The role of hemostatic agents in preventing complications in laparoscopic partial nephrectomy

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Introduction
Nephron-sparing surgery is currently the treatment of choice for renal cell carcinoma stage T1a. During the past years, several hemostatic agents (HA) have been developed in order to reduce surgical complications. We present the results of our series and the impact of the use of HA in the prevention of surgical complications in laparoscopic partial nephrectomies (LPNs).

Material and methods
We retrospectively analyzed all LPN performed in our center from 2005 to 2012. A total of 77 patients were included for analysis. Patients were divided into two groups: Group A (no use of HA) and Group B (use of HA). HA used included gelatin matrix thrombin (FloSeal) and oxidized regenerated cellulose (Surgicel). Demographics, perioperative variables, and complications were analyzed with a special interest in postoperative bleeding and urinary leakage.

Results
Median age was 57.17 years old (±12.1), 72.7% were male, most common comorbidities were hypertension (33.8%) and diabetes mellitus (18.2%). All patients had one solitary tumor, and 87% had a tumor ≤4 cm. Renal cell carcinoma was found in 79.2% of cases, and 78.7% were stage pT1a. and were used in 36 cases (46.8%). No differences were found in demographics, perioperative variables, and complications between groups. No conversions to open surgery or perioperative mortality were reported.

Conclusions
We conclude that in our series the use of a hemostatic agent did not offer benefit in reducing the complication rate over sutures over a bolster.

Key Words: hemostatic agents • partial nephrectomy • laparoscopic • renal cell carcinoma

INTRODUCTION
Nephron-sparing surgery (NSS) or partial nephrectomy (PN) has become the standard of care in the management of small and asymptomatic renal masses, avoiding overtreatment in cases with benign histology and preventing the renal function impairment that would result from a radical nephrectomy. At first, it was the preferred treatment in cases of a solitary functional or anatomical kidney, but because of the multiple benefits, today it is widely used in patients with a healthy contralateral kidney [1, 2, 3].

Recent studies have demonstrated an improvement in non-oncological outcomes for low-stage tumors in patients treated with PN [3], and similar oncologic outcomes for selected cases compared to radical nephrectomy [6, 7, 8]. The European Association of Urology guidelines recommend this type of surgery in the management of patients with renal carcinoma stage T1a, and favor it over radical nephrectomy in patients with a stage T1b whenever feasible [4]. Laparoscopic partial nephrectomy (LPN) is a minimally invasive technique that has shown favorable renal function outcomes, a shorter hospital stay, and a decreased use of analgesics.
in our series of LPNs. The past decades, numerous hemostatic agents (HA) have been developed and used to assist in hemostasis and collecting system closure during open and LPN. Some of the currently available products include thrombin sealant, fibrin glue, oxidized methylcellulose and gelatin matrix [14]. Even though different HAs are widely used in urological surgeries worldwide, and specifically in partial nephrectomy, the evidence on their efficacy in reducing complications is limited [15, 16, 17].

The purpose of the present study was to evaluate the efficacy of HA in reducing post-operative complications, particularly hemorrhage and urinary leakage in our series of LPNs.

**MATERIAL AND METHODS**

After institutional review and ethics committee approval, medical records of patients who had undergone LPN at our center were collected. Between January 2005 and December 2012, a total of 101 patients underwent LPN at our center for a unique renal tumor stage T1a and T1b. Exclusion criteria were: missing crucial data during follow-up for the statistical analysis, or intraoperative conversion to radical nephrectomy. After reviewing medical records, we excluded 16 patients who had missing data or continued their follow-up at another center; and 8 patients that had an intraoperative conversion to radical nephrectomy. Seventy-seven patients were included in the final analysis.

We reviewed patients’ demographics (age, hypertension, diabetes, prior abdominal surgery, blood analysis etc.), tumor characteristics found on contrast-enhanced CT scan (tumor size, location, growth pattern), intraoperative data (operation time, ischemia time, use of hemostatic agent, suturing of the collecting system, transfusions), immediate post-operative data (transfusions, complications, blood analysis) and postoperative data (re-admissions, blood analysis, definitive pathological diagnosis).

