

Sutureless laparoscopic partial nephrectomy using fibrin gel reduces ischemia time while preserving renal function

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Summary *Objectives: We evaluated the efficacy of sutureless laparoscopic partial nephrectomy (LPN), using a fibrin gel in order to minimize renal ischemia time and preserve kidney function.*

Materials and Methods: Nineteen patients (mean age 58.3 ± 7.1) undergoing sutureless LPN using a fibrin gel were compared with a control group consisting of 21 patients (mean age 57.9 ± 7.5) subjected to LPN with standard suturing. Intra- and post-operative data for the two groups were compared. The following parameters were recorded: patient demographics, Charlson Comorbidity Index, tumor characteristics according to the RENAL score, warm ischemia and operative times, estimated blood loss, mean hospital stay, post-operative complications referring to the Clavien-Dindo classification, renal function parameters pathologic and follow-up data. The main outcome measure was renal ischemia time and maintenance of kidney function.

Results: Median warm ischemia time was 13 minutes (range 11-19) in the group treated with fibrin gel and 19 (range 17-29) in the control group, with a statistically significant difference ($p < 0.001$). The two groups were homogeneous in terms of the Charlson Comorbidity Index (4.6 vs 4.8) and RENAL score (9.6 vs 9.4). Median operative time differed significantly in the two groups, 183 minutes (range 145-218) in the group treated with fibrin gel and 201 (range 197-231) in the control group ($p < 0.001$). A negative surgical margin was reported in 18 patients (94.7%) in the group treated with fibrin gel and in 21 patients (100%) in the control group. No difference in renal function was found between the two groups.

Conclusions: Sutureless LPN with fibrin gel can reduce warm ischemia and total operative time while preserving kidney function.

KEY WORDS: Laparoscopic partial nephrectomy; Renal cell carcinoma; Haemostatic agent; Fibrin sealant; Complication.

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INTRODUCTION

Laparoscopic partial nephrectomy (LPN) is the “first-choice treatment” for patients with small renal masses (≤ 4 cm). Oncological outcomes are similar to those observed after a radical procedure, with well demonstrated benefits such as a lower risk of long-term renal insufficiency and consequently better prospects for the quality of life (1-4). However, LPN remains a technically complex procedure

because of the difficulties in hemostasis and management of collecting-system injuries (4). Various techniques, instruments and agents have been proposed to minimize intracorporeal suturing and warm ischemia time, but there is no consensus regarding the best approach when dealing with these issues (5). A wide variety of hemostatic agents (HA) and tissue sealants have been employed, the majority approved for use in urology (6). Levinson *et al.* described the first series of 7 partial nephrectomies with these agents, highlighting the safety of the procedure, its contribution to lowering warm ischemia time and the absence of any reported complications (7). Hidas compared changes in renal function after *Nephron-Sparing Surgery* (NSS) using HAs alone versus standard suturing; and reported renal functional loss of 11% versus 20%, respectively, highlighting how the surgeon should aim for shorter warm ischemia times (8). The present study assessed the efficacy of sutureless LPN using a fibrin gel (*Tissucol*®) in order to minimize renal ischemia time and preserve kidney function, when compared with LPN standard suturing.

MATERIALS AND METHODS

Study design

Data from 19 patients (mean age 58.3 ± 7.1) who had undergone sutureless LPN using *Tissucol*® between October 2008 and July 2009 were compared with those from a control group of 21 patients (mean age 57.9 ± 7.5) subjected to LPN with standard suturing during the same period. All patients underwent standard laboratory examinations and radiologic evaluations before tumour staging and surgical planning. Demographic and tumor characteristics following the RENAL score were recorded and the Charlson Comorbidity Index was calculated. All procedures were carried out by a single dedicated uro-oncologic surgeon (G.M.). The following variables were also recorded: operative time, warm ischemia time, estimated blood loss, intra-operative transfusion and complications (intra-operative data); post-operative complications using the Clavien-Dindo classification and any subsequent treatment, post-operative hospital stay, renal function, pathologic and follow-up findings (post-operative data). Renal function was evaluated through a change in serum creati-

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nine or estimated glomerular filtration rate (eGFR) from the baseline according to Gill *et al.* (9). Percent change in serum creatinine and eGFR was determined by calculating the difference between pre-operative and follow-up data. Follow-up visits were scheduled every 6 months after surgery. Here, we present the long-term follow-up (12 months) results of renal function preservation.

