BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Clinical Trial Evaluating the Use of Perioperative Intravenous Lidocaine Infusion to Decrease Pain Scores and Opioid Consumption after Robotic-Assisted Prostatectomy and Robotic-Assisted Partial Nephrectomy

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PROTOCOL SUMMARY AND/OR SCHEMA

We propose a prospective, randomized, double-blinded, placebo-controlled clinical trial on the use of perioperative intravenous lidocaine infusion in order to decrease pain scores and opioid consumption after robotic-assisted prostatectomy and robot assisted partial nephrectomy. Patients undergoing urological robotic assisted surgery will be randomized 1:1 to receive either intraoperative 0.8% lidocaine or normal saline at 1 mg/kg/h for patients younger than 65 years and 0.5 mg/kg/h for patients greater than or equal to the age of 65 to be delivered by continuous infusion for 24 hours intra- and post-operatively. Opioid use will be monitored for up to 14 days post-operatively as well as pain scores.

OBJECTIVES AND SCIENTIFIC AIMS

Clinical Hypotheses:

Primary Hypothesis:
We hypothesize that use of perioperative lidocaine infusion for 24 hours in urology robotic surgeries would result in less pain and less opioid use compared to the placebo.

Exploratory Hypotheses:
We hypothesize that the use of the lidocaine infusion compared to placebo would:

1. result in less opioid consumption in first 24 hours and 14 days post-operatively
2. decrease length of stay in the PACU and improve SpO2 levels in PACU
3. decrease postoperative nausea and vomiting
4. decrease time to first ambulation after the surgery
5. improve recovery of bowel movements after surgery
6. improve patient satisfaction levels after surgery
7. decrease length of stay in hospital

Therefore:

Primary Endpoint is:

- Difference in post-operative pain

Secondary Endpoints are:

- Difference in opioid consumption in first 24 hours, discharge and 14 days post-operatively (utilizing morphine equivalents)
- Difference in length of hospital stay determined by surgeon excluding social factors that may delay discharge (discharge readiness; hours)
- Difference in post-operative Ileus duration (hours)
- Difference in time in the Post Anesthesia Care Unit (PACU) after surgery (discharge readiness and actual discharge; minutes)
- Difference in return of flatus after surgery (hours)
- Difference in time to out of bed to chair after surgery (hours)
- Difference in time to first ambulation in the hallway after surgery (hours)

BACKGROUND AND STUDY DESIGN/INTERVENTION

In recent years, the risk of opioids in the post-operative period has gained interest due to the growing epidemic of addiction, dependence, and overdose[1]. The rate of drug overdose secondary to opioids has continued to increase at an alarming rate (Figure 1)[2]. This has been a primary point of concern in all fields of medicine and Urology has not been an exception[3]. This is also a nationwide government and public health concern. This has generated an increased focus on the use of non-opioid analgesics after surgery such as intravenous lidocaine[4].

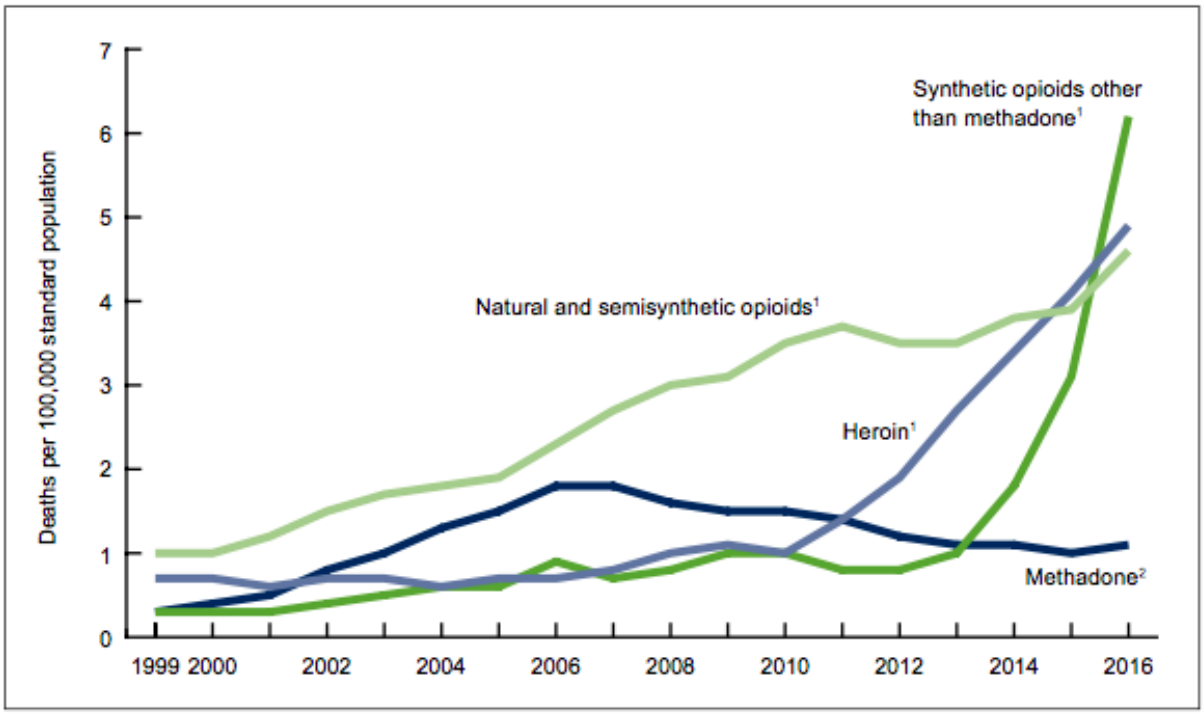

Figure 1: CDC report of age-adjusted drug overdose death rates, by opioid category: United states, 1999-2016.

