

Impact Of Catheter Size On Peri-Operative Pain After
Robotic Assisted Laparoscopic Prostatectomy

NCT04098809

06/20/2018

**IMPACT OF CATHETER SIZE ON
PERI-OPERATIVE PAIN AFTER
ROBOTIC ASSISTED LAPAROSCOPIC
PROSTATECTOMY**

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**IRB17-095
CRP17082**

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Background

Robotic assisted laparoscopic prostatectomy (RALP) is now the standard surgical approach to prostate cancer in the appropriate clinical setting. It is a commonly performed operation with an estimated 138,000 prostatectomies performed in 2010 in the United States¹. Well known post-operative complications such as urinary incontinence and erectile dysfunction make RALP a frequent target for improvement in post-operative outcomes.

Continence after RALP is usually the central peri-operative concern for most patients other than oncologic outcome. Additionally, week long catheter duration and urethral pain is frequently the most bothersome post-operative complaint. Given this, a significant amount of effort and technical considerations have been made to improve post-RALP continence rates and decrease anastomotic complications.

Many different approaches to the urethro-vesical anastomosis have been described aiming at improving post-operative continence. Typically, this anastomosis is sewn over a urinary catheter.

For example, some providers have advocated use of robotically placed suprapubic catheter drainage to improve post-operative pain and potentially improve anastomotic healing². Multiple studies have corroborated that SPT drainage was significantly less bothersome to patients, but that post-operative voiding parameters did not differ^{3,4,5}. Bladder neck sparing or reconstruction are other methods developed with the intent of improving continence rates. Many different techniques have been described, and some studies have found improved rates of continence with these approaches, usually by narrowing the urethral junction⁶.

Initially, many surgeons used larger catheters (22Fr) to promote an open anastomosis, but some groups have found this to be associated with fossa navicularis strictures⁷. As a result, most surgeons now leave an 18 or 20 French Foley catheter to drainage for approximately 1 week post-operatively⁷. Interestingly, no study to our knowledge has assessed whether catheter size has an impact on continence, post-operative pain, and long term complication rates such as bladder neck contracture. We would expect urinary flow rates to differ based on urethral or catheter diameter according to Poiseuille's law, and several studies have shown this to be the case⁸.

In this study, we will randomize our RALP patients to either a 16 French or 20 French catheter to assess the effect of catheter size on post-operative catheter pain. Additionally, we will investigate pads per day, urinary flow rates, post-void residual urine volume (PVR), International Prostate Symptom Scores (IPSS) and Quality of Life (QoL) score, as well as long term complications. We hypothesize that patients with a smaller catheter will have improved pain scores and less opioid use. In terms of return to continence, we predict that use of a smaller urethral catheter will decrease flow rates and consequently protect against urinary leakage without higher risk of urinary retention. We expect this group to use less pads per day at the 6 week post-operative visit. We do anticipate a higher risk of bladder neck constriction (BNC) would be expected as well in the long term given the smaller diameter anastomosis.

Study Purpose and Objectives

The purpose of this clinical study is to assess the effect of catheter size on post-operative catheter pain, urinary continence, urinary flow rates, PVR, IPSS and QoL scores, as well as long term complications. The details of data collection are described in the "Data Collection Procedures" section below. Study objectives will be measured by:

Primary Outcome:

- Mean catheter related pain score on POD5-7

Secondary Outcomes:

- IPSS and QoL Scores at 6 and 12 weeks
- Opioid use after discharge until POD7
- Pads per Day at 6 and 12 weeks
- Urinary flow rate at 12 weeks
- PVR at 12 weeks
- Long-term complications at 12 weeks, 1 and 2 years

Risks and Benefits

As with any major surgery done under general anesthesia, there is a certain amount of risk, including heart attack, stroke and death. Preoperative assessment of a patient's overall health is part of the surgical workup at Virginia Mason Medical Center. Prostatectomies, including those done with a robotic-assisted surgery system, are also associated with the risks of impotence, incontinence, bleeding, infection, and bladder neck contracture.

Restoration of erectile function varies by patient and can be supported through the use of medications such as Viagra and Cialis and other types of treatment such as intraurethral suppositories or intracavernous injections.

