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ORIGINAL PAPER

Bleeding during laparoscopic partial nephrectomy: Can a hemostatic matrix help to improve hemostasis?

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Summary ***Objectives: To evaluate the possible role of an hemostatic matrix on hemostasis, perioperative outcomes and complications in patients who underwent laparoscopic partial nephrectomy (LPN).***
Materials and methods: Patients charts were analyzed retrospectively and their demographic characteristics, operative parameters and follow-up results were recorded. Patients were divided into two groups, according to those who used an hemostatic matrix as Group 1 (n = 41) and those who did not used as Group 2 (n = 44). Demographic characteristics of patients, tumor features, operation time, clamping of the renal vessels, ischemia time, suturing of the collecting system, perioperative hemorrhage and complications were evaluated. Histopathological results, surgical margin status, creatinine level and recurrence at the 3rd month of follow up were analyzed. Statistical analyses were performed with SPSS 17.0 and significance was set at p value of < 0.05.
Results: The mean RENAL nephrometry score was 5.9 ± 2.0 and the mean tumor size was 35 ± 12 mm. All patients had a single tumor and 44 of them had a tumor in the right kidney. The renal artery was clamped in 79 cases and the mean ischemia time was 20.1 ± 7 minutes. The mean tumor size and the mean RENAL nephrometry score was statistically higher in Group 1 (p: 0.016 and p < 0.001, respectively). Pelvicaliceal repair was more common in Group 1 due to deeper extension of tumors in this group (p: 0.038). In Group 1, less hemorrhage and blood transfusion requirement, with shorter ischemia and operation time was detected.
Conclusion: The outcomes of the recent study showed that adjunctive use of an hemostatic matrix improves hemostasis and decreases hemorrhagic complications during LPN. Further prospective studies are required to assess the potential role of an hemostatic matrix in LPN.

KEY WORDS: *Hemostatic matrix; Partial nephrectomy; Renal cell cancer.*

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INTRODUCTION

Previous studies demonstrated that nephron-sparing surgery has similar oncologic outcomes in selected patients when compared to radical nephrectomy (1, 2). Laparoscopic partial nephrectomy (LPN) is a minimally invasive nephron sparing technique with favorable renal function outcomes, shorter hospital stay and decreased postoperative analgesic use (3). However, LPN is a technical challenging procedure and associated with potential complications including urinary leakage and bleeding requiring transfusion (4). Since LPN was firstly reported, several techniques for tumor excision and hemostasis have been investigated to achieve a bloodless operative field for precise tumor excision is an acceptable ischemia time and with the least possible deterioration of renal function (5). However, use of the suture techniques is time consuming and may cause additional tissue damage (6). Some renal hemostatic agents have been previously described for use during LPN, to improve hemostasis and decrease complication rates. However, there is no consensus on the routine use of hemostatic agents during LPN. In a recent study, we aimed to investigate the possible role of an hemostatic matrix *FloSeal* (©*FloSeal Baxter Healthcare Corporation*) on hemostasis, perioperative outcomes and complications in patients who underwent laparoscopic partial nephrectomy (LPN).

MATERIAL AND METHODS

In our clinic, laparoscopic partial nephrectomy (LPN) for renal tumours was performed in 85 patients by a single surgeon between May 2009 and February 2014. In patients with organ confined renal tumours with up to 7 cm in size, without lymph node and venous involvement, LPN was performed. Informed consent was obtained from all the patients.

Patients' charts were analyzed retrospectively and their demographic characteristics, operative parameters and follow-up results were recorded.

Patients were divided into two groups, according to those who used *FloSeal* as Group 1 (n = 41) and those who did not used as Group 2 (n = 44).

A transperitoneal technique in the extended flank position with three trocars was preferred in all the patients. If necessary, additional trocar was inserted for liver or spleen retraction and re-postioning of the kidney. After incision of the Todt line, dissection continued medially to expose the renal artery and vein. Endoscopic bulldog clamps were used to interrupt blood flow, and peripheral small lesions were resected without hilar clamping. Partial nephrectomy was performed with monopolar scissors. Major transected intrarenal were stiched up with eight sutures, while renal parenchymal hemorrhage was kept.

