

Randomized, prospective evaluation of hemostatic agents in robotic-assisted laparoscopic partial nephrectomy. Version 15. 10/10/2018.

1. Introduction

Partial nephrectomy is a surgical procedure wherein a diseased segment of a kidney is surgically removed, leaving behind the remaining healthy kidney parenchyma¹. This surgical procedure is typically performed to remove mass lesions suspicious for malignancy¹. A major goal of partial nephrectomy is to spare as much renal function as possible by preserving the healthy portion of the kidney while removing only the pathologic portion of the kidney¹.

Hemostatic agents (HA) are commonly used during robotic-assisted laparoscopic partial nephrectomy (RALPN) due to the risk of bleeding posed by incising a highly vascular organ. The use of various HAs as part of the surgical technique for RALPN is well-described¹. Potential benefits such as lower blood loss, lower rate of urine leak, and lower blood product transfusion rates have been suggested in small case series^{2,3,4}. However, larger prospective studies have failed to demonstrate these benefits of HAs. They report similar patient outcomes regardless of HA use^{5,6,7}. However, these studies are subject to selection bias given the lack of randomization, and they had a small relative number of partial nephrectomies performed without HAs. The largest by far of these studies did collect data prospectively from multiple institutions throughout France with fairly similar pre-operative patient characteristics. However, only 15.7% of these patients underwent a RALPN (most underwent open partial nephrectomy), and 80.9% of these patients undergoing RALPN had a HA used⁷.

To our knowledge, no randomized trials have addressed the use of HAs in RALPN. Randomized, controlled trials for partial hepatectomy and knee arthroplasty have shown no benefit when using hemostatic agents to control bleeding^{8,9}.

At our institution, surgeons routinely use HAs in the resection bed during RALPN. Available commercial agents include Floseal, Surgiflo and Nu-Knit. The University of Chicago spends approximately \$750,000 annually on hemostatic agents for the entire operating room services. Each unit of HA costs \$150 - \$419 per unit, and often multiple units are used during a given procedure. The hospital is paid a set amount based on the patient's insurance for performing the procedure regardless of use of HA. The use of HAs therefore increases costs incurred by the hospital when performing these procedures. It is imperative to determine if this expenditure is justified.

The primary aim of this study is to compare surgical outcomes in patients undergoing RALPN with and without the use of hemostatic agents. Given the small nature of and conflicting information from the aforementioned cohort studies, it is imperative to remove selection bias and perform a randomized comparison of HA use. This study will provide a much more definitive head-to-head comparison of the overall utility of HAs.

Additionally, it may provide more information about differential patient selection for more appropriate and judicious use of HAs. No study has evaluated differential patient selection for HA use, and therefore any finding in this realm would be novel.

2. Overview

We will perform a randomized, prospective clinical trial at the University of Chicago Medical Center. Patients undergoing RALPN will be consented for randomization to one of two potential operative techniques agreed upon by two participating surgeons, both of whom are experienced robotic surgeons (Drs. Arie Shalhav and Scott Eggener). The explanation of the trial, determination of eligibility, and consent for participation will be obtained at the pre-operative visit. The patients will be blinded to the use of a HA, but it is not feasible to blind the participating surgeon throughout the duration of the trial. An external randomization process will be performed on the day of the operation.

3. Objective

Our aim is to evaluate whether HAs make a significant clinical difference in patient outcomes when used for RALPN. The result of this trial will determine whether HAs are necessary for use during RALPN or if they can be omitted from the surgical tools available during this procedure. This study has a direct clinical implication on a patient's outcomes following RALPN, specifically whether patients will have better, worse, or unchanged outcomes with RALPN if HAs are used.

4. Hypothesis

There will be a smaller decrease in the absolute change in hemoglobin and there will be a reduced rate of major bleeding complications in patients undergoing RALPN using standard HAs relative to patients who do not receive HAs.

5. Patient Selection and Recruitment

Patients will be recruited during their initial clinic consultation with either Dr. Shalhav or Dr. Eggener. An overview of the trial will be presented to the patients, including information about blinding of the surgeon and the patient to each intervention arm prior to the surgery. A promotional flyer will be displayed within the urology clinic alerting patients to the study. Additionally potential participants (i.e. all patients undergoing RALPN) will be provided a detailed handout explaining the trial after initial consultation. Patients will be counseled that their participation is entirely voluntary and that there is no pressure to participate. A trial consent form will be signed by the patient and the physician either at the time of the clinic visit or at the time of surgery.