A laparoscopic transperitoneal technique in the extended flank position with four trocars was performed in all cases. Lateral attachments of the colon were carefully taken down in order to deflect the colon medially. On the right side, the duodenum was exposed and then mobilized medially by means of the Kocher maneuver until the vena cava was clearly visualized. On the left side, mobilization took place from the splenic flexure downwards. The ureter and gonadal vein were identified and retracted laterally. Dissection was carried cephalad along the psoas muscle until the renal hilum was identified and dissected, depending on the tumor size and location, clamping (en bloc or selectively) was performed or not depending on each case. The tumor was identified, in cases with the use of a laparoscopic ultrasound probe, and excised with cold scissors (partial nephrectomy or enucleation). An excisional biopsy of the base was sent for frozen section analysis. The tumoral bed was closed with a hemostatic running 2-0 Vicryl suture, which was also used to close the collecting system in case there was a need to divide it to achieve an adequate margin. Injection of dilute methylene blue via a preplaced ureteral catheter was performed in selected cases to confirm adequate closure.

The renal parenchymal repair was completed using simple 0 or 2-0 Vicryl sutures secured with Hem-o-Lok clips (Weck Closure System, Research Triangle Park, NC). If the surgeon decided to use a hemostatic agent, this was applied to the cut surface. In cases where a hemostatic agent was not used, parenchymal sutures were positioned over a bolster of Surgicel, with the objective to cause a compression effect and to prevent sutures from pulling through; this was not intended as a hemostatic effect. The excised tumor was placed in a sac and extracted through a minimally extended lower abdominal port incision. Drainage was placed via a port incision.

All surgeries were performed by two surgeons from the same institution, under equal circumstances. The decision to use a HA or not was based on each surgeon’s preference in each individual case. The two HAs used in our series were gelatin matrix thrombin tissue sealant (FloSeal; Baxter Healthcare, Deerfield, IL, USA) and oxidized regenerated cellulose (Surgicel; Ethicon, Somerville, NJ, USA).

We divided patients into two groups for analysis, according to those in which a HA was used or not; Group A: no use of HA, Group B: use of HA. Significant hemorrhage was defined as the need for perioperative blood transfusion. Complications were classified according to the Clavien-Dindo classification, the need for a perioperative blood transfusion and development of urinary leakage/fistula were analyzed separately.

Serum hemoglobin was measured pre-operatively and at postoperative day one, serum creatinine was measured preoperatively and at the first-month visit. Pathological diagnosis included TNM stage and histology of the tumor. We sought to compare if any perioperative variables or if the use of a HA could protect for significant for complications, especially for hemorrhage and developing a urinary leakage/fistula. Statistical analysis was performed using
SPSS 17.0 (New York, USA). Results were described as numbers and percentages, means, and standard deviations. Comparisons were made using chi-square test and Student t-test. Significance was set at p value of <0.05.

RESULTS

Seventy-seven patients that underwent a LPN for clinical T1a or T1b renal tumors between 2005 and 2012 were analyzed. Demographics, clinical tumor characteristics and perioperative data of the entire cohort are summarized in Table 1.

The most common final diagnosis was a primary renal cell carcinoma (clear cell carcinoma) in 61 patients (79.2%), the rest of patients had: oncocytoma (11 cases), angiomyolipoma (3 cases), renal papillary adenoma (1 case) and 1 case of metastasis of an adenoid cystic carcinoma of the submandibular salivary gland, treated with radiotherapy three years before. HAs were used in 36 patients (Group B). Comparisons between both groups are shown in Table 2. The two groups were comparable in age, gender, past medical history of abdominal surgery, preoperative hemoglobin and serum creatinine levels, radiological tumor characteristics (size, location, and endophytic or exophytic growth pattern), ischemia time, suturing of collecting system and rate of malignant tumors. In group A, nine complications were noted in eight patients. Two patients developed transitory renal insufficiency that recovered with intravenous fluids (Clavien I), three patients received a perioperative blood transfusion and two patients developed paralytic ileus (Clavien II). In both groups, three patients required ureteral stenting with a double J stent because of a urinary leakage (Clavien III). In group B, only one case required prolonged analgesic control and two patients developed transitory renal insufficiency (Clavien I). Four cases received perioperative blood transfusions, two developed paralytic ileus and one had a surgical wound infection (Clavien II). No postoperative mortalities were registered, and no recurrences were documented within a mean follow-up of 31.4 months.