Opioids remain the primary source of relief for postoperative pain and have the potential to lead to significant morbidity[5]. Opioids may delay recovery following surgery and have many well-known adverse effects including, but not limited to, nausea, vomiting and prolonged post-operative ileus[6,7]. Furthermore, in one study, they inadequately provided pain control in 50-60% of postoperative patients. This is a frequent report of patients because of the less than optimal utilization of the medications in fear of their dose dependent adverse effects and various contraindications[7]. On the other hand, surplus medication following surgery is another prominent component of the opioid problem in Urologic practices. Bates et al. found that of the 586 patients that underwent a urological procedure that they reviewed, 67% of them had collected surplus medication[1]. It is both necessary and beneficial for surgeons and patients to utilize dose-sparing strategies following surgery to decrease overall opioid usage and outpatient requirement.

One mechanism that has already been employed for overall improvement in prostatectomies and partial nephrectomies is the use of the robotic assisted approach. Robot assisted partial

nephrectomies (RALPN) and robotic assisted laparoscopic prostatectomies (RALP) are becoming a mainstay in urologic surgery and increasing annually. This coincides with a continuous downward trend of laparoscopic and open urologic procedures[8]. RALPN has been shown in a meta-analysis to be more favorable than laparoscopic partial nephrectomies and will continue to be the surgical procedure of choice in the near future[9]. RALP is also now the dominant surgical approach while open and laparoscopic prostatectomies becoming less frequent. Robotic assisted surgery is associated with improved functional outcomes**,** pain scores, shorter hospital stays, and increases in patients satisfaction in many studies [8,10–12].

While there has been a pronounced increase in robotic surgery over the past 10 years that has demonstrated benefits for patients, there has been limited studies regarding the pain management for these patients. Robotic assisted surgery itself decreases pain levels compared to other approaches, but patients continue to experience mild to moderate pain levels in the postoperative period, which are classically managed with NSAIDs and opioids[6,11,13].

Recently, Enhanced Recovery after Surgery protocols (ERAS) have been implemented in an attempt to decrease pain and opioid use as one outcome. ERAS utilizes multimodal analgesia and has shown improvement of patient satisfaction and perioperative opioid use[14]. Systemic lidocaine is becoming more popular and regularly applied through this protocol and, other practices, in due to its analgesic, anti-hyperalgesia and anti-inflammatory properties that it contains[15]. Systemic lidocaine mechanism of action is not fully understood, but it appears to be multifaceted[16]. Systemic lidocaine inhibits voltage-gated sodium channels in both the peripheral and central nervous system. This is believed to cause an additive effect when combined with inhaled anesthetics which also work on the voltage-gated sodium channels in the central nervous system[17]. Despite this summative effect, this is likely not the primary mechanism of action. Instead, it is believed to predominantly act on anti-inflammatory signaling and through inhibiting neuronal effects[4]. Additionally, it reduces nociception and cardiovascular response to surgical stress and pain.[16]

The use of perioperative lidocaine has been studied and shown beneficial effects in patients undergoing surgery[4,14,25–29,17–24]. Outcomes have included: improved postoperative pain scores, decreased nausea, postoperative ileus, shorter length of hospital stays and a reduction in opioid use [18–20]. In addition to its positive effects, there is a significant lack of negative effects. Weibel et al. evaluated 45 small, randomized studies and found that there is no current evidence of any major toxicities with usage of systemic lidocaine[21]. There is no great evidence for optimal pain management in laparoscopic urological procedures, especially in robotic assisted laparoscopic surgery. However, evidence from laparoscopic surgeries in other fields should be extrapolated[12].

The systematic review by Weibel et al.[21] in 2016, revealed that patients who received intravenous perioperative lidocaine had lower pain scores for the first 24 hours after surgery. The effects were seen in a broad spectrum of patients and demonstrated clear evidence of the positive effects of pain reduction and decreased amounts of opioid use. These were most pronounced in laparoscopic abdominal surgery. A similar meta-analysis was completed in 2012

and exhibited benefits consistent with the most recent data[22]. Dunn and Durieux[4] reviewed the use of intravenous lidocaine and generated a table of results that clearly illustrates the studies that have investigated systemic lidocaine and the resultant effects until 2017 (Table 1).