6. Methods

6a. Management of the Trial

The mechanics of the trial and database management will be coordinated by the urology resident physicians in the PGY-3R academic year. These individuals will be referred to as clinical trial assistants (CTA).

The study will be monitored by the clinical trials coordinator at University of Chicago within the genitourinary (GU) cancer section. This is primarily coordinated by a Clinical Research Associate. Patient information will be stored and maintained in a confidential, password protected electronic database on a computer in a locked office in the hospital. Any paper records will be locked in a secure office and destroyed at the earliest possible juncture of the study.

6b. Study Groups

All study participants will be undergoing RALPN, with the laterality (right or left) determined by the side of their renal mass. Each patient will be randomized into one of two groups:

Group 1 (HA+): Patients undergoing RALPN *with* the use of HAs by a surgeon.

Group 2 (HA-): Patients undergoing RALPN *without* the use of HAs by a surgeon.

The two surgeons, Drs. Shalhav and Eggener, will perform RALPN in the same way, as outlined in section 6d. Each surgeon will be performing RALPN on patients in Groups 1 and 2.

6c. Blinding

The surgical team and the patient will be blinded as to which arm (Groups 1 and 2, see section **6b**) the patient will be assigned both at the time of recruitment in the clinic and at the start of surgery. The patient and surgeon will both be blinded at the start of the surgery (RALPN). The surgeon will be informed intra-operatively during the renorrhaphy portion of the procedure as to which arm the patient will be assigned, at which point he will be unblinded. Following completion of the entire surgery, the patient will also be informed as to which arm he/she was randomized upon request.

6d. Description of the Surgical Procedure

Below are the steps of RALPN.

1. Patient is taken to the operating room and given general anesthesia.
2. Patient's skin is prepped and draped in a standard sterile fashion.
3. The first incision is then made in the skin, minimally-invasive laparoscopic access to the abdomen is achieved, and the Da Vinci Robot is docked.
4. The kidney is isolated by dissection from the surrounding structures.
5. The blood vessels supplying the kidney are isolated at the renal hilum, and the tumor margins are defined.

6. The blood vessels at the renal hilum are clamped (stopping blood flow to the kidney).
7. The tumor is dissected from the kidney.
8. The renorrhaphy (repair of the kidney) is performed using a suturing technique. This can occur with or without HAs.
9. If the patient is assigned to the hemostatic agent group, they will have these agents placed on the kidney at the end of initial suture closure of renal defect. In 2018, the university switched formulary from Floseal® to Surgiflo®. Surgeons are allowed to use combination of Nu-knit and Surgiflo per surgeon preference.
10. The blood vessels at the renal hilum are unclamped (returning blood flow to the kidney).
11. Gerota's fascia is closed over the kidney if possible.
12. The tumor is removed, the Da Vinci Robot is undocked, and the patient's incisions are closed.
13. The patient is awakened and taken to the recovery room.

6e. Randomization

Each patient recruited into the trial during their clinic visit will be simultaneously scheduled for surgery (RALPN) during this clinic encounter. At this point, no randomization will have occurred.

The randomization sequence will be generated by the trial statistician and set up in REDCap. The randomization sequence will be stratified by surgeon, sex, and whether they are taking aspirin 81 mg daily at the time of surgery to ensure that patient characteristics are balanced for each surgeon.

At the start of the surgery, the patient and surgeon will both be blinded, the patient will be placed under general anesthesia, and the surgeon will begin the RALPN in the standard fashion.

Within the operating room, the circulating nurse will be the first to be informed as to which group the patient has been randomized during steps **4** and **5** as outlined in section **6d**. The circulating nurse will find this information by logging into REDCap and retrieving the randomization assignment. The surgeon will be informed as to which arm the patient is randomized during step **8** of section **6d**.

The scrub technician in the operating room will have hemostatic agents immediately available as is standard protocol for all procedures given that unblinding of the surgeon will occur after the start of the procedure. Additionally, if the patient is randomized to not receive HAs but the surgeon determines that the patient requires HAs to safely complete the procedure, the patient will receive the HA and this event will be recorded.

