

1) Protocol Title

Title: *Oxybutynin for post-surgical bladder pain and urgency*

Protocol Version Date: *February 7, 2019*

2) Objectives

Bladder pain and urgency are common after bladder surgery. Our objective is to determine if transdermal administration is superior to oral administration in alleviating pain and urgency.

3) Background

Pain after bladder surgery is typically controlled with narcotics, non-steroidal anti-inflammatory medications, acetaminophen, regional anesthesia (caudal or epidural) and/or bladder muscle (detrusor) antispasmodic medication. It is often difficult to distinguish bladder pain from a sensation of urinary urgency and most likely patients are experiencing both sensations despite the bladder being empty from the indwelling catheter.

Prior studies on adults have demonstrated the efficacy of preoperative oxybutynin and other antimuscarinics on decreasing catheter-related bladder discomfort in the postoperative period. For pediatric bladder surgery very few studies have been published. Intravenous ketorolac, epidural and caudal analgesia and intravesical ropivacaine have been shown to decrease postoperative bladder spasms. Intravesical oxybutynin has been used in the operating room in adults to decrease post-operative ureteral stent pain.

For open bladder surgery our current pain management standard is intra- and postoperative ketorolac (Q6hrs) and acetaminophen and narcotic as needed (1). Oral oxybutynin is started pre-operatively and then continued post-operatively every 8 hours. Unfortunately, the bioavailability of oral oxybutynin is poor due to first pass (liver) metabolism of the absorbed medication and a subsequent high level of desethyloxybutynin (DEO) produced by the liver. DEO, responsible for most of the side effects such as dry mouth, dizziness, over-heating, drowsiness and constipation. This metabolite and side effects are less with the transdermal route.

A prior retrospective analysis of children by us did not show a difference in pain between starting oral oxybutynin pre-operatively or initiating medication post-operatively. Whether this was due to no difference, insufficient patient numbers or inability to distinguish bladder spasms from pain is unknown. That study employed the Wong-Baker-Facies scale for pain measurement in children. At the time of that study there was no valid scale for objective measurement of bladder urgency in adults or children. Over the last five years we developed a validated scale (IRB 647657, 638967) that will allow us to better measure and distinguish bladder and incisional pain from bladder spasms/urgency (2).

Our objective is to determine if transdermal administration is superior to oral administration in alleviating pain and urgency after bladder surgery in children. Oral oxybutynin is a commonly used treatment in children with neuropathic bladder dysfunction and for adults with overactive

bladder (OAB) and incontinence. As mentioned, transdermal administration has higher bioavailability and a lower adverse event profile. Transdermal administration has been shown to be safe and efficacious in children with neuropathic bladder disease (3,4). Our hypothesis is that the transdermal route will decrease bladder pain and urgency if applied prior to surgery with a lower side effect profile.

1. Chamie, K. and Kurzrock, E.A.: Contemporary Open Ureteral Reimplantation without Morphine: Assessment of Pain and Outcomes. *J of Urology*, 182: 1147-1151, 2009.
2. Kurzrock E.A. and DeCristoforo, L.: Pictorial Urgency Scale – A New Tool for Evaluating Bladder Urgency in Children. *J of Urology* (PMID 30266334).
3. Cartwright, P.C. and Hoel, G.: Efficacy and safety of transdermal and oral oxybutynin in children with neurogenic detrusor overactivity. *J Urology*, 182: 1548-54, 2009.
4. Gleason, J.M. and Lorenzo, A.J.: Single center experience with oxybutynin transdermal system (patch) for management of symptoms related to non-neuropathic overactive bladder in children: an attractive, well tolerated alternative form of administration. *J of Pediatric Urology*, 10: 753-7, 2104.

