Effect of intraperitoneal Bupivacaine on postoperative pain control in patients undergoing pelvic organ prolapse repair

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Abbreviations

This page is optional. The list below includes some common abbreviations. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

1.0 Background & Rationale

First introduced in the 1990's, enhanced recovery after surgery (ERAS) is a multimodal perioperative approach to surgical recovery, shown to lead to early recovery and improved outcomes (1). One of the primary objectives of ERAS programs is appropriate pain control with reduction of postoperative opiate consumption. The mainstay by which most ERAS programs accomplish this goal is an interplay between NSAID's, acetaminophen and local anesthesia. For patients undergoing pelvic organ prolapse repair -following implementation of ERAS programs- it has been shown that patient post discharge recovery is greatly improved and that postoperative opiate consumption is significantly decreased (2,3). In one study of patients undergoing open gynecologic procedures, they were found to have a reduction of mean opioid consumption of 72% with 16% of the patients opioid free prior to discharge (4). Additionally, it has been well documented that patients who undergo gynecologic or pelvic reconstructive surgery are overprescribed opiates at the time of discharge (5). It is recommended that opiate naïve patients be discharged with no more than 15 doses of a given narcotic and that these patients be individualized, as many will require less (5,6).

One of the more controversial and under-investigated aspects of postoperative pain control in the field of Female Pelvic Medicine and Reconstructive Surgery (FPMRS) is the use intraperitoneal local anesthesia.

The two type of peritoneum in the human body are the parietal peritoneum (PP) and visceral peritoneum (VP). The PP is innervated by the somatic nervous system, leading to the perception of localized, sharp pain (7). The VP has sub-mesothelial tissue innervated by the autonomic nervous system, responding to traction, distension and pressure, leading poorly localized, dull pain (7). We also know that the peritoneum is a highly permeable membrane given its long-term use in peritoneal dialysis (8). Due to blockade of free afferent peritoneal nerve endings, it is plausible that intraperitoneal local anesthesia has a role in management of postoperative pain.

It has been documented that infiltration of local anesthetics has been shown to effectively control postoperative pain for patients undergoing laparoscopic, open and vaginal gynecologic procedures (9, 10, 11), but data is still limited as to the role of intraperitoneal local anesthetic lavage during pelvic reconstructive surgery. Two studies looking at the use of intraperitoneal lidocaine lavage at the time of total abdominal hysterectomy found that this offered improvement of pain control for 12 to 24 hours following the procedure with no associated reduction in opiate consumption (12, 13). In contrast, an RCT performed looking at the effectiveness of intraperitoneal Bupivacaine following laparoscopic pelvic surgery, appreciated significant improvement in pain (as demonstrated on a visual analog scale) and a decrease in analgesic requirement (14). There is also literature demonstrating improvement in patients perceived intraoperative discomfort at the time of postpartum tubal ligation, who receive intraperitoneal lidocaine (15).

While there are some studies in gynecologic literature, most studies are present in anesthesia, general surgery, colorectal surgery and bariatric surgery literature (9, 16-20). In a systematic review of 41 RCT's, 13 trials were identified comparing intraperitoneal Bupivacaine vs Lidocaine vs saline for patients undergoing laparoscopic cholecystectomy (9). In that review, seven of the 13 trials reported improved pain relief compared to placebo, with effects lasting between 2-24 hours (9). A recent RCT from bariatric surgery literature evaluated the effects of intraperitoneal

Bupivacaine vs placebo in patients undergoing bariatric surgical procedures. In this study, 106 patients were assigned to receive intraperitoneal lavage with 50 mL of 0.2% Bupivacaine or the same volume of normal saline during the procedure. Using a VAS, patients postoperative pain was rated at 1, 4, 8 and 24 hours after surgery. This study found statistically significant decreased pain scores and opiate consumption among the Bupivacaine group for the first 24 hours after surgery (19). Studies have also been performed evaluating the use of intraperitoneal Bupivacaine vs Tramadol for management of postoperative pain during same day laparoscopic surgery. In a randomized trial of 90 patients assigned to intraperitoneal Bupivacaine (20 mL at 0.25%), IV tramadol hydrochloride (2 mg/kg), intraperitoneal saline (20 mL) or IV saline (2 mL) appreciated better analgesic outcomes among the Bupivacaine group (21).