Prepackaged hemostatic agent with a combination of 1.5

No conflict of interest declared.

ml of bovine gelatin matrix and 5000 US of bovine-derived thrombin.
This syringe was applied with an application device introduced into the abdomen through a laparoscopic port.
The renal artery was then unclamped to terminate warm ischemia.
Demographic characteristics of the patients and tumor features were compared between the two groups. Intraoperative parameters including operation time, clamping of the renal vessels, ischemia time, suturing of the collecting system, perioperative hemorrhage and complications were also evaluated.
Hemorragic complication was defined as bleeding leading to convert open surgery or radical nephrectomy and intraoperative or postoperative bleeding requiring transfusion. Histopathological results, surgical margin status, creatinine level and recurrence at the 3rd month of follow up were also analyzed.

Statistical analysis

Statistical analyses were performed with SPSS 17.0 (New York, USA).
Results were described as numbers, means, standard deviations and percentages. Comparisons were performed by the chi square test, Student t test and Mann Whitney U test.
Significance was set at p value of < 0.05.

Table 1.
Preoperative demographic data of patients.

	N°	Percentage (%)
Gender		
Male	50	58.8%
Female	35	41.2%
Mean follow up time (months)	52.2+/-27.7	
Mean BMI (kg/m^2)	24.7+/-3.0	
ASA score		
1	52	61.2%
2	25	29.4%
3	8	9.4%
Comorbidities		
None	50	
Hypertension	24	
Diabetes mellitus	19	
Coronary arterial disease	6	
Chronic obstructive pulmonary disease	5	
Smoking		
Yes	53	62.4%
No	32	37.6%
Radiological tumor location		
Lower pole	42	49.4%
Middle pole	31	36.5%
Upper pole	12	14.1%
Complaint		
Follow up	34	40%
Lower urinary tract symptoms	1	1.2%
Weakness	1	1.2%
Hematuria	9	10.6%
Weight loss	2	2.4%
Abdominal pain	2	2.4%
Flank pain	36	42.4%
Mean R.E.N.A.L. score	5.9+/-2.0	
Mean tumor size (millimeters)	35+/-12	

Results

The mean age and the mean BMI of all patients were 58.8+/-10.9 years old and 24.7+/-3.0 kg/m2.
All patients had a single tumour and 44 of them had a tumour in the right kidney. Eight patients had an ASA score of three, while hypertension and diabetes mellitus were the most common comorbidities.
The mean RENAL nephrometry score was 5.9 ± 2.0 and the mean tumor size was 35 ± 12 mm.
Demographic data are listed in Table 1.
FloSeal was used in 41 patients and wedge resection was

Table 2.
Perioperative and post operative data of patients.

	N°	Percentage (%)
Mean preoperative hemoglobin (g/dl)	13.0+/-1.3	
Mean preoperative creatinine (mg/dl)	1.09+/-0.35	
Mean postoperative day one hemoglobin (g/dl)	12.0+/-1.5	
Mean postoperative creatinine at 3rd month (mg/dl)	1.07+/-0.3	
Side		
Left	41	48.2%
Right	44	51.8%
Tumor extraction technique		
Wedge resection	79	92.9%
Enucleation	6	7.1%
Hemostatic agent usage		
Yes	41	48.2%
No	44	51.8%
Suturing of the collecting system		
Yes	28	32.9%
No	57	67.1%
Turning to open surgery		
Yes	4	4.7%
No	81	95.3%
Blood transfusion need		
Yes	11	12.9%
No	74	87.1%
Mean perioperative hemorrhage (ml)	153.6+/-50.2	
Mean operation time (minutes)	136.7+/-55.3	
Perioperative complications		
Hemorrhage	5	5.9%
Clavien complications		
0	70	82.4%
1	10	11.8%
2	2	2.4%
3	3	3.6%
Mean ischemia time (minutes)	20.1+/-7	
Mean hospitalization time (days)	3.5+/-1.6	
Histology		
Angiomyolipoma	13	15.3%
Complicated cyst	1	1.2%
Oncocytoma	3	3.5%
Renal cell cancer	68	80%
Grade of RCC		
1	42	
2	21	
3	6	
Pathological stage		
T1a	65	76%
T1b	18	21.2%
T2	2	2.4%
Surgical margin		
Negative	83	
Positive	2	
Recurrance at 3rd month follow up		
Yes	0	
No	85	

the most common technique for partial nephrectomy. The renal artery was clamped in 79 cases and the mean ischemia time was 20.1 ± 7 minutes.