DISCUSSION

Nowadays, NSS is a well-established approach for patients with localized renal tumors in which preservation of renal function is desired. LPN is a demanding procedure that requires extensive knowledge of the tumor anatomy for the excising part, and advanced skills for the reconstructive part. Technical limitations remain for the control of bleeding and closure of the collecting system during the procedure [18].

Table 1. Demographics, perioperative data, and follow up of the entire cohort (n = 77)

|                                | n (%) ± |
|--------------------------------|---------|
| Median age, years (±sd)        | 57.17 ±12.1 |
| Male / Female                  | 56 (72.7%) / 21 (27.3%) |
| Comorbidities, n               |         |
| Hypertension                   | 26 (33.8%) |
| Diabetes Mellitus              | 14 (18.2%) |
| Ischemic cardiopathy           | 4 (5.2%) |
| COPD                           | 4 (5.2%) |
| Previous abdominal surgery     | 29 (37.6%) |
| Radiological tumor location    |         |
| Upper pole                     | 20 (26%) |
| Middle aspect                  | 27 (35.1%) |
| Lower pole                     | 30 (38.9%) |
| Right side                     | 45 (58.4%) |
| Left side                      | 32 (41.6%) |
| Radiological tumor size        |         |
| Mean diameter, cm (±sd)        | 2.91 ±0.99 |
| ≤4                             | 67 (87%) |
| >4 cm                          | 10 (13%) |
| Mean hemoglobin, g/dl (±sd)    | 14.59 ±1.49 |
| Pre-operative                  | 12.25 ±1.62 |
| Mean serum creatinine, mg/dl (±sd) | 0.98 ±0.21 |
| Pre-operative, 1 month         | 1.14 ±0.37 |
| Mean ischemia time, min (±sd)  | 27.7 ±6.7 |
| Suturing of the collecting system, n | 31 (40.2%) |
| Perioperative blood transfusion, n | 7 (9.1%) |
| Urinary leakage                | 5 (6.5%) |
| Acute renal failure            | 5 (6.5%) |
| Infection (any)                | 2 (2.6%) |
| Histology                      |         |
| Renal cell carcinoma           | 61 (79.2%) |
| Oncocytoma                     | 11 (14.3%) |
| Angiomyolipoma                 | 3 (3.9%) |
| Renal papillary adenoma        | 1 (1.3%) |
| Metastasis                     | 1 (1.3%) |
| Pathological stage (out of 61 RCC) |         |
| pT1a                           | 48 (78.7%) |
| pT1b                           | 5 (8.2%) |
| pT3a                           | 8 (13.1%) |
| Positive margins, n            | 9 (14.7%) |
| Mean hospital stay, days (±sd)  | 4.85 ±3.6 |
| Mean follow-up, months         | 31.4 ±23.2 |
Initially, PN was used to treat patients with an anatomically or functionally solitary kidney, bilateral renal tumors, or comorbidities that might affect renal function [19]. Today, PN is an established and well-known approach for most patients with a localized renal mass, since cancer-specific survival and metastasis-free survival are similar in all T1N0M0 renal tumors treated with PN or radical nephrectomy [6, 18]. The most important complications of PN are severe bleeding (requiring blood transfusions) and urinary fistulas. In the prospective, randomized European Organization for Research and Treatment of Cancer intergroup phase 3 study, reported by Van Poppel et al., rates were 3.2% for hemorrhage and 4.4% for urinary leakage [9]. In the Prospective National Observational Registry on the Practices of Hemostasis in Partial Nephrectomy, conducted in France, involving 570 patients, the overall postoperative bleeding requiring transfusion rate and urinary leakage rates were smaller, at 2.7% and 1.9%, respectively [14].