Of the local anesthetic options available, Bupivacaine is known to have a longer duration of action compared to its counterparts (22). The maximum dose of Bupivacaine that should be administered is 2.0 mg/kg without epinephrine and 2.5 mg/kg with epinephrine (22). Therefore, the maximum allowable dose of Bupivacaine without epinephrine 0.25% should not exceed 56 mL in a 70 kg patient. While toxicity caused by local anesthesia can have CNS (nausea, vomiting, chills, pupil constriction, tinnitus, nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest as noted in the package insert) and CVS (depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest as noted in the package insert when high doses or unintentional intravascular injection is administered) manifestations, these formulations have relatively wide safety margins and toxicity only occurs when these thresholds are exceeded (22, 23). One systemic review set out to evaluate the safety profile and systemic levels of local anesthesia following intraperitoneal administration (23). In this review, 415 patients were included, 11 (2.7%) were found to have systemic levels close to or above threshold and no cases of clinical toxicity were observed (23).

The purpose of this study is to evaluate the effects of 30 mL intraperitoneal Bupivacaine without epinephrine 0.25% on postoperative pain control in patients undergoing pelvic organ prolapse repair. We hypothesize that use of intraperitoneal Bupivacaine will decrease postoperative pain scores and opiate consumption in the postoperative period, following pelvic organ prolapse repair.

2.0 Objective(s)

2.1 Primary Objective
2.2 Secondary Objective

2.1: To determine whether intraperitoneal Bupivacaine will decrease pain scores at approximately 4 hours, as determined by a numeric rating scale (NRS) in patients undergoing pelvic organ prolapse repair.

2.2: Pain scores as determined by NRS at approximately 8, 12 and 24 hours, total opiate consumption postoperatively while inpatient as determined by morphine milligram equivalents (MME), time to first narcotic dose during inpatient stay, and hospital length of stay.

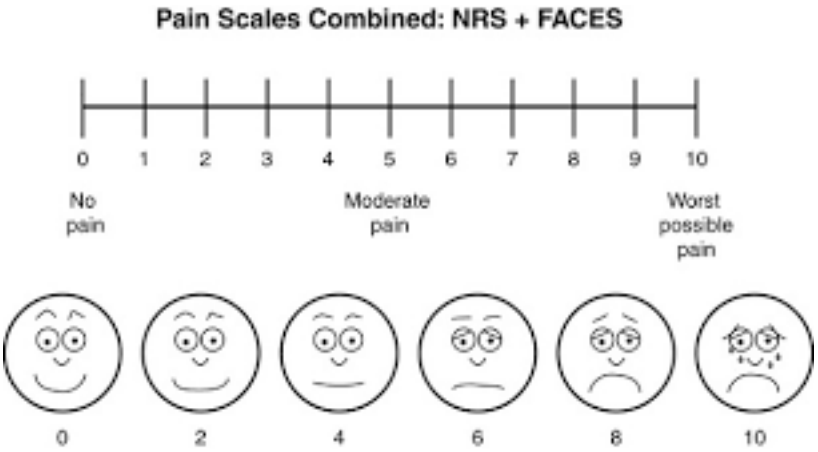
3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures
3.2 Secondary Outcome Measures

3.1: Patient pain will be measured by means of a NRS at 4 hours after surgical pelvic organ prolapse repair.

