Preoperative Acetazolamide for Improved Pain Control Following Laparoscopic Hysterectomy	
Principal Investigator	**Paul B. Miller, MD**
Co-Investigator(s)	**Briana Rice, MD; Erica Robinson, MD; Savannah Micolucci, MD; John Van Deman III, MD**
Study Location(s)	**Prisma Health Greenville Memorial Hospital**

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I. ABSTRACT

Provide a concise summary (a few sentences) that includes objectives, population, design, and outcome measures:
This randomized controlled trial is designed to evaluate if a preoperative dose of acetazolamide will reduce pain overall and, specifically, right shoulder referred pain following total laparoscopic hysterectomy (TLH). This will be measured in patients undergoing TLH using a visual analog scale postoperatively, comparing patients who received acetazolamide and patients who received placebo.

II. INTRODUCTION

A. BACKGROUND

Describe the rationale for the study, including the disease or condition being studied, citations, and synthesized earlier preclinical and clinical research on the topic of the study:
Pain control following surgery is integral to surgical success, allowing faster recovery and return to function and increasing patient satisfaction. Minimally invasive surgery, such as laparoscopy, is becoming increasingly common as it involves smaller incisions and theoretically less discomfort. However, in order to perform laparoscopy, one must insufflate the abdomen with gas in order to create space in which to operate. The most commonly used gas today is carbon dioxide, as it is highly soluble and reduces the risk of air embolism compared to room air if absorbed. A consequence of using carbon dioxide is that it is converted to carbonic acid that can be irritating to the peritoneum and specifically the diaphragm, causing referred pain to the right subscapular (shoulder) region. Multiple strategies have been undertaken to help reduce this discomfort, one of which is using acetazolamide (a carbonic anhydrase inhibitor) to help reduce peritoneal acidification. Multiple studies have demonstrated an improvement in shoulder pain following preoperative administration in laparoscopic cholecystectomy, but studies evaluating use in pelvic surgery have had mixed results. The goal of this study is to add to this understanding and determine if acetazolamide is a useful adjunct to current pain control methods in laparoscopic gynecologic surgery.

B. IMPORTANCE / JUSTIFICATION FOR STUDY

Describe the research question you intend to answer with findings from this study:
Does use of acetazolamide preoperatively help reduce pain following total laparoscopic hysterectomy (TLH)?
Explain why the current research question is pertinent, important, interesting, or novel:
Reducing pain following surgery shortens hospital stays, reduces postoperative analgesic use, allows for faster return to activity, and improves patient satisfaction. Acetazolamide is a cheap and easy intervention which has been studied in general surgery literature but has not been specifically evaluated for gynecologic procedures.

III. HYPOTHESIS & OBJECTIVES

A. HYPOTHESIS

Describe the hypothesis/hypotheses that your study is intended to demonstrate, and your objectives are based:
Preoperative acetazolamide will decrease postoperative pain scores on a visual analog scale following laparoscopic hysterectomy.

B. OBJECTIVES

Describe the details of each objective that will lead to the achievement of the study goal including a summary of the outcome measures:
1. Abdominal/pelvic pain scores as determined on a visual analog scale (VAS; see Appendix 1) evaluated at five points: preoperatively, when first responsive in the post-anesthesia care unit (PACU), two hours postoperatively, four hours postoperatively, and 24 hours postoperatively. 2. Right shoulder pain as determined on a VAS evaluated at five points preoperatively, when first responsive in the post-anesthesia care unit (PACU), two hours postoperatively, four hours postoperatively, and 24 hours postoperatively. 3. Cumulative analgesia use during the first 24 hours postoperatively.