The mean perioperative hemorrhage was 153.6+/-50.2 ml and blood transfusion was required in 11 patients. Suturing of the collecting system was performed in 28 patients. The most common histopathology was renal cell carcinoma and angiomyolipoma. Patients' preoperative data and pathological results are detailed in Table 2.

The mean tumor size and the mean RENAL nephrometry score was statistically higher in Group 1 ($p = 0.016$ and $p < 0.001$, respectively).

Pelvicaliceal repair was more common in Group 1 due to deeper extension of tumors in this group (p: 0.038).

In Group 1, use of *FloSeal* provided better bleeding control with less hemorrhage and blood transfusion requirement. Because of the less stiches requirement in group 1, the mean ischemia time and the time operation were 18.2 and 115.6 minutes, respectively and these parameters were shorter in group 1 when compared with Group 2 ($p = 0.038$). None of the laparoscopic procedures in Group 1 was converted to open surgery whereas in Group 2, four patients were converted to open surgery due to uncontrolled bleeding in two, decision for radical nephrectomy in one and technique difficulty in one. Comparison between the two groups is summarized in Table 3.

Table 3.
Comparison of patients according to perioperative hemostatic agent usage.

	Hemostatic agent usage		
	Yes	**No**	**P value**
Number	41	44	
Mean age (years)	56.8	60.7	0.101
Mean follow up time (months)	39+/-17.2	64.4+/-24.5	< 0.001
Mean BMI (kg/m^2)	25.2	24.3	0.169
ASA score			0.365
Tumor size (mm)	38.2	32	0.016
Mean R.E.N.A.L. score	6.8	5.1	< 0.001
Mean hemoglobin drop (g/dl)	1.01	1.07	0.842
Mean creatinine level change (mg/dl)	0.04	- 0.02	0.143
Mean perioperative hemorrhage (ml)	132.9	172.9	< 0.001
Mean operation time (minutes)	115.6	156.4	< 0.001
Mean ischemia time (minutes)	18.2	21.9	0.013
Mean hospitalization time (days)	3.4	3.6	0.555
Comorbities			
None	27	23	0.399
Hypertension	9	13	
Diabetes mellitus	8	10	
Coronary arterial disease	0	5	
Chronic obstructive pulmonary disease	2	3	
Complaint			0.151
Follow up	19	15	
Lower urinary tract symptoms	0	1	
Weakness	1	0	
Hematuria	1	8	
Abdominal pain	1	1	
Flank pain	17	19	
Smoking			
Yes	23	30	0.251
No	18	14	
Radiological tumor location			
Lower pole	18	24	
Middle pole	17	14	
Upper pole	6	6	
Tumor extraction technique			0.108
Wedge resection	40	39	
Enucleation	1	5	
Turning to open surgery			0.048
Yes	0	4	
No	41	40	
Blood transfusion need			0.005
Yes	1	10	
No	40	34	
Clamping of the renal vessels			0.112
Yes	36	43	
No	5	1	
Perioperative complication			0.084
Hemorrhage	0	5	
Clavien complications			0.422
0	35	35	
1	4	6	
2	1	1	
3	1	2	
Histology			0.264
Angiomyolipoma	7	6	
Complicated cyst	0	1	
Oncocytoma	0	3	
Renal cell cancer	34	34	
Grade of RCC			0.044
1	16	26	
2	15	6	
3	3	3	
Pathological stage			0.298
T1a	29	36	
T1b	10	8	
T2	2	0	
Surgical margin			0.960
Negative	40	43	
Positive	1	1	

Discussion

Although previous studies have shown that LPN is a feasible and effective minimally invasive technique in the surgical treatment of selected patients with renal tumors, its potential risk of bleeding requiring transfusion is well known (7, 8). Bleeding should be minimized to avoid hypovolemia, anemia, hemodynamic deterioration and exposure to the risk of transfusion (9). It is also important to achieve optimal visualization of the surgical site to enabling an acceptable ischemia time and oncologic outcome (10). Control of bleeding in LPN, is an active area of investigation since uncontrolled hemorrhage negatively affects the mortality and morbidity rates, as well as the convalescence period.