3.2: Patient pain will be measured by means of a NRS at 8, 12 and 24 hours after surgical pelvic organ prolapse repair. Total opiate consumption will be measured in MME, obtained from the electronic medical record. Time to first narcotic dose will be measured in hours and minutes. Hospital length of stay will be measured in days, hours and minutes.

Patients receiving an opioid prescription after short stay surgeries have a 44% increased risk of long term opioid use. The first 4-24 hours postoperatively is the time when these prescriptions are provided. With appropriate control of postoperative pain in the first 4-24 hours, patients may be able to be discharge without opiate prescription.



4.0 Eligibility Criteria

4.1 Inclusion Criteria

List the criteria:

- Age >= 18 years
- Access to cell phone with text messaging capabilities (for same day surgery discharge)
- Patients undergoing pelvic organ prolapse repair with peritoneal access

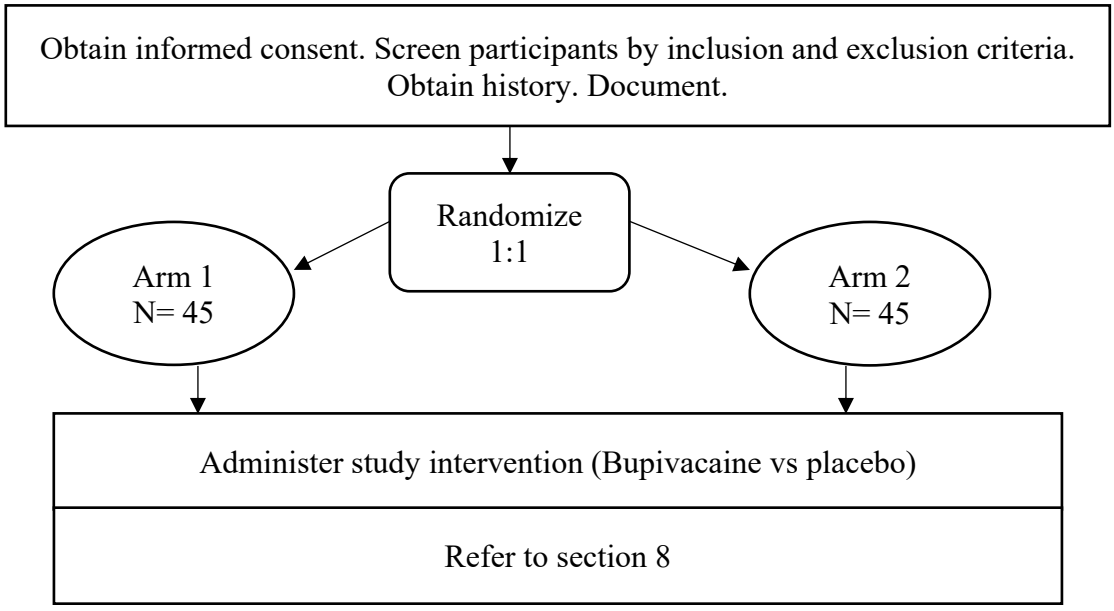
4.2 Exclusion Criteria

List the criteria:

- Bupivacaine allergy
- History of epilepsy or other seizure disorder
- EKG demonstrating asymptomatic sinus bradycardia <40 bpm, symptomatic sinus bradycardia <60 bpm, first degree AV block, second degree AV block, third degree AV block, prolonged QT, atrial fibrillation, supraventricular tachycardia, or myocardial infarction
- Chronic liver disease proved by any ALT or AST elevation greater than 2x upper limit of normal
- Serum bilirubin elevation in excess of 5 mg/dL
- G6PD deficiency
- Weight less than 100 lbs
- Chronic opiate use

5.0 Study Design

This will be a double blinded randomized controlled trial. This is the ideal study design as it will serve the purpose of measuring the effectiveness of an understudied intervention (intraperitoneal Bupivacaine) in the management of postoperative pain. Randomization and blinding will help to reduce bias and better assess cause-effect relationships between the intervention and outcome. This study will be done in conjunction with Investigational Drug Services (IDS), who will manage randomization and blinding according to their division protocols. Covariate to be collected include age, BMI, menopausal status, type of surgical procedure, surgical time, and intraoperative complications (Y/N).