Urinary continence depends on the internal, involuntary sphincter and the voluntary striated external sphincter. The internal sphincter is removed during RALP, as it is anatomically at the junction of the prostate and bladder. Practicing Kegel exercises returns function to the external sphincter after RALP and leakage can be decreased or eliminated over several weeks or months.

We would expect catheter size to impact urinary flow rates according to Poiseuille's law, and several studies have shown this to be the case⁸. We also anticipate that risks of anastomotic stenosis may be influenced by catheter size. We anticipate return to urinary continence and pain scores may be influenced by catheter size, which is the purpose of the study. Specifically, if randomized to the 16Fr group, we anticipate a possible increased risk of decreased urinary flow or bladder neck contracture in the future. If randomized to the 20Fr group, we hypothesize a possible risk of increased catheter related pain and time to regain post-operative continence.

Study design

This is a physician-sponsored, randomized, prospective study of patients identified to receive RALP. Patients will be eligible for this study if they:

- Are identified as candidates for RALP
- Are greater than 18 years of age

Patients will be excluded from the study if they:

- Have filled a prescription for opioid medications in the last 2 months. This will be reviewed by the medical record prescription history.
- Have a known latex allergy or are suspected to have developed an allergic response to the latex catheter during their clinical course.
- In whom pre-operatively, the catheter is anticipated to be left in place greater than 14 days based on clinical decision
- Have a significant deviation from the normal operative protocol such as significant bladder neck reconstruction or conversion to open (these patients will be considered a screen fail during the operation and will not be randomized to a certain catheter size)
- Have a history of pelvic radiation

In addition, patients who have a significant deviation from the normal post-operative course such as pulmonary embolism, myocardial infarction, stroke, or other major complications that are unrelated to study intervention but would impact outcome measures may be excluded from data analysis and further data collection per investigator's discretion.

Patient recruitment

Patients seen in pre-operative consultation by Virginia Mason Medical Center urologists will be assessed by the consulting surgeon for protocol eligibility at the time of consultation. The consent form will be reviewed with the patient in person, or by phone, at least 24 hours prior to surgery to allow time for consideration and questions. Patients may sign the consent anytime in the pre-operative setting before medication has been administered.

Early Termination

Patients may be discontinued from the study, per investigator's discretion, if any of the following conditions are met:

- Catheter remains in place greater than 14 days post operatively
- Lost to follow up (patient cannot be reached to schedule a follow up appointment after 3 attempts)
- Patient withdrawal of consent

Data Collection Procedures

Patient follow-up visits are routine and will occur at approximately 1, 6, and 12 weeks post operatively. Specific time point and methods of data collection are described below:

Post-surgical pain scores will be determined using a visual analog scale (VAS) with patients rating their mean post-operative pain on a scale from 1- No Pain to 10- Worst Possible Pain (Figure 1). Patients will be asked to indicate their pain specifically related to the catheter on this

scale. This information will be collected at POD7 just prior to catheter removal. This will be done in clinic if the appointment is that day or by telephone/mail/email/fax if the patient's appointment is not that day. A post-operative form including the VAS pain scale (Figure 1) and a pre-paid mailing envelop will be given to the patient in their study packet.

Opioid use will be collected at POD7 using the post operative pain form (Figure 1). Patients will be asked to count the number of pills left in their opioid prescription to determine number of tabs taken from discharge to POD7. If the patient is discharged after POD1, opioids taken as an inpatient on POD2 from the medical record will be included in opioid use. All opioid data will be converted a standardized morphine equivalency for comparison.

Pads per day: The patient will be asked to indicate the number of pads per days they are using. This data will be collected at 6 and 12 week follow up visits. This will be done in clinic if the appointment is that day or by telephone/mail/email/fax/REDCap (patients contact information, including email address, will be obtained from Cerner when available or by asking patient) if the patient's appointment is not that day. We recommend use of the Depend® Incontinence Guard for men (<https://www.depend.com/mens-solutions/products/10544>), or a comparable generic version.

