not participate in the study. Ureteroscopy will still be offered to all patients who meet the appropriate indications, regardless of their participation in this study. Patients will be give a pre-operative survey to determine the severity of any bladder spasms they are

experiencing before surgery and to gauge their level of narcotic usage in the acute setting pre-operatively.

-2. The patients will be divided into three research arms. Patients will be randomly selected for one of the groups using a random number generator between 1 and 3. There will be a "Control Group" which will receive a rectal exam while still in the operating room in the lithotomy position after the procedure. There will be a "Postoperative OR" group which will receive a B and O suppository while still in the operating room in the lithotomy position after the procedure. Finally, there will be a "Preoperative OR" group which will receive a B and O suppository after the induction of anesthesia prior to beginning the urologic procedure in the lithotomy position. The "Control Group" will receive a rectal exam in the operating room after the procedure but before extubation to simulate the effects of suppository administration so that we know that any effects are due to the medication and not to the placement of the suppository itself. Those patients in the "control group" may receive a B and O suppository as part of standard procedure in the post-operative period if these individuals experience any bladder spasms and wish to have this as a treatment. This administration will be at the discretion of the operating surgeon as it is in standard cases. Patients may also receive Ditropan in the post-operative setting, which is part of the standard procedure for treating bladder spasms following urologic procedures. Patients in the postoperative and preoperative OR groups will be offered Ditropan for any bladder spasms in the post-operative setting to control symptoms, which is part of the normal standard of care for anyone who has already received a B and O suppository with inadequate control of symptoms. All patients will be treated with a normal post-operative pain regimen which may include narcotics. This will be at the discretion of the treating physician.

-3. In the post-operative setting, all subjects will be given a quick survey within 24 hours to assess their amount of discomfort related to bladder spasms/urinary discomfort. In addition, subjects medical charts will be reviewed to determine the amount of antimuscarinics that the patient received 24 hours post-operatively and the amount of narcotic and non-narcotic pain medication that subjects required. Patients not in the experimental arm will be given oral anti-muscarnics to treat any bladder spasms that they may have, but will not be given suppositories.

-4. Data will be entered into the database following the procedure as available.

-5. Subjects will have clinically appropriate follow-up per the attending urologist. If, as part of that follow-up, clinically relevant events occur, the corresponding data will be recorded in the database.

Note that, with the exception of which particular study arm the subjects are enrolled into and the recording of data as detailed above and below, there will be absolutely

no difference in the care received by patients choosing to participate in this study and those who elect not to participate.

Data will be analyzed using commercially available statistical software. T-tests will be performed for continuous variables and Pearson's Chi-squared tests for categorical variables. Analysis will be tailored to compare B and O Supporettes Suppositories and placebo/no suppository in order to best answer the research question.

1. Describe any new methodology and its advantage over existing methodologies.

There are no methodologies in this protocol which are new.

2. Discuss potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

The procedure is designed so that patients receive a B and O suppository as they would as part of standard protocol in the post-operative period if bladder spasms were experienced. The only difference is regarding timing of administration. Therefore, there are no potential difficulties or limitations of the proposed procedure since B and O administration is already a well-accepted treatment for bladder spasms following urologic procedures.

3. Provide a tentative sequence or time table for the study.

November 2015 - IRB approval and begin recruiting patients for study

December 2015 - June 2016 Conducting study according to aforementioned protocol

July 2016 - Begin data analysis and manuscript preparation

4. Specify procedures, situations, or materials that may be hazardous to personnel and the precautions to be taken to ensure safety.

None

5. Provide justification of the sampling procedure and sample size. Gender and Minority Inclusion, it is required that all research involving human subjects and human materials include minorities and women, as well as males and females of all ages. If one gender and/or minorities are excluded or are inadequately represented in a protocol, particularly in proposed population-based studies, a clear compelling rationale for exclusion or inadequate representation should be provided. The composition of the study population must be described in terms of gender and

racial/ethnic group, together with a rationale for its choice (by age distribution, risk factors, incidence/prevalence, etc.)

All participants undergoing lithotripsy procedures at GW hospital with the included physicians will be asked to participate in the study.

We determined the expected effect sizes based on previous studies of this same treatment in patients who received robot-assisted laparoscopic surgery for prostate CA.