6.0 Enrollment/Randomization

The patients will present to the office for a preoperative visit. At that appointment, the patient will be screened based on the inclusion and exclusion criteria. Consents will be obtained at that visit by a fellow or faculty in the female pelvic medicine and reconstructive surgery (FPMRS) department.

Alternatively, patients can be screened by scheduled operation date and informed of the study during a preoperative phone call. In these circumstances, patients will be consented on the day of surgery. Consents will be obtained by a fellow or faculty in the FPMRS department.

This study will be done in conjunction with Investigational Drug Services (IDS), who will manage randomization and blinding according to their division protocols. This will be done by means of a randomization log that is provided to IDS by the statistician involved.

Patients will be randomized 1:1 to the two pain strategies using stratified randomization with surgery technique being the strata. Block randomization will be used with blocks of size 4. Randomization lists will be constructed by the study statistician using statistical software.

7.0 Study Procedures

In the study, patients will be randomized to one of two groups. Arm 1 will be participants who receive intraperitoneal bupivacaine and arm 2 will be participants who receive placebo (saline).

All patients involved in the study will be undergoing pelvic organ prolapse surgery with peritoneal access and will receive either 30 mL of 0.25% Bupivacaine or 30 mL of saline by means of intraperitoneal lavage. This will be performed at which point peritoneal access will no longer be available, and the solution will be left in the abdomen upon completion of the procedure.

Preoperatively, patients will receive a standardized pain control regimen of Ibuprofen and Tylenol in accordance with hospital ERAS protocol. Postoperatively, patients will receive standardized pain control regimen of Ibuprofen and Tylenol in accordance with hospital ERAS protocol. Patients can be given as needed narcotics if pain is poorly controlled on the initial regimen.

All patients will have pain scores measured at approximately 4 hours using a NRS following completion of the procedure. All patient will have pain scores measured at approximately 8, 12 and 24 hours by means of text message NRS (in the event of same day surgery discharge) vs inpatient in person NRS (for planned admission), following completion of the procedure, which will be stored directly into REDCap. Time to first narcotic dose will be obtained through the hospital electronic medical record. Hospital length of stay will be obtained through the hospital electronic medical record.

8.0 Study Calendar

Enrollment	Surgery day	4h	8h	12h	24h

Consent	Either intervention or placebo	Pain assessed with NRS	Pain assessed with NRS	Pain assessed with NRS	Pain assessed with NRS

9.0 Reportable Events

Adverse Event (AE):

Any medical occurrence in a human study participant, assessed by the principal investigator (PI) that is:

- Unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, and the characteristics of the subject population being studied
- Related or possibly related to study participation
- Suggests that the research places subject(s) or others at greater risk of harm than was previously known.

Serious Adverse Event (SAE):

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity

AE's and SAE's will be reported as required in accordance with the IU HRPP Policy on Reportable Events..

10.0 Data Safety Monitoring

A data safety monitoring board (DSMB) composed of Douglass S. Hale (FPMRS faculty), Jennifer Hamner (FPMRS faculty), Elizabeth Fuller (FPMRS faculty) and Krystine Haglin (FPMRS fellow) will be scheduled to meet every 6 months and review the data for patient safety. This will be monitored as part of the Data Safety Monitoring Plan (DSMP): data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects.

The purpose of this committee will be to evaluate logistical problems and determine if the study should be stopped. Examples of logistical problems would include enrollment rates, follow up rates, or dropout rates. Reasons to stop the study would include if the objective is met prematurely, if the study gives sufficient data against the premise, if the study is proven to be futile, or if there is high index of suspicion that the intervention is harmful. The DSMB will also advise about study progress and performance, protocol changes, and if additional monitoring is necessary.