Type of Surgery	References	Bolus	Infusion	Duration	Results	Evidence
Open abdominal	Colorectal				Decreased pain scores and opioid consumption; decreased nausea, duration of ileus, and length of hospitalization	Strong: benefit shown in multiple studies or meta-analyses
	Kuo *et al*. 2006[23]	2 mg/kg	3 mg · kg^{-1} · h^{-1}	30 min before to end surgery		
	Herroeder *et al*. 2007[24]	1.5 mg/kg	2 mg/min	Before induction to 4 h PO		
	Swenson *et al*. 2010[21]	No bolus	1–3 mg/min	Before induction to return of bowel function		
	Abdominal					
	Koppert *et al*. 2004[25]	1.5 mg/kg	5 mg · kg^{-1} · h^{-1}	30 min before incision to 1 h PO		
	Baral *et al*. 2010[26]	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	30 min before incision to 1 h PO		
Laproscopic abdominal	Colectomy				Decreased pain scores and opioid consumption; duration of ileus	Strong: benefit shown in multiple studies or meta-analyses
	Kaba *et al*. 2007[3]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1} during surgery, 1.33 mg · kg^{-1} · h^{-1} PO	Induction to 24 h PO		
	Wongyingsinn *et al*. 2011[27]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1} during surgery, 1 mg · kg^{-1} · h^{-1} PO	Before induction to 48 h PO		
	Tikuišis *et al*. 2014[28]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1} during surgery, 1 mg · kg^{-1} · h^{-1} PO	Before induction to 24 h PO		
	Cholecystectomy					
	Lauwick *et al*. 2008[29]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Induction to end of surgery		
	Saadawy *et al*. 2010[30]	2 mg/kg	2 mg · kg^{-1} · h^{-1}	Before induction to end surgery		
	Gastrectomy					
	Kim *et al*. 2013[31]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Preoperatively to end surgery		
	De Oliveira *et al*. 2014[32]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Before induction to end surgery		
	Appendectomy					
	Kim *et al*. 2011[33]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	2 min before induction to end surgery		
Prostate	Lauwick *et al*. 2009[34]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Induction to end surgery	Decreased pain, opioid consumption, ileus duration and length of hospital stay	Moderate: small benefit, limited number of studies
	Groudine *et al*. 1998[35]	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	Before induction to 60 min after skin closure		
Breast	Terkawi *et al*. 2014[36] and 2015[37]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Induction to 2 h after surgery	Decreased incidence of chronic pain at 3 and 6 months	Moderate: small benefit, limited number of studies
	Choi *et al*. 2012[38]	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	30 min before incision to skin closure	No effect on pain scores, opioid consumption, or PONV	
	Grigoras *et al*. 2012[39]	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	Before induction to 60 min after skin closure		
Thoracic	Cui *et al*. 2010[40]	No bolus	33 μg · kg^{-1} · min^{-1}	Induction to skin closure	Decreased pain and opioid consumption	Moderate: small benefit in one study
Ambulatory	McKay *et al*. 2009[41]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Before induction to end surgery	Decreased pain PACU, faster discharge	Moderate: small benefit, limited number of studies
	De Oliveira *et al*. 2012[42]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Before induction to end surgery		
Multilevel spine	Farag *et al*. 2013[43]	No bolus	2 mg · kg^{-1} · h^{-1}	Induction to PACU discharge (maximum 8 h)	Decreased pain score, improved quality of life 1 and 3 months PO	Moderate: small benefit in one study
Cardiac	Insler *et al*. 1995[44]	1.5 mg/kg	30 μg · kg^{-1} · min^{-1}	After induction to 48 h in ICU	No effect on pain scores or opioid consumption	No support from limited number of studies
	Wang *et al*. 2002[45]	1.5 mg/kg bolus and 4 mg/kg to CPB priming solution	4 mg/min	Opening of pericardium to end surgery	Decreased PO cognitive dysfunction	
	Mathew *et al*. 2009[46]	1 mg/kg	4 mg/min for 1 h, 2 mg/min for second h, 1 mg/min to end	After induction to 48 h PO		
Laparoscopic renal	Wuethrich *et al*. 2012[47]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}, then 1.3 mg · kg^{-1} · h^{-1} PO	Induction to 24 h PO	None	No support from single small study
Abdominal hysterectomy	Bryson *et al*. 2010[48]	1.5 mg/kg	3 mg · kg^{-1} · h^{-1}	Before induction to skin closure	None	No support from two small studies
	Grady *et al*. 2012[49]	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	Induction to 24 h PO		
Hip arthroplasty	Martin *et al*. 2008[50]	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	30 min before incision to 1 h PO	None	No support from single small study

CPB = cardiopulmonary bypass; ICU = intensive care unit; PACU = postanesthesia care unit; PO = postoperative; PONV = postoperative nausea and vomiting.

Table 1: Table from Dunn and Durieux in 2017[4] that shows the systemic lidocaine studies that have been conducted prior to 2017. It includes the type of study, bolus, infusion, duration, results and evidence.