IV. DESIGN & METHODS

A. STUDY DESIGN

Briefly describe the study design (systematic review, randomized controlled trial, other controlled clinical trial, observational [cohort, case-control, cross-sectional], or case study):
This study is a randomized, double-blinded, controlled trial comparing levels of postoperative pain in patients undergoing TLH with and without pretreatment with oral acetazolamide. Patients scheduled to undergo TLH for benign indications (e.g., pelvic pain, endometriosis, uterine fibroids) will be identified by their surgeon as potential study candidates. On the day of their preoperative appointment, they will have an opportunity to discuss the study with their provider and to sign consent forms for participation. Demographic data will be recorded at that time (see Appendix 1). The study coordinator will alert the Research Pharmacy when a patient is scheduled. The Research Pharmacy will randomize the patient and have the study drug available for the research coordinator to pick up at the satellite pharmacy on the 2nd floor of Greenville Memorial Hospital on the day of surgery. Subjects will be met in the preoperative area by a research study coordinator who will provide the study drug to the participant. Preoperative assessment of pain using a VAS and administration of either study drug or placebo will be performed by the study nurse coordinator. Members of both the anesthesia team and the surgeons will be unaware of the study group. All patients will receive perioperative medications according to our institutional Enhanced Recovery After Surgery (ERAS) protocol (Appendix 2). Surgery will be performed via whatever method is deemed appropriate by the surgeon with recording of surgical indication, pre- and intraoperative medications, length of surgery, intraoperative complications including transfusion, and blood loss. Upon first alert response in the PACU, subjects will be asked to provide pain scores for abdominal/pelvic pain and right subscapular pain using a VAS. Pain scoring will then be repeated in the PACU or postoperative holding area at hours 2 and 4, with a final pain scoring at home via phone call on postoperative day 1. Postoperative analgesics used

in the PACU and at home per patient report will be recorded along with length of PACU stay and length of hospital stay until discharge.

B. SETTING

List the locations, with descriptions, of where procedures will be performed:

Prisma Health Greenville Memorial Hospital, in the OR and the PACU.

1. Resources Available

List all research team members including contact details (e-mail addresses and telephone numbers):

Paul Miller, MD: Paul.Miller@prismahealth.org; 864-455-5890
Briana Rice, MD: Briana.Rice@prismahealth.org; 864-455-1607
Erica Robinson, MD: Erica.Robinson@prismahealth.org; 864-455-1607
Savannah Micolucci, MD: Savannah.Micolucci@prismahealth.org; 864-455-1607
John Van Deman, MD: John.VanDeman@prismahealth.org; 864-483-5732

Briefly describe the qualifications (include approximate years of research experience) of the PI and co-investigators as well as their specific roles in the study:

Dr. Miller: Current Vice Chair of Academics and Research for the Prisma Department of OBGYN; Professor, University of SC School of Medicine-Greenville; 30 years of research experience; will oversee recruitment, any adverse events, IRB submission, funding approval, eventual data analysis and publication.
Dr. Rice: Current fellow in Minimally Invasive Gynecologic Surgery (MIGS); will assist Dr. Miller with the above and be a participating surgeon.
Dr. Robinson: Current Vice Chair of Operations for the Prisma Department of OBGYN; Associate Professor, University of SC School of Medicine-Greenville; MIGS division member; 15 years of research experience; participating surgeon
Dr. Micolucci: Assistant Professor, University of SC School of Medicine-Greenville; 4 years of research experience; participating surgeon
Dr. Van Deman: Assistant Professor, University of SC School of Medicine-Greenville; MIGS division member; 17 years of research experience; participating surgeon

Describe availability/access to needed equipment and resources including access to the population of interest:

Patients will be recruited from the respective clinics of the participating surgeons noted above. The Greenville Memorial Hospital Central Pharmacy will assist with randomization and dispensing of study drug/placebo. Placebo capsules will be purchased from Compounding Solutions Pharmacy (1607 Laurens Road, Suite 110, Greenville, SC 29607: point of contact: Pam Bramlett, RPH; ph: 864-558-0507). Funding for study medications and personnel will be obtained from intradepartmental research funding sources. Funding budget will be uploaded into the IRB documents.