11.0 Study Withdrawal/Discontinuation

Participants will be withdrawn from the study if they refuse to answer the NRS at the approximate 4 hour mark. Participants may elect to discontinue their involvement in the study at any time. In events of participant withdrawal, we will assess if they would like complete withdrawal of all data or up to that point of their involvement.

12.0 Statistical Considerations

Sample size/Power

This is a double-blind randomized controlled study to compare two techniques of pain management strategies for woman undergoing advance-organ prolapse surgery with the primary outcome being the numeric rate scale (NRS) at 4 hours post-surgery. Secondary outcomes will be the NRS collected at 8, 12, and 24 hours, and an indicator of whether woman required opioids (Y/N) within 4 hours of surgery.

Assuming a SD = 2.14[2] in the NRS at 4 hours, to detect a meaningful change of 1.3 would be an ES = 0.60 (1.3/2.14). To have 80% power to detect an effect size of this magnitude (i.e., a 0.6 SD difference in the NRS between treatment arms) based on a two-sided two-sample independent t-test with type I error set at 0.05 requires a total sample size of N = 90 (45 per group). As we expect no attrition or missing data on the primary outcome, N = 90 will be our planned sample size.

Randomization

Patients will be randomized 1:1 to the two pain strategies using stratified randomization with surgery technique being the strata. Block randomization will be used with blocks of size 4. Randomization lists will be constructed by the study statistician using statistical software.

Statistical Methods

Descriptive statistics of N, mean, standard deviation, median, minimum, and maximum or frequency and percent will be provided for all baseline characteristics overall and by treatment arm. Baseline characteristics which will be reported include surgical procedure (uterosacral ligament suspension vs sacrocolpopexy), age, BMI, menopausal status, surgical time, and intraoperative complications. Intraoperative complication will be a dichotomous variable of whether any complication occurred (Y/N). Baseline characteristics will be compared between the two study arms to verify randomization achieved balanced groups. Any characteristics that significantly differ will be considered in subsequent analyses.

Assuming baseline characteristics are balanced between the two study arms, we will use a linear mixed model fit to all timepoints (4, 8, 12, and 24 hours) with effects of surgery technique, treatment group, time, and the time x treatment group interaction to estimate the mean difference in treatment groups at each time point. All model assumptions will be checked for adequacy. The mean difference and 95% confidence interval at each time point will be reported. A p-value of 0.017 will be used to indicate statistical significance in the NRS collected at the three other time points (8, 12, and 24) to maintain familywise type I error at .05. For

the dichotomous outcome of whether patients required opioids in the first 4 hours following surgery, a Fisher's exact test will be used.

Other outcomes can only be assessed among those that required opioids thus will have lower power. Thus, caution will be used in interpretation of results. These include the amount of MME in the first four hours and time to first dose. Descriptive statistics by study group will be estimated. For outcomes which may be normal, then a linear regression model will be fit with effect of surgery technique and treatment, to estimate the mean difference in the outcome by treatment and associated 95% confidence interval. If any outcome is non-normal, then a generalized linear regression model will be used instead with an appropriate distribution and link function to detect the effect of treatment.

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13.0 Statistical Data Management

Primary and secondary objective data will be collected and stored electronically in one REDCap. The storage location will be backed up automatically every day. Quality assurance steps will include testing of database by study team prior to moving to production mode. The following quality control methods will be used extraction and cleaning of data that will be used for analysis every 6 months.

14.0 Privacy/Confidentiality Issues

Every effort will be made to keep personal information confidential, but we cannot guarantee absolute confidentiality. No information which could identify participants will be shared in publications about this study. All data will be stored on an encrypted database (REDCap), and only team members who have appropriate training requirements will have access to private health information.

15.0 Follow-up and Record Retention

Data will be retained in accordance with the IU HRPP Policy on Research Data Management.

16.0 References

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