Overall, the use of intravenous lidocaine in abdominal laparoscopic surgery was found to be beneficial in multiple studies. Kaba et al.[24], Wongyingsinn et al.[23] and Tikuisis et al.[25] showed a

decrease in pain, opioid use and post-operative ileus in laparoscopic colectomies, along with decreased inhaled anesthetic usage during the surgery[23,24]. Lauwick et al.[26] demonstrated a reduction of inhaled anesthetics and opioid usage in laparoscopic cholecystectomies. Kim et al.[30] and De Oliveira et al.[27] had consistent findings of improvements with pain, opioid use and duration of ileus in laparoscopic gastrectomies. Kim et al.[28] further showed intravenous lidocaine to be an improvement in pain for laparoscopic appendectomies. All laparoscopic abdominal surgeries studies that have been conducted with intravenous lidocaine have exhibited patient benefits, which further suggest the value of intravenous lidocaine in laparoscopic abdominal surgeries.

There have been no randomized, double-blinded trials on the proper analgesia for post-operative course after robotic surgery. There have only been a handful of studies conducted on the use of lidocaine infusions in urological surgeries, with a majority of the studies showing significant success with its use[14,17–20,29,31]**.** Joshi et al indicated in their review of pain management in prostatectomies, there is a need for randomized clinical trials to investigate intravenous lidocaine as well as enhanced rehabilitative protocols especially in minimally invasive procedures, as the studies were done in open surgical procedures[6].

Most recently in 2018, Nakhli et al.[17] used adjunctive intravenous lidocaine in renal surgery in comparison to saline placebo. They infused 1.5mg/kg bolus followed by a continuous infusion of 2 mg/kg/h until skin closure. The lidocaine infusion patients had a reduction of 31% ($p<0.001$) in isoflurane concentration requirement and 27% ($p<0.001$) reduction in their intraoperative remifentanil. This reduction of intraoperative anesthetic has been shown before in other species including both cats and dogs[32,33]**.** They additionally found a significant recovery from anesthesia with shorter extubation time 5.8 ± 1.8 minutes compared to control of 7.9 ± 2.0 minutes ($p<0.001$).

Lauwick et al.[18] investigated functional walking capacity as a measure of recovery from a laparoscopic prostatectomy and discovered that patients who received lidocaine infusion were able to walk further over a shorter amount of time (56 vs. 43.5 meters) compared to saline. They received 1.5mg/kg bolus, 2mg/kg during the operation and 1mg/kg in the PACU for 24 hours after surgery. They also had 12% reduction (5.6 vs 6.3) of desflurane during the operation.

Groudine et al.[19] demonstrated value of intravenous lidocaine in patients undergoing radical retropubic prostatectomy after infusing 1.5mg/kg bolus, followed by 1.5mg/kg/h infusion from beginning of surgery until 1 hour postoperatively. Patients had quicker return of flatulence, regained of bowel function faster ($p<0.05$), 1.1 fewer days in the hospital ($p <0.05$), and decreased postoperative pain[19].

Jendoubi et al.[14] looked at the use of intravenous lidocaine or ketamine compared to saline for acute and chronic pain following open nephrectomy. They gave 1.5 mg/kg bolus at anesthesia induction followed by infusion of 1 mg/kg/h intraoperatively and continued for 24 hours. They found that both ketamine and lidocaine significantly reduced morphine consumption by about

33% and 42%, respectively (p<0.001), improved 6-minute walk distance at discharge from a mean of 27 meters to 82.3 meters in the lidocaine group (0.001), and also reduced development of neuropathic pain at 3 months (p<0.05).

Tauzin-Fin et al.[29] found significant enhancement of recovery with several endpoints revealing reduction of morphine 8.5mg in lidocaine infusion vs 25mg control group, improved post-operative pain (P<0.05), time to first flatus (P<0.001) and 6-minute walk time (p<0.001) after a nephrectomy. Effective analgesia in the post-operative period considerably improves rehabilitation.

Weinberg et al.[20] looked at radical prostatectomy patients with perioperative lidocaine 2% or saline. A pre-operative intravenous bolus of 0.075mg/kg followed by peri-operative and 24-hour post-operative infusion of 0.075mg/kg/h. They found it decreased hospital stay an average of 1.3 days (P=0.017), reduced pain at rest by 1.8 hours (p=0.001), and morphine consumption by a mean of 13.9mg (p=0.021).

Only one study, Wuethrich et al.[31], did not find any benefit from the use of intravenous lidocaine in renal surgery. They were unable to identify significant difference in length of hospital stay, post-operative pain, return of bowel function, stress response, fentanyl dosage used or anesthetic sparing effect following intra-operative and 24-hour post-operative lidocaine[31]. This small study of 64 patients stands alone as the only urological operation to not show benefits.

The study that we propose targets an area of urology that is underrepresented in the current literature despite its increasing importance. To the best of our knowledge, this has not been directly studied before, although it has been utilized numerous times in the ERAS protocol at the University of Missouri Hospital throughout the Division of Urology and Anesthesiology & Perioperative Medicine in patients undergoing robotic surgery. The benefits of intravenous lidocaine have been clearly demonstrated in other areas and these results warrant a prospective, randomized, double-blinded, placebo controlled study to assess the lidocaine infusion effects for robot assisted laparoscopic prostatectomies and partial nephrectomies. As the number of robotic assisted surgeries and emphasis on opioid reduction continues, the evaluation of systemic lidocaine will be important in improving patient outcomes in Urology.