2. Multi-Site Research

If applicable, list sites involved in this study outside of Prisma Health and indicate the primary and satellite site(s):

N/A

C. PROPOSED INTERVENTION

1. Treatment

List the experimental treatment of interest and comparative treatment as applicable:
Patients will be randomized to receive preoperative acetazolamide 500 mg ER capsule or a matching placebo within one hour of scheduled incision time. There will be no other deviation from standard of care treatment.
2. Drugs
List the primary drug intervention of interest and any additional drugs used:
Acetazolamide ER 500 mg capsule
3. Devices
List the primary device intervention of interest:
None

D. POPULATION

Briefly describe the population of interest:
Patients scheduled to undergo TLH for benign indications (e.g., pelvic pain, endometriosis, uterine fibroids)
1. Inclusion Criteria
Describe the inclusion criteria for the population of interest:
NOTE – inclusion criteria should, at a minimum: identify the disease or condition people must have to participate, define the acceptable age range, and delineate all other factors required to be in the study.
Women (aged 21-65) undergoing TLH for benign indications with or without bilateral salpingoophorectomy, with or without cystoscopy, who are not undergoing concurrent reconstructive procedures.
2. Exclusion Criteria
Describe the exclusion criteria:
NOTE – exclusion criteria should focus primarily on the protection of participants, with careful consideration of criteria needed to exclude those for whom participation would be unsafe.
Allergy to acetazolamide or sulfonamides Known electrolyte disturbances Pregnancy Kidney failure or creatinine >1.5 Diuretic or lithium use Chronic obstructive pulmonary disease (COPD) or other lung disease Central nervous system disorders Liver disease Glaucoma Preoperative or chronic opioid use Diagnosis of fibromyalgia Preoperative shoulder pain Conversion to laparotomy Intraoperative bladder or bowel injury Inability to understand or utilize visual analog scale
3. Sample Size

If applicable, show the power calculation for the estimated sample size:

Based on previous literature (Pourladian et al., 2016), we conducted several power calculations for various means and respective standard deviations for VAS scores at first response, postoperative day 11, and overall average VAS score. We expect similar responses at our institution. N per group is presented here for power of 0.8-0.9 and an alpha of 0.05.

Computed N per Group – Postoperative day 1				
Index	**Nominal Power**	**Actual Alpha**	**Actual Power**	**N per Group**
1	0.800	0.0502	0.808	16
2	0.825	0.0502	0.833	17
3	0.850	0.0502	0.856	18
4	0.875	0.0502	0.875	19
5	0.900	0.0501	0.907	21

Computed N per Group – Overall VAS Scores				
Index	**Nominal Power**	**Actual Alpha**	**Actual Power**	**N per Group**
1	0.800	0.05	0.807	48
2	0.825	0.05	0.831	51
3	0.850	0.05	0.852	54
4	0.875	0.05	0.876	58
5	0.900	0.05	0.901	63

Given previous literature, current power calculations, and expectations for response rate (phone call) on postoperative day 1, we propose an of n=120 with n=60 in each study arm.

4. Local Number of Participants

List the number of expected participants within Prisma Health:

100

5. Study-Wide Number of Participants

For multi-site studies, list the number of expected participants in total (study-wide):

100

6. Recruitment Methods

Describe the recruitment process, including the source of participants:

NOTE – if the screening procedures are done as part of the study, they must be incorporated into this protocol with a description of the methods and their risks or discomforts. If participants are screened separately from the protocol, the method should be briefly acknowledged.
Subjects will be recruited from the clinic populations of each of the participating surgeons. After initial identification, their charts will be reviewed for inclusion and exclusion criteria by an assigned study coordinator. If they meet criteria, they will be informed of the study by their surgeon at their preoperative visit and will be asked to sign an informed consent document if they choose to participate.
If applicable, list and describe recruitment materials:
NOTE – recruitment materials should inform potential participants about the availability and nature of the study.
NA

E. SPECIFICS OF STUDY PROCEDURES

Describe all participant research procedures, preferably in chronological order and from the participant's viewpoint. State where procedures will be done and if inpatient admission is required. Identify the required and optional study procedures. Identify the risks discomforts, and inconveniences of each procedure and intervention:
• Patient is consented at preoperative appointment • Patient is randomized per study protocol • In preoperative area, patient reports a baseline pain score and a right shoulder pain score to the research nurse • Patient receives intervention or placebo in the preoperative area within one hour of proposed start of surgery • Patient undergoes surgery • When first awake and responsive in postoperative care, patient reports an abdominal/pelvic pain score and a right shoulder pain score • Pain scores are repeated at two and four hours postoperatively • Patient is given a copy of a visual analog scale to take home with them from the PACU or short-stay unit • Patient receives a phone call from a research coordinator at 24 hours postoperatively for report of pain scores and analgesics used • Patient's chart will be abstracted and analgesic use in the perioperative period will be calculated in morphine equivalents
Describe all standard care procedures related to this study, preferably in chronological order and from the participant's viewpoint:
Except for administration of study drug or placebo preoperatively, the patient will receive standard of care.
If applicable, differentiate the procedures or combinations or schedules of the same procedures between study cohorts:
None
If applicable, describe the plans for the participants' end of participation, including transfer of care back to their own physicians:
None