Ethical consideration

The retrospective nature of the study did not require the Ethical Committee approval. The study was, however, conducted in line with Good Clinical Practice guidelines, with ethical principles laid down in the latest version of the Declaration of Helsinki.

Inclusion and exclusion criteria

Requirements for inclusion were the presence of a single, solid, contrast-enhanced parenchymal renal mass (attenuation increase > 15 H on contrast-enhanced CT or > 15% on gadolinium-enhanced MRI) consistent with renal cell carcinoma on pre-operative imaging and scheduled for LPN (10). Patients with severe medical or psychiatric illness barring adequate informed consent, under 18 or over 85 years, with major concomitant diseases precluding surgical treatment or who had had radiation therapy to the retroperitoneum or previous abdominal major surgery, with an ASA score ≥ 3 , poor performance status (ECOG 3-4), known anatomical abnormalities of the uro-genital tract, renal vein involvement, lymphadenopathy, extrarenal tumor extension or pre-operative CT scan documenting invasion of the collecting system were all excluded. Patients with positive cytologic urine analysis or with a previous history of urothelial carcinoma were also excluded.

RENAL score and Charlson comorbidity index

The R.E.N.A.L.-Nephrometry score (NS) was calculated according to Kutikov *et al.* (11). In brief, standardized points (1-3 points per descriptor) are assigned based on tumour size, endophytic/exophytic properties, proximity to the collecting system and lesion location relative to the polar lines. The Charlson Comorbidity Index was calculated using the specific software available on the Institute for Algorithmic Medicine website (A Texas Non-profit Corporation) (<http://www.medal.org/OnlineCalculators/ch1/ch1.13/ch1.13.01.php>) (12).

Surgical technique description (TISSUCOL® group)

Patients were positioned in strict lateral decubitus and four trocars were routinely inserted. LPN was performed via a transperitoneal approach. No pre-operative ureteral stent was routinely placed. Gerota's fascia was opened, the ureter identified and the renal artery isolated (Figure 1). Vascular control was achieved by clamping the renal artery before tumour resection (Figure 1) (warm ischemia time included tumour resection, evaluation of bleeding and application of sealant). During warm ischemia, resection was performed with an electrocautery device and cold-cut endo-shears (Figure 2). The perinephric fat was dissected from the kidney at the level of the renal capsule, leaving only the fat overlying the tumour. In all cases, fibrin glue (Tissucol® - Baxter AG) was used as the sealant (Figure 3). No addi-

Figure 1.
The figure shows renal vein (V) and artery (A) isolation (above) and the subsequent renal artery clamping (below).

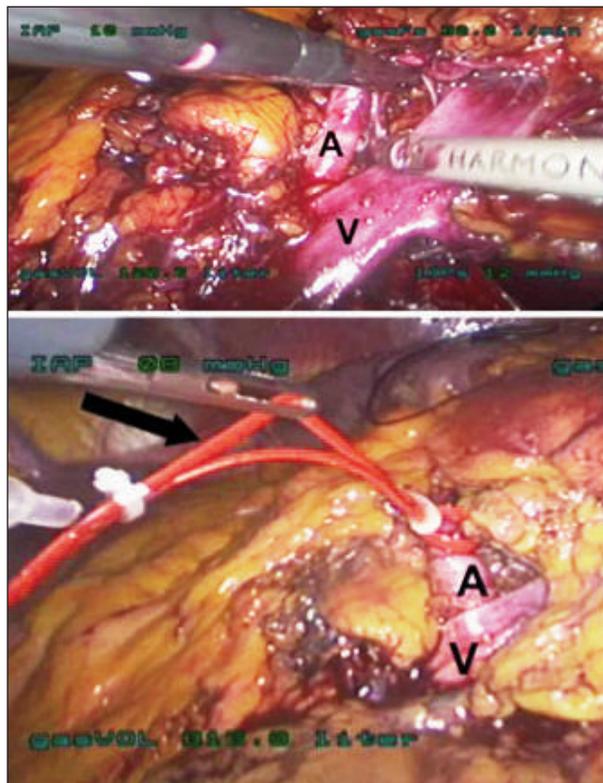
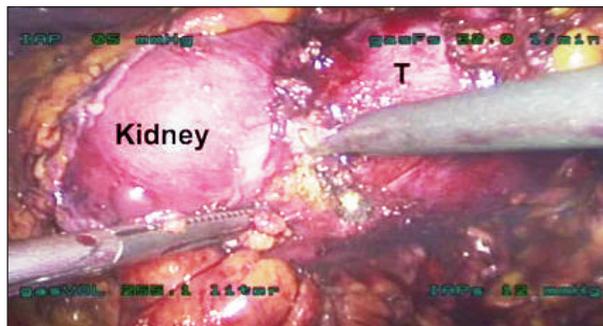