CRITERIA FOR SUBJECT ELIGIBILITY

Subject Population

- Undergoing robotic assisted prostatectomy or robotic assisted partial nephrectomy at University of Missouri Hospital for prostate cancer or kidney mass

Subject Inclusion

- Age $\geq$ 18 years
- ASA I-III

Subject Exclusion

- Inability to obtain written informed consent
- Allergy to lidocaine or other amide local anesthetics
- Atrioventricular conduction blocks
- CV instability and concomitant use of alpha agonists or beta blockers
- Recent myocardial infarction (≤ 6 months ago)
- Cardiac arrhythmia disorders
- Stokes-Adams syndrome
- Wolff-Parkinson-White syndrome
- Seizure disorders
- Liver failure or hepatic dysfunction
- Significant renal disease with a serum creatinine ≥ 2 mg/dl
- A family history of malignant hyperthermia
- Current use of opioids or documented history of opioid abuse
- Typically, have less than 3 bowel movement per week
- Combined surgical cases that include robotic prostatectomy or robotic partial nephrectomy

OVERVIEW OF STUDY DESIGNATION

Design

This is a prospective, randomized, double-blinded, placebo-controlled clinical trial on lidocaine infusion for pain control and opioid consumption in patients undergoing either robotic-assisted laparoscopic prostatectomy or robotic-assisted laparoscopic partial nephrectomy at University of Missouri Hospital. Patients will be randomized in a 1:1 fashion and stratified by the type of surgery to receive a perioperative intravenous 0.8% lidocaine infusion at 1 mg/kg/h if < age 65 and 0.5 mg/kg/h if ≥ age 65 or an equal volume and rate of normal saline as a placebo. The infusion will be started 15 minutes after endotracheal intubation and continue for 24 hours.

After obtaining written consent, subjects will be randomized to receive lidocaine or normal saline. The anesthesiologist, surgeon, nurses, research staff, and patient will be blinded to the intervention. Masked infusion bags of 0.8% lidocaine or normal saline will be prepared by the investigational pharmacy at University of Missouri Hospital. To avoid any compromise in the blinding process, the investigational pharmacist will enter “Study Medication” in the medical record.

Perioperative care, surgery and anesthesia, for all subjects will be per standard hospital protocol.

In short:
Upon arrival to the operating room, patients will be placed supine on the operating table and intravenous (IV) lines connected to allow initiation of IV lidocaine or saline following anesthetic induction. IV antibiotics will be utilized if clinical necessary based on the discretion of the anesthesiologist and attending surgeon. Standard perioperative monitoring including a

continuous electrocardiogram, pulse oximetry, urine output, non-invasive arterial pressure measurement, end-tidal CO2 and temperature will be utilized. Intravenous fluid use during surgery will be provided by the anesthesiology team as clinically indicated. Anesthesia will be standardized. Induction will be with lidocaine 1.5 mg/kg, fentanyl 1 mcg/kg, propofol 1.5 to 2 mg/kg, and rocuronium 0.6 mg/kg. Patient will then be prepared and draped in sterile fashion. Timeout will be performed.

Anesthesia will be maintained with 1 MAC sevoflurane, additional fentanyl and rocuronium will be given per anesthesia discretion. Quantity of all anesthetic and analgesic medications during the operation will be documented. Local 0.25% bupivacaine (10mL) without epinephrine injection will be used post-operatively during closure in all patients regardless of being in the study group or control group as a part of normal operational procedure. Reversal of neuromuscular blockade will be with sugammadex 2 mg/kg. When standard extubation criteria are met the subject will be extubated and transported to PACU.

Intervention

Fifteen minutes following endotracheal intubation, subjects will be intravenously infused with either 0.8% lidocaine at 1 mg/kg/h if < age 65 and 0.5 mg/kg/h if ≥ age 65 or an equal volume and rate of normal saline placebo as determined by the randomization table. The infusion will be continued for 24 hours after surgery. Masked infusion bags of 0.8% lidocaine or normal saline will be prepared by the Investigational Pharmacy at the University of Missouri Hospital according to the subject randomization table. Infusion preparation will occur in a blinded fashion to all clinical and research personal involved with the study case. To maintain blinding, the investigational pharmacist will enter “Study Medication” in the medical record.

In PACU patient will receive additional fentanyl or hydromorphone. Postoperative pain scores, vital measures, and opioid use will be documented. Once patient is able to tolerate oral intake, they will be switched to oral narcotics. Patient fentanyl consumption and 10 cm visual analog scale (VAS) will be utilized. VAS will be scored from a 0 “no pain” to a 10 “worst pain ever” and will be recorded by blinded research staff at 1, 2, 4, 6, 12, 24 hours post-operatively, postop day 2, any additional day during hospitalization, at time of discharge and 14-day follow up. The nurse that will be caring for these patients will document the time of first bowel movement, return of flatus and any adverse reactions per standard of care. Post-Anesthesia Patient Satisfaction Assessment will be performed at 24 h post-surgery.

Patient may go to the floor or ICU with the infusion. Orders will be included in surgeon's post-operative orders including the stop time at 24 hours. The infusion pump will be programmed using Guardrails settings, it will be on separate infusion pump from IV fluids with sign for pump - local toxicity, obtained from anesthesia pain nurse.