International Prostate Symptom Score (IPSS) and Quality of Life Score: This validated questionnaire is an 8 question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of prostate disease. This is a clinician rated, validated scale. It will be administered and scores collected at the 6 and 12 week follow up visits. This will be done in clinic if the appointment is that day or by telephone/mail/email/fax/REDCap (patients contact information, including email address, will be obtained from Cerner when available or by asking patient) if the patient's appointment is not that day.

PVR: Post void residual volumes will be measured by having the patient void to their best effort (into a uroflowmeter described below) and then using a standard suprapubic bladder scanner to measure the remaining urine volume immediately after voiding. This will be measured at the 12 week follow up visit per investigator's discretion if clinically indicated.

Urinary flow rates will be measured by using a uroflowmeter. The patient voids into the device and is records the max flow rate, void time, and voided volume. This will be be measured at the 12 week follow up visit per investigator's discretion if clinically indicated.

Post Operative Complications will be recorded during the hospital stay or at clinic follow up visits and include any significant deviation from the normal post-operative course. Transient and permanent complications will be evaluated as part of this trial. At the long term follow up visits at 1 and 2 years, investigators capture long term complications such as bladder neck contracture.

Timing of Data Collection

Follow up visit #1 will occur 7 days +/- 7 following discharge, although as indicated above, pain scores and opioid use will be collected on POD7 regardless of clinic visit day. If the clinic appointment is not on POD7, we will collect this data by telephone or by mail. Timing of catheter

removal will be determined by the surgeon and is not affected by the study. Follow up visit #2 will occur 6 weeks +/- 4 weeks following discharge. Follow up visit #3 will occur 12 weeks +/- 5 weeks following discharge to account for patient availability. Patients will have annual follow-up thereafter and long term complications such as bladder neck contracture (BNC) will be recorded at 1 and 2 years post treatment (+/- 3 months). No other study data will be collected at these long term follow up visits. The specifics of how data will be collected and analyzed for each outcome are listed below.

Duration of Study participation

It is estimated that each patient who enrolls in the study and completes the routine follow-up visits will be participating for approximately two years.

Treatment Methodology and Statistical Considerations

Patients will be randomized by chance to either a 16 French or 20 French catheter in a 1:1 ratio. Subjects will be randomly assigned to either the standard of care or multi-modal group using Microsoft Excel ® randomization function.

A 2 year follow-up was chosen to allow for transient postoperative abnormalities to resolve so that the incidence of both transient and permanent complications can be evaluated.

Statistical evaluation of this study was completed by Axio during protocol development to ensure proper design and statistical power. We will use an ANOVA statistical variance model to test the hypothesis that the 20Fr group will have a higher mean pain score than the 16 French group. Secondary outcomes will also be measured with ANOVA analysis.

Sample Size and Accrual

We performed a pilot study of 25 patients to assess catheter related pain after transurethral resection of the prostate. Using this data, we calculated an average and standard deviation for catheter related pain of 3.2 and 2.45 respectively. In order to detect a difference in pain score of 0.6 between groups, at a power of 80% and alpha of 5%, we determined 44 patients should be included. Predicting a dropout rate of 20%, we plan to enroll approximately 55 patients to achieve 44 patients with full participation.

Data Monitoring

The Clinical Research Program will assess the risk of this trial and will devise and implement an internal monitoring and/or auditing plan for this trial. This plan will be revised as necessary during the life of the trial based upon a variety of factors, including but not limited to: protocol amendments, staff turnover, enrollment metrics, and compliance issues noted. An interim data analysis at 15 patients will be performed to assess pads per day, pain scores between groups, and assess for any difference in complications. If there is a significant difference in major post-operative complications, or patient safety concerns, the study will be terminated.

Data Analyses

Variables to be included in data analysis include aspects of the patient's history as outlined above. Additionally, operative details such as bladder neck reconstruction, change in technique from the stand running robotic vesico-urethral anastomosis or other significant alterations from the standard RALP approach will be included.

Outliers will be double-checked for accuracy. Subjects lost to follow-up will be included in short-term analysis only. Missing post-op data will be evaluated on a case-by-case basis with likely only long-term data being an issue. Missing operative data will be clarified with the operating surgeon. Any data that are not able to be collected with reasonable efforts will not be considered protocol deviations. Data analysis will specifically include risk ratios with 95% confidence intervals for those factors outlined above.