Figure 2.
The figure shows the renal mass resection with an electrocautery device and cold-cut endoshears. T: tumour.



tional methods of hemostasis (including suturing) were applied. Fibrin glue was spread on the tumour bed using a specific device that allowed the two major components to be applied simultaneously. We used a dual chamber delivery system, in which fibrinogen and factor XIII contained in one chamber were admixed with thrombin in the other directly at the application site. Clot formation required 3 minutes and final elimination by macrophages occurred within 2-4 weeks without inducing fibrosis or foreign body reactions (13). The surgical specimen with the tumour and any detached perinephric fat was immediately placed in an *Endo-catch*® bag which was removed at the end of the procedure through the 12-mm port site, extending the incision if necessary (Figure 4). Biopsy and frozen sections of the resection bed were only performed when tumour infil-

Figure 3.

The figure shows the intraoperative TISSUCOL® application on the bed of resection.

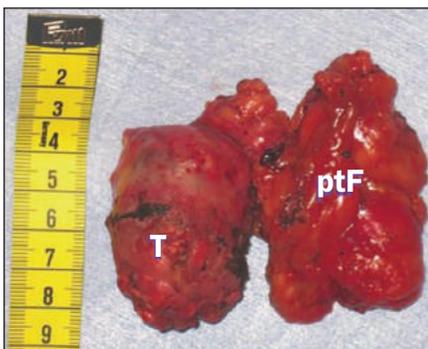
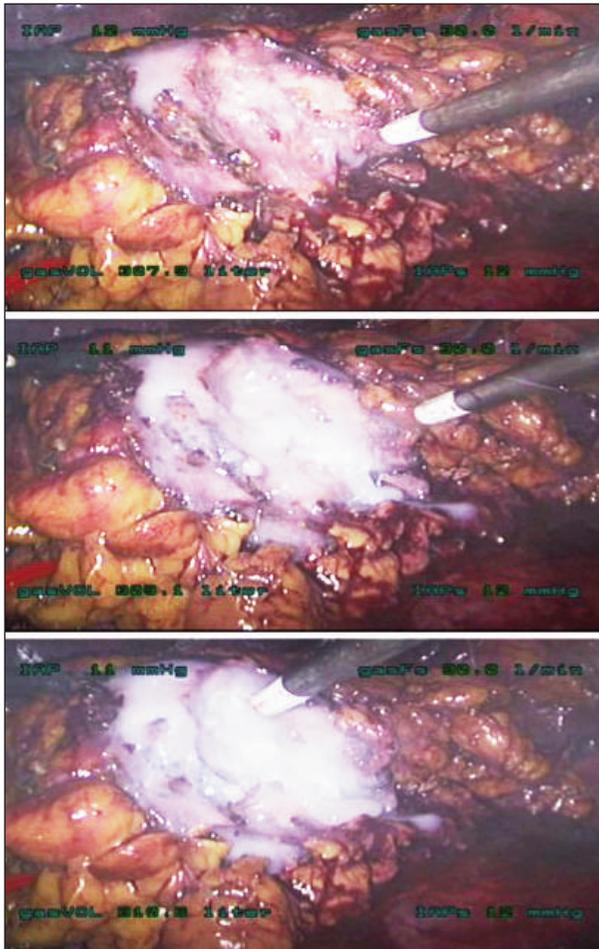


Figure 4.

The figure shows the resected tumour (T) with the overlying fat (ptF).

tration was suspected, as suggested by *Porpiglia* (14). In the case of a positive biopsy, radical nephrectomy or deeper resection depended on the individual case.