Based on morphine equivalent dose in both Scavonetto, Lamborn, McCaffrey et al. (Can J. Urol 2013) and Lukaswycz, Holman, Kozlowski et al. (Can J Urol 2010), we would like to detect a 4 mg eq. difference between groups, with an expected standard deviation (sd) of 5, i.e., an effect size (d) of 0.8. For post-op pain rated on a 10-point scale both of the previous studies found sd ~2.0. We would like to detect a 1-point difference, so will power for an effect size of 0.5. Scavonetto et al. found approximately 20% of patients required use of rescue B&O suppositories and 60% requiring Oxybutynin for post-op bladder spasm. Thus, for this outcome we will try to detect a difference in percent positive of 20%. For all comparisons, we will use 2-tailed tests with  $\alpha=0.05$ .

Immediate post-op morphine equivalent dose.

In order to have power  $>.80$  to detect an effect size of 0.8 in morphine eq. dose, we would need  $n=26$  per group, or total  $N=51$ . For power  $>.90$ , we would need 34 per group or total  $N=68$ .

Post-op pain.

For an effect size of 0.5, in order to have power  $>.80$ , we would need 64 per group, or total  $N=128$ . For power  $>.90$ , we would need 86 per group, or total  $N=172$ .

Use of medication for bladder spasms.

Here, we will want to detect a 20% difference between groups. Assuming that in the treatment group, 20% of patients need rescue medication for bladder spasm, while 40% need such meds in the control group, we would need  $n=82$  per group (total  $N=164$ ) in order to detect a difference this large with power  $>.80$ .

Therefore, in order to have adequate power across all 3 outcome measures, we plan to enroll a total of 180 subjects, randomized equally across treatment and control groups.

6. Identify all drugs and devices to be used, if applicable,. If the drug or device is investigational under FDA policy, list the actual IND/IDE number and respective source, supplier, and/or sponsor. If an IND/IDE has been assigned provide the FDA

stage status. Note the proposed dosage related information including instructions for administering, adverse effects, compatibility in infusions, and stability.

Please see package inserts for B and O supprette suppositories attached to this submission. We are also including Ditropan, which is the oral anti-muscarinic to be included in this study. The dosage of B&O will be 16.2mg/30mg which is in the formulary at GW. Ditropan will be given in the normal 5 mg dosage.

7. Identify all procedures that will be used for the purpose of this research. If blood is to be drawn, indicate amount to be withdrawn per single withdrawal, and the total amount of blood to be drawn. If transfusions are anticipated, include assurance that the volume of blood removed for research purposes will not necessitate a transfusion. [Refer to Section 1.5.5]

#### E. Study Population –(Gender and Minority Inclusions):

1. Describe the characteristics of the subject population, include the anticipated number of normal volunteers, age ranges, sex, ethnic background, and health status.

Identify the criteria for inclusion or exclusion (especially women and/or minorities).

Explain the rationale for the use of special classes of subjects, such as fetuses, pregnant women, or others who are likely to be vulnerable, especially those whose ability to give voluntary informed consent may be questionable.

The subject population will be patients seen at GW for lithotripsy procedures. This will include men and women ages 18-89. It will include all ethnic backgrounds, and anyone who has been cleared for surgery.

The criteria for exclusion for those patients who agree to participate in the study will be patients with glaucoma, severe hepatic or renal disease, bronchial asthma, respiratory depression at the time of administration, convulsive disorders, allergy to anti-muscarinics or opiates, history of anorectal surgery, pre-operative use of antimuscarinics, chronic pain, chronic use of analgesics, or a history of alcohol or opioid dependency, pregnant women and nursing mothers.

#### F. Human Subjects (Risks & Benefits)

1. Identify sources of research material obtained from individually identifiable living human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data. Subjects with specific diseases or conditions are often identified as potential subjects through some type of record

(e.g., medical records, patient charts, registries for cancer cases, surgical or X-ray log books, school records). Controls may come from the same population as the subjects (which is always the case in a randomized clinical trial), be persons with unrelated conditions or be volunteers from the general population.

No material from individual human subjects will be used. All information obtained will be through patient surveys and the patient's medical records.