4) Inclusion and Exclusion Criteria

- Inclusion Criteria:
- Patients who will undergo bladder surgery that requires an indwelling bladder catheter after surgery.
- Exclusion Criteria:
- Patients who have had prior bladder surgery.
- Patients who have neurologic disease that could impair bladder sensation.
- Patients who are already taking antimuscarinic or antispasmodic medications.
- Patients with glaucoma, any neurologic disease, dementia, impaired mentation or disorder of the central nervous system.
- Patients taking any medication that affects the central nervous system such as antidepressant, anxiolytic or antipsychotic medications.
- Age Range: Four to 8 years of age are eligible for the study.
Reason: less than four years of age cannot have the transdermal patch due to fixed dose.
Over 8 years of age: less than 5% of our patients, who undergo this surgery, are over 8 years of age and is usually a rare adolescent. Data in an older cohort may confuse the

results since they respond differently to bladder surgery due to larger incision and longer hospital stay with a catheter.

5) Study Timelines

I will be obtaining consent and enrolling subjects until: Dec 31 2025

The estimated date for the investigators to complete this study (complete primary analyses):
From approval of IRB to Dec 31 2026.

Based upon the power analysis by Blythe Durbin-Johnson, Ph.D. we plan to evaluate up to 100 patients with early termination if endpoints are reached before 100 subjects. Outcomes will be compared between groups using two-sample t-tests if the outcome is sufficiently normally distributed, and Wilcoxon-rank sum tests otherwise. With 60 subjects divided among two groups, the two-sample t-test will have 80% power to detect a 0.74 standard deviation difference in outcomes.

6) Study Endpoints

Our hypothesis is that transdermal formulation will lower bladder urgency and pain. The study will be terminated if the benefit is proven. This will be objectively measured with mean and peak urgency scores, mean and peak pain scores and narcotic usage (mg/kg) (reference 1 above).

The data will be analyzed after enrollment of ten, twenty, thirty, and (aggregate of 10) so on patients. Study enrollment will be stopped if one formulation is shown to have two of three outcomes noted above to differ between the two groups (oral vs transdermal) by greater than 10% ($P < 0.01$).

7) Procedures Involved

Enrollment

We propose to enroll pediatric patients who are scheduled to have bladder surgery that requires an indwelling bladder catheter after surgery. If a patient is a potential candidate, the medical record will be reviewed by Drs. Kurzrock or Yang. If they are deemed eligible, the research study will be presented to the patient at the visit when surgery is presented as a treatment option or at the preoperative visit. We realize that presentation of the study might occur at a stressful period but the time period between determining surgery is necessary and performing surgery is generally only one week to two months. If possible, the study will be presented prior to the preoperative appointment.

First and foremost we will describe the current standard at our institution which is to administer oral oxybutynin before or after bladder surgery. We will explain that oxybutynin has been shown to decrease catheter-related bladder discomfort in adults but not children. We

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will also explain the common adverse reactions to oxybutynin including dry mouth, blurry vision and constipation and that the transdermal route may or may not be superior.

Current treatment

Of note, all patients are given an anxiolytic, typically Versed, in the PACU prior to surgery, ordered by the anesthesiologist. Currently, oxybutynin is ordered by the urologist. Nurses mix the two solutions together so that children do not have to swallow two dosages.

Randomization

If the guardian chooses to enroll in the study and the consent has been signed, patients will be randomized in the following format:

Patients will be randomized based upon a computer generated table of random numbers into two groups at 1:1 ratio.

Group A: oral administration, current standard treatment at U.C. Davis Children's Hospital

Oral oxybutynin (5mg) is administered in the preoperative area prior to surgery. Our current regimen is to mix the oxybutynin with the standard preoperative Versed so children do not have to take two dosages.

Post-operatively oral oxybutynin (5mg) is administered every 8 hours in the hospital.

Along with pain medications, a prescription for a liquid formulation of oral oxybutynin 5mg po TID prn bladder spasms or frequency is sent to their pharmacy electronically with a 6 week supply.

Post-operative appointment is at 6week with renal/bladder sonography same day.

Group B: transdermal administration

Guardian will be given the transdermal patch (3.9mg oxybutynin) at the preoperative appointment with instructions to apply the day prior to surgery. The patch is good for 3-4 days.

While in the hospital no oral oxybutynin will be prescribed.

Along with pain medications, a prescription for the liquid formulation of oral oxybutynin 5mg po TID prn bladder spasms or frequency is sent to their pharmacy electronically with a 6 week supply.

Post-operative appointment is at 6week with renal/bladder sonography same day.

