Cover Sheet

Title: Cytoscopic Antibiotic Irrigant to Reduce Postoperative Urinary Tract Infection
ID: IRB15-00769

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Study Protocol and Statistical Analysis

MATERIALS AND METHODS

This was an investigator-initiated double-blind randomized controlled trial approved by the Institutional Review Board at MetroHealth Medical Center in Cleveland, OH and registered with clinicaltrials.gov (CT03099863). We conducted and reported this study according to the consolidated standards of reporting trials guidelines for randomized controlled trials.[1] An independent data safety monitoring committee oversaw this trial. We had no extra-institutional funding.

DESIGN, SETTING, AND PARTICIPANTS

This study was performed between May 2016 and September 2019 at a single academic medical center. Adult women were eligible to participate if they were scheduled to undergo elective surgery by two female pelvic medicine and reconstructive surgery or minimally invasive gynecology surgery staff that would require intraoperative cystoscopy, including POP repair, mid- urethral sling placement (MUS), hysterectomy, and complicated excision of endometriosis. Cystoscopy is routinely performed with these procedures in our practice. Exclusion criteria included history of neurogenic bladder, recurrent UTIs, nephrolithiasis, congenital urogenital anomaly, allergy to neomycin or polymyxin, pregnancy, or surgery planned to include intradetrusor onabotulinumtoxin A injection, mesh excision, or fistula repair. Women were excluded if they were found to have a positive urine culture on routine preoperative testing, independent of symptoms, or from an intraoperative urine sample. All subjects provided written informed consent. Participation in this study did not have any direct benefit to individual subjects.

INTERVENTION, RANDOMIZATION, AND BLINDING

Patients were randomized 1:1 at the time of surgery into two groups based on the type irrigation to be used with intraoperative cystoscopy: control (normal saline) or antibiotic (Neosporin G.U. [200,000 U polymyxin B sulfate +40 mg neomycin sulfate] in 1 L NS). The randomization scheme was assigned by a statistician using randomization software in blocks of 10. Allocation was concealed in an opaque envelope until the time of randomization. The patients and attending surgeon, who performed all evaluation and treatment of postoperative UTIs, remained blinded. Neosporin G.U. (Pfizer, 200,000 U polymyxin B sulfate 40 mg neomycin sulfate) is Food and Drug Administration approved for short-term use as a bladder irrigant to prevent bacteriuria associated with the use of indwelling catheters.[2] The prepared solution is completely clear, bactericidal, and used as indicated, neomycin and polymyxin B are absorbed in clinically insignificant quantities.[2] A neomycin or polymyxin solution was used in Hares' 1981 cystoscopy irrigation study, has been used successfully in spinal cord injury patients with bacteriuria, and is well tolerated.[3,4,5] Additionally, the medication is inexpensive and readily available in our operating room pyxis.

STUDY PROTOCOL

At the time of surgery, the randomization allocation envelope was opened by the surgical fellow. If indicated, this individual prepared the antibiotic solution by injecting 1 ml of neomycin or polymyxin into 1 L normal saline. The fellow remained independent of postoperative UTI diagnosis and treatment for study participants. The steps of the surgery remained standard; the study protocol made no alterations to usual care involving patient preparation, intravenous antibiotics, and instrumentation. We routinely use cefazolin for antibiotic prophylaxis for all surgeries, with the addition of metronidazole for hysterectomy in premenopausal patients, except in the case of associated allergies. Upon routine urinary catheter insertion, a urine sample was collected and sent for culture. Patients with a positive intraoperative urine culture were later excluded from analysis.

Intraoperative cystoscopy was performed in normal fashion with the previously designated bag of irrigation fluid. At the completion of cystoscopy, the bladder was drained as per standard operating procedure. To determine the volume of fluid used during cystoscopy, the fluid bag was weighed before surgery and again after cystoscopy. A foley catheter was replaced per surgeon discretion. Upon hospital discharge, standardized post- operative instructions were given to all patients, including signs and symptoms of infections or other concerning postoperative sequelae.

Postoperatively, patients were called at three time points (3 days, 2 weeks, and 4 weeks after surgery) to assess for urinary complaints and adverse events, including patient-reported diagnosis and treatment of UTI. Subjects were treated for postoperative UTI per attending surgeon discretion.

OUTCOME MEASUREMENTS

The primary outcome was the rate of postoperative UTI within 6 weeks after surgery. The Center for Disease Control and Prevention's definition of a symptomatic UTI was adapted to include the following: (1) at least one sign or symptom accompanied by positive urine culture with ≥105 colony-forming units/ml, (2) symptomatic UTI with clinician decision to treat as reported by the patient, or (3) at least one sign or symptom with positive urine dipstick (UA).[6] Timing of diagnosis was recorded as either the date of the positive urine culture or the timing of the postoperative phone call when the patient reported treatment of a UTI (3 days, 2 weeks, or 4 weeks after surgery). A sensitivity analysis was performed of UTIs treated within 2 weeks of surgery and any adverse effects related to the use of antibiotic irrigation. We also evaluated outcomes in the subgroup who had a vaginal prolapse repair procedure, which was previously reported to be at highest risk for postoperative UTI.[7]

STATISTICAL ANALYSIS

Based on 20.3% incidence of postoperative UTI,[8] we determined that a sample size of 186 would provide 80% power to detect a 50% absolute reduction in postoperative UTI rates at a two-sided $\alpha = .05$. To account for an estimated 30% dropout rate with positive intraoperative urine culture or loss to follow up, we adjusted the total sample size to 242 patients total, with 121 subjects in each study arm.

Data was collected in our institutional REDCap database, and statistical analysis was performed with Stata version 15.1 (StataCorp). Covariates included in the analysis were patient-specific characteristics and medical comorbidities (age, race, obesity, smoking status, menopausal status, and history of Type 2 diabetes, recurrent UTIs, thyroid disease, asthma, hypertension, reflux dis- ease, depression, or anxiety) and volume of cystoscopy fluid used. Surgeries were characterized as primary vaginal or laparoscopic, and all concurrent procedures were noted. The randomized groups were compared using Pearson's $\chi 2$ test for categorical variables and the Student's t test for normally distributed continuous variables. Multivariable logistic regression analysis was used to adjust for possible confounding variables impacting the effect of antibiotic irrigation on postoperative UTI rates. Covariates significant on univariate analysis with $p < .2$ or with notable clinical relevance were included in the logistic regression. All results yielding $p < .05$ were deemed statistically significant.

FOOTNOTES

1. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
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