1. Study Timelines

List the duration of individual procedures and cumulative time commitment, including number and timing of visits and total duration of participation in the study:

NOTE – the duration of the study should reflect the disease or condition and intervention being studied. Define the frequency of study measurements needed to capture the primary outcome measure.

All prospective collection of data will be completed by 24 hours after surgery

2. Study Endpoints

For clinical trials, list the study endpoints:

Study endpoints will be a phone call for pain scoring 24 hours postoperatively, breach of study protocol, or voluntary withdrawal.

3. Outcome Measures/Data

List all outcome measures/data that will be collected including explanations/definitions of measures as necessary:

- Abdominal/pelvic pain and right subscapular pain rated on a VAS at five perioperative points
- Total analgesic use perioperatively
- Demographic data, medications, surgical data, length of stay – per Data Sheet

4. Data Collection Methods and Instruments Used

Describe how data will be collected including a copy of the data collection instrument/data collection form:

Data will be collected from the electronic medical record and from direct patient interview by the surgeon, research coordinator, and PACU nurses. All data will be entered into a secure REDCAP file within the Research Division of the Department of OBGYN. Participants will be deidentified and will be given an alpha-numeric identifier.

5. Data Management

Describe the data monitoring procedures to assist in determining trends that affect the integrity of the study or participant safety. Include details on who will monitor, what they review, and how frequently data is reviewed. Also include any policies and procedures if a problem is identified, and the study needs to be suspended or stopped:

Investigators will monitor participants for any adverse events during participation to identify any trend that may indicate a risk to subjects. If such a risk is identified, the study will be halted until evaluation can be completed. Interim analyses will occur after 30 and 50 subjects have been enrolled to assess for any adverse effects.

6. Data and Specimen Banking

Describe the storage and management plan of research samples and/or data to assure their integrity and availability for analyses to fulfill the objectives of the study:

NOTE – clearly articulate if samples and data will be retained after the study is complete, whether data and/or samples may be shared with others, the purposes for which they may be used, and any restrictions on use. The protocol management plan must reflect information in the consent form on the additional use of data and samples. If participants are offered options, the participants' choices as to further use should be outlined.

Randomization scheme will be maintained and available to unblinded team members by the Research Pharmacy. Data will be kept in REDCAP in an encrypted format for 5 years after study completion.

7. Statistical Analysis

Describe how the data and samples will be analyzed to achieve all study objectives:

Sociodemographic characteristics will be assessed using Chi-square test or Fishers Exact test where appropriate. Data distribution will be assessed for normality using Kolmogorov–Smirnov test. A multivariable linear regression will be used to analyze the association between treatment and VAS pain scores over time. This will allow us to account for the treatment effect (between-subject factor) and the within-subject effect of VAS overtime. Accounting for the within-subject effect is critical because of the subjective nature of pain scores. Significance is defined as $p<0.05$.

V. ETHICAL CONSIDERATIONS

A. RISKS AND POTENTIAL BENEFITS TO PARTICIPANTS

1. Risks to Participants

Define the study as "minimal risk" or "more than minimal risk" considering all risks and burdens of participation:

NOTE – If there are multiple study populations and the overall risk and benefit is different for individual populations, then define the risk for each population separately.

Minor increase over minimal risk as the treatment includes an FDA approved medication

Describe in detail all risks to participants (consider the physical, social, and psychological implications of the research):

The study drug is already FDA approved and has a low side effect profile. The placebo is an inactive

2. Potential Benefits to Participants

Describe any benefits to participants:

NOTE – the classification of benefit should be weighed based on reasonable expectation of benefit for the individual participant. The possibility of indirect benefit, such as gaining generalizable knowledge may be sufficient depending on the nature and risks of the study.

Subjects may have improved postoperative pain.