2. Describe plans for recruitment of subjects and the consent procedures to be followed; including the circumstances under which consent will be sought and obtained, who will seek it, who will give consent, the age range of the individual who will give consent, the nature of the information to be provided to prospective subjects, payment for participation (if applicable), the prospective subjects, and the method of documenting consent. (State if you are requesting a 'waiver of consent' from the IRB and why.) [Refer to Section 3.0]

Subjects will be recruited from patients who are determined to need a lithotripsy procedure with the above attending Urologists. They will be asked to consent to participate in the study at some time before their procedure. This could be in the clinic weeks beforehand, this could be in the ER when the patient presents with a stone, and it could be pre-operatively while the patient is being consented for the procedure. The consent will be done in a quiet area one on one with the patient and the patient will be given time to ask questions. The consent form, which is attached, will be given to the patient.

#### G. Risks and Side Effects:

1. Describe any potential risks--physical, psychological, social, legal, or other and assess their likelihood and seriousness. Describe the alternative treatments and procedures that might be advantageous to the subjects.

The potential risks of this study are mainly those associated with the B & O suppositories: Belladonna may cause drowsiness, dry mouth, urinary retention, photophobia, rapid pulse, dizziness and blurred vision. Opium usage may result in constipation, nausea or vomiting. Pruritis and urticaria may occasionally occur. These risks are relatively mild as far as medication side effects go. Alternative treatments or procedures for patients undergoing lithotripsy who may experience bladder spasms include the option of treating bladder spasms with narcotic pain medications, oxybutynin, an oral antimuscarinic, or not treating the patient at all. Any of these choices carry side effects or negative consequences. Not all patients who undergo lithotripsy procedures will experience bladder spasms post-operatively, but those that do will be exposed to possible side effects with treatment. Side effects of oxybutynin are included on the package insert attached to this form.

2. Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness. Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Describe the provisions for monitoring the data to insure the safety of subjects.

Risk will be minimized by strictly adhering to the exclusion protocol to ensure that patients at an increased risk for adverse effects are not exposed to the suppositories.

To reduce the risks to confidentiality, all data will be recorded in electronic format, kept on a computer meeting the GW university standards for antivirus software, and will require password entry for access to the computer itself as well as the document in which the data is stored. Data transferred from the electronic medical record system to the computer database will be de-identified and given a new unique identifier. The key document to justify the new unique identifier with the subject MRN and DOB identifying information will be stored on a separate computer with the same protections in place as described above. This key will be deleted at the conclusion of the study. If at any time during the study any materials or the computers with the electronic documents pertaining to the study are found to be missing or otherwise compromised, the GW OHR will be immediately notified.

Patient's will be monitored in the post-operative setting, and any adverse effects will be treated as part of the normal post-operative course of care.

3. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may be reasonably expected to result.

The risk to subjects are very minor side effects, while the benefit is that they could gain relief from the severe discomfort of bladder spasms in the post-operative setting. The importance of this knowledge is in trying to find a better, more efficient way to prophylactically treat bladder spasms.

4. List all risks that are more than minimal (no greater probability or magnitude than those ordinarily encountered in daily life or during routine medical tests). Include physical, psychological, social, economic, legal or other risks, where present.

The physical risks that are more than minimal include those side effects listed above. Psychological risk should be minimal. Social risk will be none. Economic risk, patient's only are exposing themselves to a slightly added cost. Legal risk should be none.



5. Describe the severity and probability of all material risks, and the implications, in understandable terms. Use a table for Common (21-100/100), Occasional (5-20/100) and Rare (<5/100) risks sorted by Immediate (1-2 days of treatment), Prompt (within 2-3 weeks before next course), Delayed (any later time during treatment) and Late (after completion of treatment) onset wherever possible.

All risks are considered immediate (1-2 days of treatment).

Common: constipation, dry mouth

Occasional: difficulty urinating

Rare: blurred vision, dizziness, nausea, vomiting, sensitivity to light

H. Benefits:

1. The risks must be reasonable in relation to anticipated benefits, if any, to subjects, and to the importance of the knowledge reasonably expected to result.

2. The use of modest compensation for the burdens imposed by the research may be permitted, especially if benefits are minimal, but should be incremental and not conditioned on completion of the entire study.

3. Explain the expected benefits, if any, and their likelihood. If none, say so.

4. You may mention general benefits for science, or for other persons, if any.

These results will potentially help inform protocol for urologic procedures in the future. The use of B&O suppositories according to this protocol could help reduce the pain and discomfort of bladder and ureteral spasms that patients experience following lithotripsy procedures as well as decrease these patients' need for pain medication and thus reduce associated side effects of those medications in the post-operative period.