All patients in the control group underwent standard suturing LPN, as described by *Porpiglia* (14).

Histological analysis

Histopathology was reviewed according to the 2004 WHO classification (15). All renal cell carcinomas were classified according to the TNM staging system (16), while nuclear grade was assigned according to the criteria proposed by *Fuhrman et al.* (17).

Preoperative complication evaluation

Perioperative complications were classified according to the Clavien-Dindo system (18).

Statistical analyses

Data were entered into a Microsoft Excel database and transferred to SPSS 11.0 for Apple-Macintosh (*SPSS, Inc., Chicago, Illinois*). Descriptive analysis was used to evaluate all the variables considered. Qualitative analyses were compared using the Chi-2 or Fisher exact tests where applicable, and quantitative analyses with Student's t-test. Data are presented as the mean \pm standard deviation (SD) or percentage. Correlations were assessed by Pearson or Spearman test. Statistical significance was achieved if p was less than 0.05. All reported p-values were two-sided.

RESULTS

Patient characteristics at baseline

In the TISSUCOL® group, the mean age-adjusted Charlson comorbidity index was 4.6 (range 4-7) and mean RENAL score 9.6 (range 8-12), and in the control group 4.8 (range 4-7) and 9.4 (range 8-11), respectively. Table 1 gives the clinical, laboratory and pathologic characteristics of the enrolled patients.

Intra-operative and peri-operative data

TISSUCOL® group

After 2-3 minutes of applying the fibrin glue to the resection site, hemostasis was immediate in all cases. All surgery was performed intracorporeally and without hand assistance. Median vascular clamping time was 13 minutes (range 11-19) and median operative time 183 minutes (range 145-218). Median blood loss was 300 ml (range 150-600). No open conversions were required. Five patients (26.3%) presented low-grade complications (Clavien II). Four patients (21%) needed blood transfusions, while one patient showed intraoperative invasion of the collecting system that had not been documented pre-operatively by CT scan. This patient was treated with ureteral stenting for 7 days.

Control group

All surgery was carried out intracorporeally without hand assistance. Median vascular clamping time was 19 minutes (range 17-29) and median operative time was 201 minutes (range 197-231). Median blood loss was 290 ml (range 150-550). There were no open conversions. Eight patients (38%) showed low-grade complications (Clavien II), while five patients (23.8%) required blood transfusions.

Statistically significant differences were found between the two groups for mean ischemia time ($p < 0.001$), median operative time ($p < 0.001$) and mean blood loss ($p < 0.02$). All intra and peri-operative data are summarized in Table 2.

Histological results

In the TISSUCOL® group, 18 cases were classified as conventional RCC and 1 as angiomyolipoma, while in the control group 19 were diagnosed as conventional RCC

Table 1.
Patient anamnestic and clinical characteristics at enrolment time.

Group	TISSUCOL®	Control	P
No. of patients	19	21	-
Mean age (years) (± SD*)	58.3 ± 7.1	57.9 ± 7.5	0.86
Gender			0.72
Male	13	16	
Female	6	5	
Mean tumor size at CT scan (cm) (± SD*)	3.1 ± 0.9	2.9 ± 0.8	0.78
Charlson CI§	4.6	4.8	-
R.E.N.A.L score	9.6	9.4	-
Side of lesion			0.74
R°	6	8	
L†	13	13	
Location of lesion			0.68
Superior pole	5	4	
Inferior pole	7	9	
Central	7	8	
Location of lesion in renal parenchyma			0.72
Exophytic	13	16	
Deep	6	5	
Pathological results			-
Renal cell carcinoma	18	19	
Angiomyolipoma	1	-	
Oncocytoma	-	2	
Fuhrman grade in malignant tumors			0.80
G1	6 (33.3)	7 (36.9)	
G2	7 (38.9)	9 (47.4)	
G3	5 (27.8)	3 (15.7)	
G4	0	0	
Stage according to UICC classification in malignant tumour			0.65
pT1b	16 (88.8)	15 (78.9)	
pT2	2 (11.2)	4 (21.1)	

Table 2.
Peri-operative parameters, complications and renal function.