B. PARTICIPANT CONFIDENTIALITY AND PRIVACY

1. Participant Confidentiality

Describe the plan to protect participant confidentiality including controls on storage, handling, and sharing of data. If applicable, include a schedule for destruction of identifiers associated with the data:

NOTE – confidentiality is the researcher's agreement with participants about how their identifiable private information (data) will be handled, managed, and disseminated. It protects the participants' personally identifying data and records. Confidentiality can be maintained by assigning records, data, and samples a code that does not embed personal identifiers and keeping the key to the code separately and securely. Further protections may include limiting access to identifiable data and the key to the code, and keeping records secured in double-locked storage and on secure, protected servers and computers.

Research staff will be trained in protection of patient confidentially. Captured data will be maintained on password protected electronic files, accessed through password protected computers that are housed behind locked office doors.

2. Provisions to Protect the Privacy Interests of Participants

Describe the plan to protect participant privacy, including how the investigator(s) will access information from or about participants:

NOTE – privacy refers to a person's desire to control the access of others to themselves (concerns people). Consider the methods used to identify and contact potential participants, the settings in which an individual will be interacting with

an investigator, and the appropriateness of having all personnel present for research activities. Consider the methods used to obtain information about participants, the nature of the requested information, and how to access the minimum amount of information necessary to complete the study.
Individual patient data collected as part of this investigation will remain confidential. Composite results from this investigation, however, will be disseminated to the scientific community. The data sheet will contain the patient's name and medical record number for later chart review. Actual data collection will only be performed by the investigators for their study or their designated research personnel. Once the data are collected, each patient will be assigned an alpha-numeric identifier which will allow entry of de-identified data in a computer database. The original data sheets will be stored in a secure location in the Department of Obstetrics and Gynecology.

C. VULNERABLE POPULATIONS

Describe any vulnerable populations required to complete the study objectives as well as the plan to offer extra protection of confidentiality and privacy:
NOTE – for studies enrolling minors, it should also be determined if a "more than minimal risk" study is no more than a minor increment over minimal risk. For minors, the risk level of the study, along with consideration of whether there is direct individual benefit, determines whether the study fits into a category of approvable research.
None

D. CONSENT PROCESS

Describe the procedures to provide informed consent to potential participants:
NOTE – be sure to include any therapeutic alternatives (may include standard care). It should be acknowledged if the drug, device, or intervention under study can be obtained outside of the study, such as through a prescription for off label use. Clearly describe risks and potential benefits including confidentiality and privacy risks. Clearly delineate who will have access to the participant's information and under what circumstances data may be shared (i.e., with government agencies, sponsors, etc.).
When obtaining consent, required federal regulations will be incorporated into the consent process. Participants will be given information in a language they understand. This study will have both English and Spanish consent versions available. Participants will be allowed ample time to review consent form. Any questions will be answered by study investigator. Subject will voluntarily sign and date the IRB approved ICF prior to any study activity. The participant may withdraw consent at any time. If the participant chooses not to participate in the study, they will receive usual care.

E. PARTICIPANT ECONOMIC BURDEN/COMPENSATION & OTHER STUDY DETAILS

1. Economic Burden to Participants
If applicable, describe any potential economic burdens to participants:
None
2. Compensation for Research-Related Injury
If applicable, provide details on the amount, method, and timing of compensation:

NOTE – if there are more than one study cohort, include descriptions if they will be compensated differently.
None
3. Debriefing Participants
If applicable, describe the procedures to debrief participants including what data and information will be released:
Patients may request to see a copy of any publication that results from this study.
4. Community-Based Participatory Research
If applicable, describe the details on Community-Based Participatory involvement with this study:
Note – "Community-based Participatory Research (CBPR)" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