Patients will be monitored clinically for toxicities during the postoperative period. Per standard of care the nurse caring for the patient will be required to document any adverse events to lidocaine every four hours and anesthesiology pain nurses will monitor these reports. If patients experience the presence of perioral paresthesia, metallic taste, tinnitus, confusion, agitation,

muscle spasms, and seizures, the lidocaine infusion will be stopped and a lidocaine toxicity protocol will start by the standard of care. The subject will be removed from the study.

At initial follow-up appointment, patient will be asked to bring in prescribed opioids, if applicable, to determine how much was required in their outpatient recovery. Pill count will be done and compared to distributed quantity. VAS score will be also assessed.

THERAPEUTIC AND DIAGNOSTIC AGENTS

Lidocaine is the intravenous analgesic. Lidocaine infusion will be stored and dispensed by the Investigational Pharmacy at University Hospital. A 0.8% Lidocaine infusion will be injected intravenously using an administration set with a filter at a constant rate of 1 mg/kg/h for ages < 65 and 0.5 mg/kg/h for ages ≥ 65. Patients with BMI ≥ 40 will be dosed using ideal body weight.

RECRUITMENT PLAN

Patients will be recruited from the practices of the Division of Urology, Department of Surgery. The study will be introduced to every eligible patient scheduled for robot assisted laparoscopic prostatectomy and robot assisted laparoscopic partial nephrectomy by the participating consenting physicians from the Department of Surgery-Urology Division and a written consent obtained prior to surgery by the consenting research personnel. Candidate subjects will be provided time to consider the study, to read the informed consent document at their convenience, and discuss the study with family and others, as desired.

PRETREATMENT EVALUATION

This study does not require any additional pretreatment evaluations other than those which are part of current clinical care standards for a patient undergoing RALP or RALPN at University of Missouri. Preoperative evaluations follow recommendations from the NICE[34,35].

For RALP these include:

- Routine history and physical examination to include documentation of any comorbidities, medications (including complementary and alternative medications), family history, social history (alcohol and tobacco usage), height, body weight, Karnofsky performance status within 30 days of surgery
- Chest X-ray or CT scan of the Chest within 30 days of surgery
- Pre-operative laboratory investigations: CBC, BMP, urinalysis (dipstick, microalbumin, creatinine, microscopic evaluation if indicated), urine culture if indicated within 30 days of surgery
- Baseline EKG

For RALPN these include:

- Routine history and physical examination to include documentation of any comorbidities, medications (including complementary and alternative medications), family history, social history (alcohol and tobacco usage), height, body weight, Karnofsky performance status within 30 days of surgery

- Abdominal and pelvic CT scan and/or MRI and/or renal ultrasound within 60 days of surgery.
- Chest X-ray or CT scan of the Chest within 30 days of surgery
- Pre-operative laboratory investigations: CBC, BMP, urinalysis (dipstick, microalbumin, creatinine, microscopic evaluation if indicated), urine culture if indicated within 30 days of surgery
- Baseline creatinine values will be converted to eGFR using the CKD-EPI equation
    - This value will be recorded from the MU pre-surgical testing blood work mandatory for all patients undergoing surgery at MU.

SURGICAL INTERVENTION PLAN

The technique of surgery will have been determined to be robotic assisted laparoscopy based on the discretion of the surgeon and patient. None of the techniques utilized in the study are considered experimental and all are considered standard therapeutic options for the patient with either a prostate cancer or a renal mass concerning for cancer amenable to prostatectomy or partial nephrectomy, respectively. Since patients will be undergoing the same approach, impact from physiologic differences between the 2 approaches are expected to be equally distributed between the 2 arms and the randomization will be additionally stratified by the type of the surgery. Patient medications will be recorded from the home medications list and managed perioperatively per institutional standards.

The operating team will consist of surgeons on faculty at University of Missouri Department of Surgery-Urology Division. The procedures are performed under standardized general anesthesia with standard intraoperative vital sign monitoring.

EVALUATION DURING TREATMENT/INTERVENTION

This protocol does not require any additional evaluations after the subject is admitted for surgery other than those routinely part of clinical care for a patient undergoing robot assisted laparoscopic prostatectomy or robot assisted laparoscopic partial nephrectomy other than inquiring for subjects' satisfaction on postop day one and monitoring for signs of lidocaine toxicity during inpatient hospitalization. Signs of possible lidocaine toxicity include the presence of perioral paresthesia, metallic taste, tinnitus, confusion, agitation, muscle spasms, and seizures. If toxicity is suspected the infusion will be stopped per the standard of care at University Hospital.