While in the hospital, all patients, both groups, will be maintained on current pain management protocols: 1. Intra-operative ketorolac (0.5 mg/kg IV up to 15mg) will be administered during bladder closure, 2. ketorolac (0.5 mg/kg IV up to 15mg) every 6 hours, 3. Acetaminophen + hydrocodone (0.1 mg/kg) PO every 4 hours prn moderate to severe pain and 4. Acetaminophen

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10 mg/kg PO every 4 hours prn mild pain; Max: 75 mg/kg/day up to 1 g/4h and 4 g/day from all sources. All pain medications administered in the hospital are recorded in EPIC EMR and will be monitored via EMR; diaries will not be utilized.

Adverse reactions

As per standard protocol, all adverse reactions to medication in the hospital will be recorded and analyzed. With our current regimen of oral oxybutynin, no patients have had therapy discontinued due to adverse reactions. Intravesical oxybutynin is known to have lower adverse reaction incidence.

8) Data Management and Confidentiality

Data will be stored on UCD computers (Department of Urologic Surgery) which are in locked offices and password protected with the following patient information: Mean and peak pain scores, mean and peak bladder urgency scale scores, weight, analgesic usage, gender and type of surgery will be recorded. Only the PI and his designated research support staff on the Research Personnel List (i.e. CRC, Residents, etc.), will have access to the database and the password will not be shared with anyone outside of the Research Team.

The PI or Administrator will be responsible for the receipt and/or transmission of the data as needed.

If the subjects choose to participate in this Study and later change their minds, no additional information will be collected about the subject; however data already collected will be included in the analysis.

9) Data and/or Specimen Banking

De-identified data will be stored, indefinitely, on a password protected computer and may be used for future IRB approved research depending on the PI's need.

10) Provision to monitor data for safety

Assessment of pain and urgency

1. Pain will be assessed using current standard UCDMC protocols in the preoperative and postoperative period. Depending upon the age of the child and development, the Wong-Baker-Facies scale or numerical scale will be utilized in the hospital.
2. Bladder urgency will be assessed with the bladder urgency scale (2) at the same time and frequency of pain assessment in the hospital.
3. Narcotic usage will be assessed. Morphine and hydrocone mg/kg will be recorded and evaluated over the hospitalization period.

Mean and peak pain scores, mean and peak bladder urgency scale scores, weight, analgesic usage, gender and type of surgery will be recorded.

Statistical analysis

Outcomes

Mean urgency score

Peak urgency score

Mean pain score

Peak pain score

Narcotic usage (mg/kg)

Outcomes will be compared between groups using two-sample t-tests if the outcome is sufficiently normally distributed, and Wilcoxon-rank sum tests otherwise. With 60 subjects divided among two groups, the two-sample t-test will have 80% power to detect a 0.74 standard deviation difference in outcomes.

Safety Assessments

Patients enrolled in this study will be monitored in the hospital in the same manner as all children after bladder surgery. Our current standard is oral oxybutynin administration every 8 hours. Standard protocol is to check patients for adverse events for all the medications administered in particular antibiotics which more often elicit allergic reactions. For oxybutynin we will determine if the patient is having any of the common side effects such as dry mouth, dizziness, insomnia or flushing. Upon discharge from the hospital, families are educated on all medications that they are prescribed and indications for discontinuation or calling our office. Patients are usually discharged with a prescription for pain medication, stool softeners, daily antibiotics and oral oxybutynin. Some of the patient on this study will be using oxybutynin dermal patch. They will be counseled equally except for the additional education on looking for a patch reaction which is a rash and/or irritation. Since the patch will be applied prior to

admission, most of these reactions will be evident prior to discharge.

11) Withdrawal of Subjects

Patient may withdraw from the Study at any time.

The only situation where we anticipate withdrawal is if a patient has side effects that the parents felt outweighed the benefits of decreasing bladder spasms..

If the subjects choose to participate in this Study and later change their minds, every effort will be made to destroy the data. The patient must notify the Research Team verbally, or upon written request. Any research results/data already obtained cannot be destroyed or recalled.

12) Risks to Subjects

The main risks of this study is the risks associated with the drugs used in this study.