VI. BIBLIOGRAPHY

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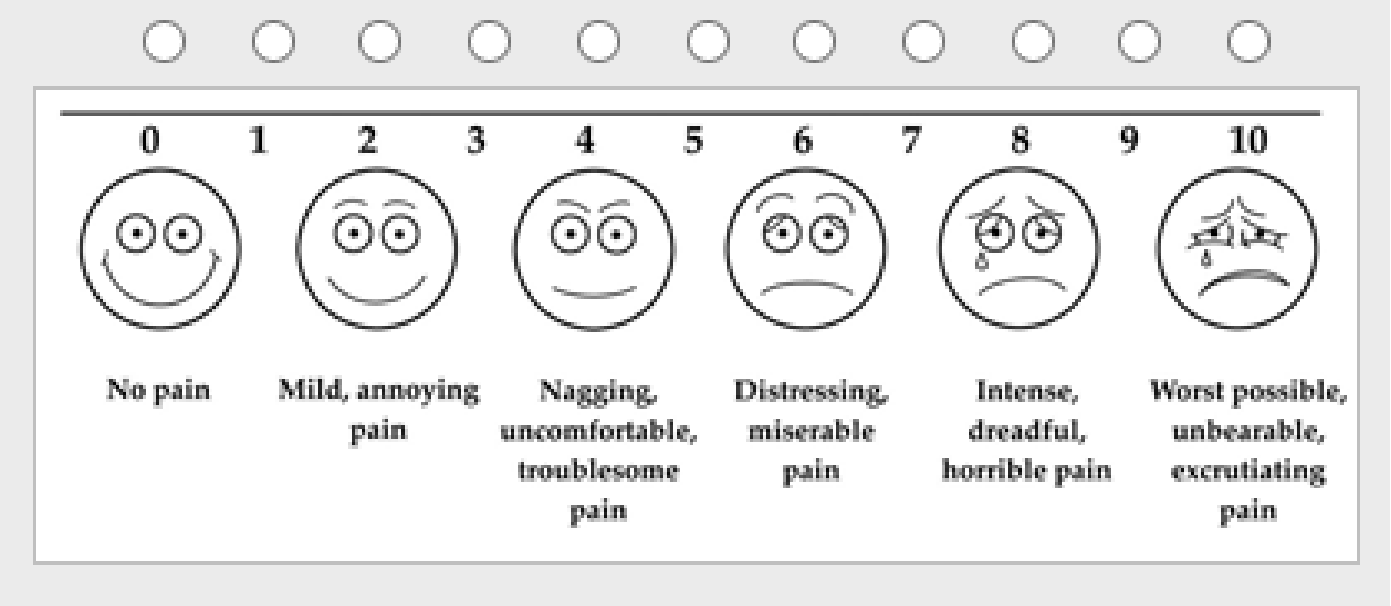
Woehlck HJ, Otterson M, Yun H, Connolly LA, Eastwood D, Colpaert K. Acetazolamide reduces referred postoperative pain after laparoscopic surgery with carbon dioxide insufflation. Anesthesiology 2003;99:924-8

VII. APPENDICES

Appendix 1: Visual Analog Pain Scale



Appendix 2: Enhanced Recovery After Surgery Protocol

	MIGS total laparoscopic hysterectomy cases
PRE-OP	☐ Clear liquids up until 3 hours before surgery ☐ Acetaminophen 650 mg po
INDUCTION	☐ Midazolam prn ☐ Propofol ☐ Ketamine bolus 0.5 mg/kg ☐ AVOID FENTANYL
MAINTENANCE	☐ Muscle relaxant and volatile anesthetic ☐ Ketamine infusion at 4 mcg/kg/min. One hour prior to case finish, reduce to 1 mcg/kg/min ☐ Lidocaine infusion at 2 mg/min ☐ If adequate anesthesia but tachycardic, consider beta blocker ☐ If adequacy of anesthesia difficult to assess, then consider BIS monitor ☐ CRNA and anesthesiologist will confer together as to the need for narcotic. If deemed necessary, use longer acting such as hydromorphone in lowest possible dose ☐ Ketorolac 30 mg IV at end of case
IVF MANAGEMENT	☐ Receives a TOTAL of 1 liter from pre-op to induction, then IVF's go on pump starting with bag #2 at 3 ml/kg/hr for closed cases ☐ If fluid bolus needed, consider colloid
PACU	☐ Adjust ketamine infusion within 1-5 mcg/kg/min to achieve lowest effective dose (dysphoria increases at doses > 4 mcg/kg/min) ☐ Discontinue lidocaine infusion in PACU ☐ IVF's at 3 ml/kg/hr ☐ May use IV acetaminophen or hydromorphone prn