DATA COLLECTION

Records Keeping

Records and data will be kept using a password protected database. Paper source, including signed Informed Consent Form (ICF), will be stored in a secure location for the duration of the trial and securely archived for 10 years following study closure.

Secure Storage of Data

After data collection only de-identified data sets will be used for analysis and further study.

HUMAN SUBJECTS

Institutional Review Board (IRB) Review and Informed Consent

This protocol, the ICF and any subsequent modifications will be reviewed and approved by the IRB at Benaroya Research Institute at Virginia Mason. A signed ICF will be obtained from each subject.

Subject Confidentiality

All study data will be recorded in a password protected database. All computer entry and networking programs will be done using SID's only. Paper source will be stored in a secure location with access limited to study staff, Clinical Research Compliance Department staff, and outside regulatory bodies such as OHRP and FDA. Clinical information will not be released outside of the study team without written permission of the subject, except as necessary for monitoring by CRP Compliance, the FDA, and/or OHRP.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the Principal Investigator, IRB, OHRP, the FDA or other Government agencies as part of their duties to ensure that research subjects are protected.

PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Clinical Research Program. Any presentation, abstract, or manuscript will be made available for review by the Benaroya Research Institute prior to submission. No patient identifying information will be included in any publication or presentation of study results.

Figure 1 – Post-Operative Form

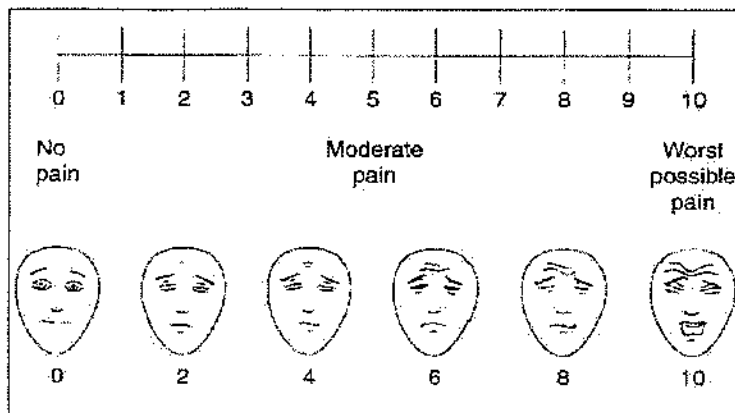
Virginia Mason Post-Operative Catheter Symptom Assessment

Name: _____

Date of Surgery: _____

Please fill out the following form on the 7th day after surgery (day of surgery is day 0, not 1)

1. Please circle your average catheter pain level at home within days 5-7 after surgery:



2. Please indicate how many tablets of opioids (oxycodone) you have taken at home (not in the hospital) in the first week since leaving the hospital. _____ tabs

Thank you for taking this survey. Please mail it back to Virginia Mason Urology using the pre-paid envelope included in your packet. If you lost the envelope, or you have questions, please call us at 206-583-6430.

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Schedule of RALP Study Procedures and Assessments

Study Day/Visit Day	Screening Day -28 to 0	Day 0	Day 7 (± 7 days)	Week 6 (± 4 weeks)	Week 12 (±5 weeks)	1 year (+/- 3 months)	2 years (+/- 3 months)
Informed consent	X		X	X	X	X	X
Baseline conditions	X		X	X	X	X	X
Randomization	X						
Medications	X		X	X	X	X	X
Physical exam	X		X	X	X	X	X
Vital signs	X		X	X	X	X	X
Medical history	X		X	X	X	X	X
Disease assessment	X		X	X	X	X	X
RALP performed		X					
Pathology Recorded *			X				
Day of Discharge			X				
Day of Catheter Removal			X				
Catheter Pain Score			X				
Home post-op opioid use			X				
IPSS/QoL score				X	X		
Pads per Day				X	X		
Max Urinary Flow**					X		
PVR**					X		
Long-term complications					X	X	X

*Pathology to include weight of gland, stage, gleason score, extra-capsular invasion, seminal vesical invasion, and pelvic lymph node dissection

**Will be obtained per investigator's discretion if clinically indicated.