6f. Inpatient Management

On the day of surgery, all patients will have a BMP and a CBC collected in the pre-operative area. They will then have these labs collected postoperatively at approximately 0400 am on post-operative day 1.

Patients typically receive 1,500 – 2,500 mL of intravenous fluid during the procedure depending on hydration status, blood pressure, and comorbid conditions such as heart failure and lung disease. This is at the discretion of the anesthesia and surgical teams, and involves real-time feedback intra-operatively based on how well the patient is tolerating the procedure. Postoperatively, patients will be given resuscitative normal saline intravenously at a rate of approximately 2.0 mL per kilogram of ideal body weight, as is standard practice at the University of Chicago.

Patients are given additional IV fluid based on the inpatient team's discretion. Patients will be given 1,000 mL of normal saline as an additional IV fluid bolus if the patient becomes hemodynamically unstable or has urine output less than 0.5 mL/kg/hr. This will be repeated until the parameter has been corrected.

All patients standardly receive 5000 units of heparin by subcutaneous route in the pre-operative suite prior to surgery for DVT prophylaxis. Patients then receive this same heparin dose every 8 hours until discharge.

7. Data Collection

7a. Primary Data Collection

Data collected will include: age, sex, BMI, basic metabolic panel, complete blood count, anticoagulant medications, clinical stage, tumor characteristics, nephrometry score (RENAL scoring system), hospital and postoperative course parameters (length of stay, charges, total additional IV fluid), comorbidities, operative time and parameters, and surgical complications as defined below. All data will be prospectively collected from patient medical records.

7b. Additional Data Collection

Patients will have basic laboratory data collected including a BMP and a CBC in the pre-operative area as well as postoperatively at approximately 0400 am on post-operative day 1. Patients will have a BMP and a CBC collected at the first post-operative visit. It will also be noted whether the patient is on dialysis in the pre-operative and post-operative setting.

8. Patient Inclusion and Exclusion Criteria

8a. Inclusion Criteria

1. Male and female patients aged 18 years and older.

2. Patients must have a solid or cystic renal mass suspicious for malignancy by imaging with ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI).
3. Patients must be initially scheduled RALPN as opposed to radical nephrectomy or other techniques for partial nephrectomy such as open surgery or pure laparoscopy without robot assistance.
4. Patients with bilateral kidneys or a solitary kidney, so long as these are native kidneys as opposed to a transplanted kidney.
5. Patients can have the common single renal artery and single renal vein, or they can have common variants such as two renal arteries and/or two renal veins.

8b. Exclusion Criteria

1. Patients on hemodialysis.
2. Patients who have had a renal transplantation.
3. Patients on therapeutic anticoagulation prior to surgery (example anticoagulants include: aspirin 325 mg daily, clopidogrel, warfarin, fondaparinux, dabigatran, and rivaroxaban). However, patients who take aspirin 81 mg daily as their daily regimen will be included.
4. Patients with bleeding disorders (example: hemophilia) and other documented coagulopathy (example: chronic liver disease) with INR > 1.0 at baseline.
5. Patients who have had a prior surgical procedure, aside from percutaneous renal biopsy, on the kidney in the current operation.
6. Patients with over 100 mL of estimated blood loss (calculated by anesthesia team using the suction canisters) prior to clamping of the renal hilum will be excluded.

9. Outcomes

9a. Primary Outcome

The primary outcome to be assessed is the absolute change in hemoglobin. This will be measured as the difference between the hemoglobin obtained postoperatively (measured at approximately 4 am in the morning after surgery) and the hemoglobin obtained preoperatively in the holding area on the day of surgery.

$$\Delta \text{ Hemoglobin} = \text{Preoperative Hemoglobin} - \text{Postoperative Hemoglobin}$$

9b. Secondary Outcomes

1. Total number of major bleeding complications. Major complications are blood loss requiring transfusion of packed red blood cells, reoperation, and endovascular ablation⁷.
2. Safety monitoring parameters: stroke, death, cardiac arrest, myocardial infarction, and urine leak.

3. Operating room parameters including number of sutures used during renorrhaphy and capsular closure, duration of renorrhaphy, and patients in Group 2 (no HA) who required HA at the surgeon's discretion.
4. Total length of all inpatient hospital stay over 30 days measured in days.
5. Total charges for all inpatient care over 30 days.