Routine evaluation and management for those undergoing robot assisted laparoscopic prostatectomy include:

- ASA classification, assigned by the anesthesiologist
- Deep venous thrombosis prophylaxis per standardized pathway
- Estimated blood loss
- Use of intraoperative fluids (crystalloid, colloid, blood products)

Routine evaluation and management for those undergoing robot assisted laparoscopic partial nephrectomy, these include:

- ASA classification, assigned by the anesthesiologist
- Deep venous thrombosis prophylaxis per standardized pathway
- Duration of warm ischemia time
- Estimated blood loss
- Use of intraoperative fluids (crystalloid, colloid, blood products)

TOXICITIES/SIDE EFFECTS

Various symptoms including perioral paresthesia, metallic taste, tinnitus, confusion, agitation, muscle spasms, and seizures have been described when the plasma lidocaine was higher than 5 μg/mL. While under general anesthesia, evidence of toxicity may be evident through bradycardia, increased intervals and widening QRS complex and may be increased with hypercapnia.[16] However, it has been shown to be more cardio-protective, rather than cardio-toxic in prospective randomized study[36]. The toxic levels of lidocaine are unlikely to be experienced at the levels used in our protocol. Our study is using the low end of the recommended dose and rate of 1-2 mg/kg/h. We additionally are utilizing a bolus only as a part of routine anesthesia induction, which is recommended to be 1-2 mg/kg and start the infusion 15 minutes after the endotracheal intubation.

Signs of lidocaine toxicity will be monitored per University Hospital standard of care protocol. This includes assessment and documentation by floor nursing staff, every 4 hours, of the signs and symptoms of lidocaine toxicity. The presence or lack of toxicity is reported in the medical record at these time points and pain nurse with the Department of Anesthesiology and Perioperative Medicine review this information. Management and review of medications will also be performed by the surgical and inpatient care teams per standard of care. Toxicity in our study will be evaluated clinically postoperatively by the presence of perioral paresthesia, metallic taste, tinnitus, confusion, agitation, muscle spasms, and seizures. Following standard of care, if there is concern of possible toxicity a lidocaine level may be ordered per standard of care.

Surgical complications will be assessed prospectively and retrospectively and reviewed using the institutional standard for complications reporting for all surgical patients as followed by the Department of Surgery. Standardized graded complications and adverse effects at UM utilize the five-point modified Clavien-Dindo system. Grade I include complications requiring monitoring but no intervention; Grade II requires bedside or medical treatment; Grade III constitute adverse events requiring surgical or procedural intervention with return to normal functioning; Grade IV includes disabling, life-threatening complications with resulting functional loss and grade V is death of the patient. This is a modification of the Clavien-Dindo system for reporting complications with defined, categorized and classified events that will be segregated into time periods of ≤30 days, 31-90 days and > 90 days after surgery and includes medication complications following NCI CTCAE version 5 guidelines.

CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

If the surgery is aborted for any reason before attempted excision of the mass or intravenous infusion fails for any reason, the patient will be removed from the study and replaced. Based on past experience these issues are rare events. If a partial nephrectomy converts to radical nephrectomy, infusion will be continued and the data will be collected. If any robotic procedure converts to an open procedure, the subject will be excluded from the study. Lidocaine infusion will be continued or started (if subject is receiving normal saline) per surgeon request.

The intraoperative period is defined as the period from anesthesia induction to the extubation of the trachea. The surgical time is determined from the incision to the final skin closure.

The postoperative period is defined as the period from the extubation to the study endpoint at 14 days ± 7 days.

Blood loss is defined as the estimate accounted from the suction device and absorptive sponges during the procedure, as described and agreed upon by the surgeon, anesthesiologist, circulating nurse, and surgical technician as covered by institutional guidelines.

Post-operative pain will be defined by the patient through the use of a 10 cm visual analog scale (VAS) and 11 point numeric scale (0-10).

Length of hospital stay will be defined as the time the subject leaves the OR until subject meets standardized discharge criteria according to the surgeons' protocol, which will exclude social factors delaying real discharge times.

Post-operative Ileus duration is defined as return of bowel function in hours from extubation per patients recall following nursing inquiry. Documentation will be done per standard of care by the nurse caring for study patient.

Flatus return is defined as return of flatus in hours from extubation per patients recall following nursing inquiry. Documentation will be done by nurse caring for patient following standard of care.

Patient satisfaction will be assessed 24 hours post-operative by Post Anesthesia Patient Satisfaction Assessment by research staff.

CRITERIA FOR REMOVAL FROM STUDY

Patients will be withdrawn from the study if they express a desire to do so, if it is determined to be in the patient’s best interest to do so, or if they do not undergo initiation of their surgical procedure as stipulated previously. If lidocaine infusion is stopped subject will be excluded from analysis. If surgery is converted from robotic assisted to open the subject will be excluded from analysis. Patients who are not evaluable for the study primary endpoint by failure to obtain

data for the primary endpoint will be excluded from the study and further analysis will not be performed.

BIOSTATISTICS

Sample Size

The primary outcome for the study is the patient's pain score at discharge. Although additional analyses are planned, the sample size estimate is based on this outcome. Assuming a common standard deviation of two-points, a sample size of 40 with 20 per treatment arm will provide 80% power to detect a 2-point difference between groups when testing a two-sided alternative at the 5% level of significance using Wilcoxon Rank Sum Test. To take into account the loss to follow up, the drop-out inflated enrollment will be 46 subject with 23 subjects in each group assuming the same power.