Group	TISSUCOL®	Control	P
Mean operative time (min) (± SD*)	183 ± 25.9	201 ± 27.8	< 0.001
Median ischemia time (min) (± SD*)	13 ± 2.3	19 ± 3.5	< 0.001
Mean blood loss (mL) (± SD*)	359 ± 142.8	460 ± 126.7	0.02
Rate of intra-operative transfusion (%)	4/19 (21)	5/21 (23.8)	-
Conversion to open nephrectomy	0/19	3/21 (14.2)	0.23
Mean hospital stay (days) (± SD*)	5.8 ± 1.6	6.0 ± 1.5	-
Post-operative acute hemorrhagic event	0/19	1/21 (4.7)	-
Post-operative hematoma with transfusion (%)	1/19 (5.2)	3/21 (14.2)	0.23
Post-operative urinary leakage with urethral stenting	1/19 (5.2)	2/21 (9.5)	-
eGFR (mL/min/1.73 m ²)			-
pre-operative (± SD*)	80.5 ± 10.9	81.2 ± 9.8	
post-operative (± SD*)	78.3 ± 11.3	79.4 ± 13.3	

and 2 as oncocytoma. There was no sign of residual tumor on frozen section examination of the resection bed in either group. All pathologic data are detailed in Table 1.

Clinical outcome results

Post-operative hospitalization times were normal for all patients in the TISSUCOL® group (median 5 days, range 4-7) with no relevant complications as regards wound healing or laboratory analyses. There were no significant

short-term bleedings from the draining tubes, which were removed before patient discharge. No adverse events were observed during hospitalization or at long-term follow-up (79.6 ± 8.9 months). As regards post-operative hospitalization times or complications, no significant differences were found between the two groups.

Kidney function preservation

Post-operative renal function remained stable in all patients. No statistically significant differences were found between the two groups in terms of eGFR results at the follow-up visit. In the TISSUCOL® group mean eGFR was 78.3 (range 42-127) and in the control group 79.4 (range 55-130). Table 2 shows laboratory data at the time of enrolment and follow-up visit.

DISCUSSION

LPN is increasingly performed all over the world and constitutes a valid procedure for the management of small renal tumours, but some technical aspects still need to be improved. Even in expert hands, rates of urine leakage and hemorrhage are not negligible (19). Despite the development of adjunctive hemostatic agents, none have proved to offer complete hemostasis by themselves (19). In this paper, we demonstrated that sutureless LPN with TISSUCOL® can reduce warm ischemia and total operative times as well as preserve kidney function, without severe complications when compared with standard suturing LPN. In particular, renal suturing during LPN is a difficult step, which increases operative and warm ischemia time. The use of HAs may well simplify the hemostatic procedure, providing similar results to those observed after suture renorrhaphy.

Our results highlight some important points. The mean ischemia time of 13.8 minutes is significantly shorter than that reported by *Lifshitz et al.* (31 min) (20). Thus, the mean total operative time (183 minutes) is also significantly shorter than described by other Authors (14, 21). These results can be explained by the fact that a sutureless technique reduces both total ischemia and operative times.

Concerning renal function maintenance, our results are promising when compared with the standard technique, probably due to the shorter mean ischemia time in the TISSUCOL® group. *Breda et al.*, in a comprehensive review of the practice patterns of urologists performing LPN and the relevant use of hemostatic agents, underlined that although these agents appear to offer some advantage, they should be limited to controlling minor bleeding and as an adjunct to sutured bolsters (22). In describing an alternative technique of LPN for central tumours, *Weight et al.* concluded that in selected patients with a tumor extending

to the collecting system, the LPN defect can be safely reconstructed with a running intraparenchymal hemostatic suture and thrombin sealant with no bolstered renorrhaphy (23).

We observed two post-operative complications (bleeding in one case and urine leak in the other), while no open conversion was necessary. In both cases the renal tumour was described as "deep". Several authors have demonstrated the association between depth of tumour invasion and rate of hemorrhage or urine leakage (21-22, 24). The present study shows some limitations that should be taken into account, such as the small number of patients and the lack of a control group. Further prospective studies in larger series are mandatory to validate the role of HAS during LPN.

CONCLUSIONS

In our experience, sutureless LPN using TISSUCOL® can reduce warm ischemia and total operative time whilst preserving kidney function with no severe complications when compared with standard suturing LPN.

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