Hemorrhagic complications are the most common severe surgical complications after NSS, being more related to the diameter and complexity of the tumor than with the surgical approach (either laparoscopic or robotic-assisted) [16]. Bleeding should be minimized in order to avoid hypovolemia, anemia, hemodynamic deterioration, and the adverse outcomes associated with allogeneic blood transfusion [20–24]. This is the main reason for the constant development and usage of hemostatic-sealant agents; available products include absorbable hemostats such as gelatin, collagen and oxidized regenerated cellulose and active hemostats such as thrombin and fibrin sealants [24]. Usage of HA in PN has a great popularity worldwide, although its significance in preventing hemorrhage and urinary leakage is not evidence-based. In 2007, Breda et al. [15], reported their results of a large multi-institutional survey, analyzing usage patterns of HAs in 1347 LPNs performed in 18 centers in the United States and Europe. The result was that up to 80% of urologists used HA intraoperatively, and 16 of the 18 centers, consistently performed parenchymal suturing over a bolster. The authors concluded that although some advantage was seen favoring the use of HA, their use should be limited to control minor bleeding in conjunction with other measurements, including parenchymal suturing over a bolster. The authors concluded that although some advantage was seen favoring the use of HA, their use should be limited to control minor bleeding in conjunction with other measurements, including parenchymal suturing over a bolster. The French multi-institutional survey, published by Lang et al., in 2014, revealed that a HA was used in up to 71.4% of patients undergoing PNs. In this retrospective study, the authors found no statistical difference between patients who received a HA with those who did not in any of the variables analyzed in the study (including blood loss and transfusion rate) [14].

Only one randomized multicenter trial compared the use of absorbable collagen (TachoSil) as HA, with sutures alone in PN, finding a shorter time to hemostasis in the HA group. The authors concluded that this HA was superior to standard treatment (sutures alone) in obtaining intraoperative control of bleed-

### Table 2. Comparison of patients according to intraoperative use of hemostatic agents. No difference was found in any of the comparisons mentioned (p >0.05 for all)

|                          | No use of HA (GROUP A) | Use of HA (GROUP B) |
|--------------------------|------------------------|---------------------|
| Number of patients, n    | 41 (53.2%)             | 36 (46.8%)          |
| Median age, years (± sd) | 58.6 ±12.2             | 56.27 ±11.8         |
| Prior abdominal surgery, n| 18 (43.9%)             | 11 (30.5%)          |
| Gender, male             | 30 (73.2%)             | 26 (72.2%)          |
| Radiological tumor size  |                        |                     |
| ≤4 cm                    | 33 (80.5%)             | 32 (88.9%)          |
| >4 cm                    | 8 (19.5%)              | 4 (11.1%)           |
| Radiological tumor location, n |                   |                     |
| Upper pole               | 11 (26.8%)             | 9 (25%)             |
| Middle aspect            | 16 (39%)               | 11 (30.5%)          |
| Lower pole               | 14 (34.2%)             | 16 (44.5%)          |
| Right                    | 26 (63.4%)             | 19 (52.8%)          |
| Left                     | 15 (36.6%)             | 17 (47.2%)          |
| Endophytic pattern       | 21 (51.2%)             | 17 (47.2%)          |
| Exophytic pattern        | 20 (48.8%)             | 19 (52.8%)          |
| Mean serum creatinine, mg/dl (±sd) |           |                     |
| Pre-operative            | 1.01 (±0.21)           | 0.95 (±0.22)        |
| Post-operative, 1 month  | 1.09 (±0.31)           | 1.12 (±0.41)        |
| Mean hemoglobin, g/dl (±sd) |                     |                     |
| Pre-operative            | 14.56 (±1.66)          | 14.52 (±1.25)       |
| Post-operative           | 12.55 (±1.67)          | 12.39 (±1.39)       |
| Mean ischemia time, min (± sd) | 26.68 (±6.9) | 28 (±6.4)          |
| Suturing of the collecting system, n | 18 (43.9%) | 13 (36.11%)       |
| Histology                |                        |                     |
| Renal cell carcinoma     | 30 (73.2%)             | 31 (86.1%)          |
| Oncocytoma               | 7 (17.1%)              | 4 (11.1%)           |
| Angiomyolipoma           | 2 (4.9%)               | 1 (2.8%)            |
| Renal papillary adenoma  | 1 (2.4%)               | 0                   |
| Metastasis               | 1 (2.4%)               | 0                   |
| Post-operative complications, n |                       |                     |
| Clavien-Dindo I          | 1 (2.43%)              | 2 (5.5%)            |
| Clavien-Dindo II         | 6 (14.6%)              | 4 (11.1%)           |
| Clavien-Dindo III        | 2 (4.8%)               | 2 (5.5%)            |
| Perioperative blood transfusion | 3 (7.3%)     | 4 (11.1%)          |
| Urinary leakage / fistula| 3 (7.3%)               | 2 (5.5%)            |
ing, and may be particularly of value in patients with only one kidney. It should be noted that in this study all patients had small, superficial tumors that did not extend into the renal collecting system [25]. No published studies have compared the efficacy between different HA, or the use of a HA versus parenchymal suturing over a bolster.