Transdermal oxybutynin side effects

In clinical studies, side effects like dry mouth and constipation were similar to placebo. When using this product, you may have itching, rash or redness where the patch was placed. Sleepiness, dizziness and blurry vision may also occur.

Oral oxybutynin

The safety and efficacy of DITROPAN® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials. These participants were treated with DITROPAN 5-20 mg/day for up to 6 weeks. Table 3 shows the incidence of adverse events judged by investigators to be at least possibly related to treatment and reported by at least 5% of patients.

Table 3 : Incidence (%) of Adverse Events Reported by \geq 5% of Patients Using DITROPAN (5-20mg/day)

Body System	Adverse Event	DITROPAN (5-20 mg/day) (n=199)
Infections and Infestations	<u>Urinary tract infection</u>	6.50%

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Psychiatric Disorders	Insomnia	5.50%
	Nervousness	6.50%
Nervous System Disorders	Dizziness	16.60%
	Somnolence	14.00%
	Headache	7.50%
Eye Disorders	Blurred vision	9.60%
Gastrointestinal Disorders	Dry mouth	71.40%
	Constipation	15.10%
	Nausea	11.60%
	Dyspepsia	6.00%
Renal and Urinary Disorders	Urinary Hesitation	8.50%
	Urinary Retention	6.00%

The most common adverse events reported by patients receiving DITROPAN 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

There is also a risk to subject's confidentiality. This risk is minimized because all data will be stored on the UCDCM password protected, encrypted hard drive. Only study personnel will have access to the data at any time.

13) Potential Benefits to Subjects

The subjects whom receive intravesical oxybutynin may benefit from less pain and urgency.

14) Sharing of Results with Subjects

Results will be shared with subjects: if requested, results of the study will be provided to patients.

15) Provisions to Protect the Privacy Interests of Subjects

We will make every effort to keep the patient at ease. We will explain that the data that we are collecting is to improve treatment in the future.

During the consent process we will inform the patient of all procedures and provide them with information on who they will be interacting with for the study procedures. We

will discuss all risks, answer all questions, and inform the patient that they can withdraw from the study for any reason, at any time, without affecting the quality of their care. Patients will be informed that during the data/specimen review, the Investigator (or research staff) will record (e.g. write down, abstract) data collected in a manner that includes indirect or direct identifiers. Confidentiality measures taken will be discussed and any questions will also be answered.

16) Compensation for Research-Related Injury

Patients will not be compensated for their participation.

17) Economic Burden to Subjects

The patient’s health plan will be billed for the costs of routine medical care received during the study. These costs may include operating room fees, pharmacy charges, treatments, hospitalization, scans, etc. The patient will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. The costs of research or experimental procedures will be paid by the study.

18) Drugs or Devices

I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

19) [ClinicalTrials.gov](https://clinicaltrials.gov) Registration

FDAAA 801 establishes penalties for Responsible Parties who fail to comply with [ClinicalTrials.gov](https://clinicaltrials.gov) registration or results submission requirements. **Penalties include civil monetary penalties and, for federally funded studies, the withholding of grant funds.**

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on [Clinicaltrials.gov](https://clinicaltrials.gov).

Yes	
<input type="checkbox"/>	This study is funded by the NIH . (If this study is not funded by NIH, go to Section 2.)
<input checked="" type="checkbox"/>	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on [Clinicaltrials.gov](https://clinicaltrials.gov).

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Yes	
<input checked="" type="checkbox"/>	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
<input type="checkbox"/>	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
<input checked="" type="checkbox"/>	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click [here](#).

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
<input checked="" type="checkbox"/>	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention <i>and</i> a health outcome.
<input checked="" type="checkbox"/>	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations .

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
<input type="checkbox"/>	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

20) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
<input type="checkbox"/>	This research involves no more than minimal risk.
<input checked="" type="checkbox"/>	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
<input type="checkbox"/>	This research is not subject to FDA jurisdiction.
<input checked="" type="checkbox"/>	This research does not include prisoners as participants.
<input checked="" type="checkbox"/>	This research is not subject to SCRO oversight.
<input checked="" type="checkbox"/>	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).

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<input checked="" type="checkbox"/>	No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study.
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