10. Study Power Analysis and Statistical Analysis Plan

Sample Size. Based on data from a recent large retrospective study⁵, a mean delta hemoglobin of 2.7 g/dL (pre-surgery minus post-surgery) was observed in the group receiving no hemostatic agents. Group sample sizes of 89 and 89 achieve 80% power to detect a delta hemoglobin difference of 0.6 g/dL between the null hypothesis that the mean delta hemoglobin is 2.7 g/dL in both groups and the alternative hypothesis that the mean delta hemoglobin in the +HA group 2.1 g/dL with group standard deviations of 1.6 g/dL (-HA group) and 1.2 g/dL (+HA group). This is estimated using a significance level (alpha) of 0.05 and a two-sided two-sample t-test.

Lang et al reported⁷ transfusion rates of 2% and 10.6% in HA and no HA groups, respectively. We will have 80% power with one-sided alpha of 0.05 to detect such a difference in transfusion rates in our study. If we do see a difference of this magnitude using the Chi-squared test, then we will conclude that the omission of HAs results in this adverse outcome.

Safety Monitoring. The secondary endpoint is the rate of serious adverse events (AEs) including stroke, death, MI (9b), which is expected to be low (~ 5%). In order to determine whether removing HAs increases the AE rate, we will use a continuous safety monitoring approach based on the sequential generalized likelihood ratio test (SGLR) for two-arm studies (Shih et al).

AEs are defined by the United States Food and Drug Administration (FDA) as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Serious adverse events (SAE) as defined by the FDA include the following outcomes: death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defect, required intervention to prevent permanent impairment or damage (devices), and other serious medical events that may require medical or surgical intervention.

Briefly, AEs are assumed to follow Poisson distribution with rates λ_t and λ_c in the treatment (HA-) and control groups (HA+), respectively. GLR tests the null hypothesis that the event rates are equal vs. the alternative $H_a: \lambda_t/\lambda_c \geq \gamma$. This corresponds to $H_a: p \geq \gamma/(1 + \gamma)$ where $p = \lambda_t/(\lambda_t + \lambda_c)$ is the proportion of events that occur in the treatment group. For example, $\gamma = 4$ corresponds to testing that the proportion of AEs in the treatment arm is $H_0: p \leq 0.5$ vs $H_1: p \geq \gamma/(1 + \gamma) = 0.8$. Boundaries for rejecting or accepting H_0 are determined empirically by an extensive search algorithm among, and satisfy the pre-specified Type I and Type II error constraints. Crossing the upper boundary provides sufficient evidence that the treatment is not safe, and the trial will be

stopped. Crossing the lower boundary suggests that treatment is "safe enough". In the proposed trial, we will only stop the trial if the upper boundary is crossed, i.e. only if there is enough evidence of an increased AE rate in the HA- arm.

The boundary for the number of events in HA- group necessary to declare the treatment unsafe is given in the table below. Safety monitoring will be performed continuously after each AE occurs in either arm, and the total number of events in the HA- group will be compared to the boundary below:

Total AEs	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Reject if $N(\text{HA-}) \geq$	5	6	7	7	8	9	10	10	11	12	12	13	13	14	15	15	16	17	17	18	18

*Estimated thresholds are $b_0=2.453$ and $b_1=1.639$ (Shih et al)

For example, if there are a total of 10 AEs in both arms, we'll conclude that HA-complication rate is unacceptably high if there are ≥ 9 AEs in the no HA group.

The boundaries were calculated using `sglr` package in R. We assumed that AE rates in the two arms are $p_{\text{HA}+} = 0.05$ vs. $p_{\text{HA}-} = 0.20$, which corresponds to $\gamma = 4$ as above, and set $\alpha = 0.1$ and $\beta = 0.2$. We conducted a simulation study to assess the performance of this boundary when only the upper boundary is used for early stopping, and the sample size is $n = 89$ per group. Based on 10,000 simulations, this design yields $\alpha = 0.0664$ and 88.09% power¹⁰.

Statistical Analysis. The primary analysis will compare changes in hemoglobin between treatment arms using two-sample t-test. T-test or Wilcoxon ranksum tests will be used to compare continuous variables between groups, and Chi-squared or Fisher's exact test will be used to compare categorical variables between treatment groups. In particular, Length of hospital stay during the first 30 days and 30-day care costs will be compared between treatment groups using the Wilcoxon ranksum test because these variables are likely to be skewed and non-normally distributed. Multivariable linear regression models will be used to adjust for other covariates, including age, gender, and side of tumor. Serious complications will be monitored as described above.