Unadjusted and Adjusted Analysis

The unadjusted analysis will be designated as primary analysis and it will be performed to assess the pain level difference between the two groups. The adjusted analysis which will be designated as secondary analysis will incorporate other covariates like type of surgery in addition to the treatment assignments as covariate.

Proposed Analyses

Two statistical analysis methods will be used to make a comparison between the two treatment groups with regard to the primary end point: (i) to assess the difference of pain level between the two groups at specific time point, Wilcoxon Rank Sum Test will be used, (ii) to assess the pattern of change in pain level over the study period between the two groups, a Generalized Estimation Equation (GEE) model will be used.

Sample Size					**Drop-out Inflated Enrollment**	
Treatment	**Placebo**	**Effect Size**	**SD**	**Power**	**Treatment**	**Placebo**
20	20	2	2	80%	23	23
27	27	2	2	90%	30	30

*A dropout rate of 10% was considered here. A Two Sample T-test using effect size sample size method was used to get an estimate of the samples needed from the PASS program.

Table 2: Sample size assuming 80% and 90% power.

RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

Randomization

Randomization will be accomplished by the method of random permuted block and stratified by the type of the surgery and subject age. Since this is a double-blind study, the subjects' treatment assignments will be kept in a blinded randomization table. The Excel column containing treatment designation assigned by a biostatistician will be occluded from view to maintain blinding. The investigational pharmacist will not be blinded and will have the randomization table. After recruitment, research staff will randomize the patient into the correct stratification and the Investigation Pharmacy will be notified. If it is clinically necessary to unblind a subjects' treatment allocation this will be done using the randomization table.

DATA MANAGEMENT ISSUES

A Research Specialist (RS) from the Department of Anesthesiology and Perioperative Medicine will be assigned to the study who will provide data management support. The responsibilities of the RS include project compliance, data collection, abstraction and entry, data reporting, IRB correspondence, problem resolution and prioritization and coordination of the protocol study team activities. The data collected for this study will be entered into a secure departmental server. Source documentation and regulatory binders will be stored in a locked filing cabinet within a locked department office space. These sites are exclusively used for research documents and only members of the research team will have access to files for this study.

Quality Assurance

Registration reports will be generated every 6 months to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations will be monitored throughout the study period. Potential problems will be brought to the attention of the study team for discussion and action.

Data and Safety Monitoring

The plans address the policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical trials" which can found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The MU Health Care Data and Safety Monitoring Plans can be found online.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response and staff education on clinical research QA) and departmental procedures for quality control, plus institutional committees that are responsible for monitoring the activities of the clinical trials program.

PROTECTION OF HUMAN SUBJECTS

Benefits and Risks

The experimental intervention (intravenous lidocaine infusion) is currently used at University of Missouri Hospital through the ERAS protocol. Numerous studies have shown significant patient benefits in all fields, including Urology. A review of 45, randomized studies demonstrated no major adverse events secondary to its usage. Therefore, we do not believe that the therapeutic aspects of this trail pose any risk different from patients undergoing robot assisted laparoscopic prostatectomy or a robot assisted laparoscopic partial nephrectomy.

Toxicities and side effects

Adverse outcomes are not anticipated with the doses of lidocaine being used in the protocol. Signs of lidocaine toxicity will be monitored per University Hospital standard of care protocol. This includes assessment and documentation by floor nursing staff, every 4 hours, of the signs and symptoms of lidocaine toxicity. The presence or lack of toxicity is reported in the medical record at these time points and pain nurse with the Department of Anesthesiology and Perioperative Medicine review this information. Management and review of medications will also be performed by the surgical and inpatient care teams per standard of care. Toxicity in our study will be evaluated clinically postoperatively by the presence of perioral paresthesia, metallic taste, tinnitus, confusion, agitation, muscle spasms, and seizures. Following standard of care, if there is concern of possible toxicity a lidocaine level may be ordered per standard of care.

Alternatives / Therapeutic options

The alternative to participation in the trial would be to undergo robot assisted laparoscopic prostatectomy or a robot assisted laparoscopic partial nephrectomy according to the surgeon's standard practice and not to participate in the study. No other aspect of patient care would differ.

Financial Costs and Burdens

Subjects will not be compensated for their participation and there are not costs involved in participation. Cost of the study medications, delivery from pharmacy, and administration will not be charged to the subject. The study is internally funded by the Department of Surgery – Urology Division and Department of Anesthesiology and Perioperative Medicine.

Privacy and Confidentiality

We will keep the study records confidential. No identifiers will be used in any reports or publications resulting from the study.

Volunteering Nature of the Study

Participation is entirely voluntary. All aspects of patient's care and monitoring will be unaffected by whether the patient chooses to consent for the study.

Serious Adverse Event (SAE) Reporting

Any SAE will be reported to the IRB as soon as possible, but no later than 5 calendar days. The reporting procedure will be followed as outlined in the University of Missouri protocol found in the "Core Standard Operating Procedure for Event Reporting.".

INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw at any time. All participants must sign and date an IRB approved informed consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant will receive a copy of the signed informed consent form. A copy of the signed informed consent form will be placed in the participant's chart and subsequently scanned into the electronic medical record under Research Consents.

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APPENDECIES

No appendices