A retrospective single-center analysis, published by Abu-Ghanem, et al in 2016, analyzed their results in 657 patients. They compared four groups of patients that underwent a PN: sutures alone vs. sutures and HA, sutures alone vs. sutures and Surgicel, sutures plus HA and Surgicel vs. sutures and Surgicel. In the proper comparisons, the addition of a HA (either to suture alone, or sutures and Surgicel) did not show a statistically significant difference in the rate of perioperative blood transfusions, prevalence of urinary leakage, postoperative renal failure, or delayed bleeding (hematuria, flank hematomat, and pseudoaneurysm) [26].

Theoretical benefits of HA in PN include: minimizing postoperative bleeding, limiting warm ischemia time by decreasing the amount of intracorporeal suturing, and in some cases potentially promoting collecting system healing and reducing urinary leakage [15]. Although both groups in our study were comparable in terms of preoperative and intraoperative variables, the complication rate was similar. The use of HA did not improve or alter the rate of perioperative hemorrhage as well as the rate of urinary leakage/fistula when compared to sutures over a bolster. In terms of surgical complexity, the number of patients who had an endophytic tumor and had suture of the collecting system was comparable between both groups, and so was the rate of developing a urinary leakage/fistula. Our results are similar to those of recent publications that did not find a reduced complication rate in patients in whom a HA was used [16, 17, 26, 27]. More precisely, authors concluded that the use of HA alone or HA plus parenchymal suturing over a bolster (of Surgicel) did not reduce rates of complications, including urinary leakage, or perioperative blood transfusion, [26, 27] and that omitting HA use in LPN and Robot-assisted LPN could be cost-effective [28]. The final cost per case may vary depending on the agent used and the quantity. Considering the economic burden in high-volume centers, and the lack of benefits reported with HA, pharmaco-economic studies are required to define in a proper manner if HAs improve safety, shorten operative time and reduce complications in NSS [26, 28].

Limitations of our study include the sample size of patients from a single center, its retrospective nature, and the lack of randomization. Also the use of only two hemostatic agents with no randomization, and that no definitive indications on the use of HAs were established. Although, it is remarkable in our study that both groups are comparable and homogeneous in their demographics and perioperative outcomes. All patients underwent a laparoscopic approach performed by expert laparoscopic surgeons, under the same environment. We need prospective randomized control studies to establish the real benefit of HAs, and to discover which patients could benefit the most in terms of reducing operative time and complications rate reduction.

**CONCLUSIONS**

In our study, the use of HA in LPN did not improve the rate of significant postoperative complications such as hemorrhage or urinary leakage in our series. A proper renorrhaphy over a bolster during partial nephrectomy may be enough to prevent hemorrhagic complications and urinary leakage. Further studies are necessary to support our findings and conclude evidence-based recommendations. Clear indications are needed for standardizing the use of HA with clear indications, and to discover if a subgroup of patients could benefit the most.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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