11. Confidentiality

Several proactive measures will be taken to maintain the privacy of the subjects. When compiling information in the database for statistical analysis, unique identifiers (ID) will be generated. All patient identifying data will be removed prior to transfer to a statistician. No individual research subject will be identified in any reports from the study, which will be statistical in nature. Every effort will be made for all the personal information and the study test results to be kept confidential and used exclusively for research purposes. There is a potential for the loss of the privacy despite the precautions described.

12. Study Risks and Benefits

12a. Surgery Risks

The risks of this surgery include but are not limited to the bleeding, infection, need for blood transfusions, need for further procedures (including reoperation and endovascular ablation), urine leak, cardiac arrest, DVT, PE, stroke, and death. These are the same risks whether RALPN is performed with the use of HAs.

12b. Hemostatic Agent Risks

The HAs (Floseal, Surgiflo and Nu-Knit) do not have any known specific risks that are independent of robotic partial nephrectomy.

The risk of not receiving HAs during surgery include blood loss requiring transfusion of packed red blood cells, reoperation, and endovascular ablation.

12c. Blood Draw Risks

There could be bruising at the site where you will be getting your blood drawn as well as possible inflammation of the vein or an infection. There is also a slight risk of fainting. Blood draws will be performed by skilled phlebotomists, nurses, and physicians so as to minimize the risk of these complications.

12d. Potential Benefits ^[L]_{SEP}

There may not be any direct patient benefits to patients in this study. It is unknown if patients who receive HAs during RALPN have better, worse, or the same outcomes as patients who do not receive hemostatic agents.

13. Safety Monitoring

Patients enrolled in the study will receive the standard pre-operative and post-operative care. This includes inpatient monitoring for recovery and complications from this surgery while the patient is an inpatient (vitals monitoring, blood draws, and rounding by nursing and physician staff); these are not specific to the study, but the blood draw values will be recorded for study purposes. During the surgery, the only difference will be whether or not a HA was used during one portion of the procedure. The standard of care for RALPN includes both use and no use of HAs, and therefore all patients will fall into receipt of standard of care. All study subjects, regardless of group, who experience a surgical complication will receive the standard of care specific to that complication.

Preliminary data will be evaluated after 25%, 50%, and 75% of the total enrollment and reviewed with a statistician, at which points we will determine whether to proceed or close. This will be reviewed as part of the weekly GU oncology clinical trials meeting. The CTAs and statistician will review and present the data. If there are more than 10 major complications in one group, the study will need to be halted for safety concerns.

14. Informed Consent

Patients diagnosed with a kidney mass will be provided with treatment options. If the patient is a candidate for robotic-assisted laparoscopic partial nephrectomy and wishes to proceed with this surgery, he/she will be offered admittance to the trial. If the patient agrees to join the trial, then consent will be obtained at that consultation encounter from which surgery will be scheduled.

15. Study Schedule

Visit Number	Visit Type	Window Allowance	Visit Location	Patient Forms, Lab tests, and Evaluation
1	Eligibility & Baseline		Office	- Medical history - Physical examination - Inclusion/Exclusion assessment - Informed consent form
2	Treatment	Up to 6 months	Inpatient	- Pre-surgery CBC upon admission to hospital - RALPN with randomization - Post-surgery CBC at 0400 am on post-operative day 1 - Assessment of major complications and additional procedures - Measurement of hospital stay - Total cost of the surgery
3	4-week	4 weeks $\pm$ 1 week	Office	- Assessment of major complications and additional procedures

16. Abbreviations

BMI:	Body Mass Index
BMP:	Basic Metabolic Panel
CBC:	Complete Blood Count
CT:	Computed Tomography
CTA:	Clinical Trial Assistant
DVT:	Deep Vein Thrombus
GU:	Genitourinary
HA:	Hemostatic Agent
ID:	Unique Identifiers
MRI:	Magnetic Resonance Imaging
PE:	Pulmonary Embolus
RALPN:	Robotic-Assisted Laparoscopic Partial Nephrectomy

17. Principal Investigator and Statistician

Study Principal Investigator: Arie Shalhav, MD

Co-Investigator: Scott Eggener MD

Statistician: Ted Karrison, PhD

18. References

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