I. Outside Consultants/Collaborators

Attach a letter from the consultant(s) and/or their signature(s) on the Application (Sign-Off) Form confirming their role in the project.

The anesthesia department at GW has attached a letter to say they have objectively reviewed the study and have listed any potential interactions with anesthetics.

J. Contractual Agreements

Describe the nature of these collaborations. Attach an appropriate letter from each individual/institution involved confirming the agreement. If the protocol originates

at another institution, explain how that institution will be involved and provide the name and department of the Institutional Sponsor. The assigned PI/IS must be a faculty/staff member of that institution.

None

K. Costs To Subjects:

Patients will not be billed for B and O suppositories, and they will not incur any additional costs above their hospitalization. All costs for B and O suppositories will be paid for by the research project.

1. The Research Plan and the consent documents must describe the costs to such compensation plans in detail, including the provision of free care or medicines related to the study.

Example: Children's Hospital will give you the medicine used in this study for free. You will not be charged for anything else we do that is part of the study. You will still have to pay for any medical care that is not part of the study.

See associated consent document.

L. Conflicts Of Interest:

1. Describe any financial or other conflicts of interest as indicated. Any interests of the investigators or provider institutions in the outcome of the research, the study product, or the sponsoring entities, any support received by the researchers or provider institutions from same in excess of \$10,000 per year, and any other relationship to the sponsor or the research that could be material to any subject.

None

2. Where such interests exist, describe the disclosures that will be made to subjects in the consent process and consent documents and discuss the factors considered in selecting the appropriate disclosures. Consult §2.3 of the Manual for a discussion of materiality and appropriate disclosure to subjects, including disclosure of sponsor identity and source of funding where potentially material to subjects.

None

3. Review the Financial Interest Disclosure form submitted to the Office of Sponsored Programs to ensure that it is current and consistent with the Application disclosure.

#### M. Confidentiality:

Include appropriate provisions to protect the privacy of subjects and maintain the confidentiality of data, and include safeguards to protect the rights and welfare of vulnerable subjects.

#### N. Subject Compensation:

The Research Plan must describe such compensation plans in detail, including the provision of free care or medicines related to the study.

There will be no monetary compensation for participation in this study.

#### O. Facilities and Equipment

Describe the facilities and equipment to be used. Indicate the extent to which these facilities and equipment are available or will be obtained for the project.

Ditropan is readily available from the hospital pharmacy. B and O suppositories will be supplied through the Investigational Drug Pharmacy. Therefore, in order to obtain the medication for the patient, we will submit a written prescription for the suppository that will then be filled in the retail pharmacy at the MFA out of their supply. The cost of the fill(s) will be billed to the study's cost center quarterly.

The packaged suppository will then be taken to the pharmacy in GWUH to be put into the computer system as a "Research Drug" and labeled with a scan code for floor administration. Once labeled IDS will reach out to a contact on the study (Dr. Mufarrij or Dr. Grant) and give the medication to that person to take to the floor where the patient is located. Because this is a schedule II drug, IDS will ask the person that they dispense the medication to sign a chain of custody log indicating change of possession. IDS will also create a general log of subject dispensation and a study binder to hold all relevant study materials.

There will be no additional equipment required for the study outside of the standard operating procedure used for lithotripsy in the GW OR and hospital.

#### P. References & Literature Cited

Compile a judicious list of relevant literature citations. Each literature citation must include the title, names of authors, book or journal, volume number, page numbers, and year of publication.

Lukasewycz S, Holman M, Kozlowski P, Porter CR, Odom E, Bernard C, Neil N, Corman JM. Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy?

Results of a single institution randomized study. Can J Urol. 2010 Oct;17(5):5377-82. PubMed PMID: 20974030

Scavonetto F, Lamborn DR, McCaffrey JM, Schroeder DR, Gettman MT, Sprung J, Weingarten TN. Prophylactic belladonna suppositories on anesthetic recovery after robotic assisted laparoscopic prostatectomy. Can J Urol. 2013 Jun;20(3):6799-804. PubMed PMID: 23783051.

#### Q. Appendix

Attach the letters of confirmation from collaborating institutions, consultants, research documents (e.g., questionnaires, scales, tables, charts, diagrams, manufacturers brochures, etc.) in this section.