Traditional surgical methods including suture, energy based coagulation systems, ligature and hemostatic clips can be used to handle bleeding (12, 13).

Available hemostatic agents include absorbable hemostats such as gelatin, collagen and oxidized regenerated cellulose and active hemostats such as thrombin and fibrin sealants (16).

Fibrin sealants were reported as easy to use but not effective in dealing with major vascular injury.

Therefore, a combination of different hemostasis methods has been investigated (17).

In a previous study the authors compared seven hemostatic agents in an animal partial nephrectomy model (17). The authors concluded that hemostatic agents were

effective for small vascular injuries. However, sutured bolsters were required for large partial nephrectomies. *Hutchinson et al.* (11) evaluated the effectiveness of fibrin pad consisting of human thrombin and fibrinogen delivered to the targeted site by an absorbable synthetic matrix in an animal model. The authors have demonstrated that fibrin pad was as effective as conventional methods for the primary management of severe bleeding without the need for hilar control with a shorter operative time.

Dalpiaz et al. (19) reviewed the use of hemostatic agents in 15 animal model studies and 11 clinical trials concluding that fibrin sealants were effective in both animal and clinical studies. *Richter et al.* and *Bak et al.* (20, 21) investigated the use of *FloSeal* in LPN in two different studies. In both studies no renal suturing was used, none of the patients underwent pelvicaliceal repair and none of the patients required blood transfusions. *Gill et al.* (6) evaluated the use of *FloSeal* during LPN.

The authors found that the adjunctive use of *FloSeal* substantially enhanced parenchymal hemostasis and decreased the procedural and hemorrhagic complications.

LPN with the use of *FloSeal* is a feasible and safe method for the treatment of small renal tumour.

FloSeal facilitates the conversion of fibrinogen to fibrin and creates an insoluble fibrin clot acting as a hemostatic sealant. *FloSeal* includes gelatin granules, which swell in case of hemorrhage and mechanically control the bleeding by creating a composite hemostatic plug. *FloSeal* can be injected through a single laparoscopic port with a short application time and does not require a completely dry surgical field to be effective.

Disadvantages of *FloSeal* include cost, possible allergic reactions and potential transmission of prion diseases (22). In the present study, *FloSeal* was used as single hemostatic agent in all the patients. None of the patients experienced adverse effect associated with *FloSeal*. Suturing was used for renal collecting system repair, in case of major transected intrarenal vessels and severe parenchymal hemorrhage.

Intraoperatively, hemostasis was sufficient in all the patients. Mean tumor size and mean warm ischemia time were 35+/-12 mm and 20.1+/-7 minutes, respectively. These were comparable with previous studies (4, 5, 17). Previous studies described an association between the depth of tumor invasion and rate of hemorrhage.

Ramani et al. (22) investigated complications associated with LPN and showed that 53% of 19 patients requiring transfusion due to hemorrhage had deep tumors.

In this study, the *FloSeal* group tended toward significantly fewer hemorrhagic complications although the depth of tumor invasion was higher. Our findings showed that *FloSeal* provides better bleeding control with less hemorrhage and blood transfusion requirements, with significantly shorter operation and warm ischemia time. Although our findings support previous trials advocating that *FloSeal* is a safe and effective hemostatic agent, we think that it should be used as an adjunctive method in conjunction with suturing techniques, for major bleedings from large vessels or renal parenchyma. Although the current study is one of the rare studies investigating the use of *FloSeal* as a hemostatic agent in LPN, it has some limitations including its retrospective design and relatively small number of patients.

In conclusion, *FloSeal* is a safe,reliable and effective hemostatic agent, which can be used during LPN to avoid hemorrhagic complications. *FloSeal* may potentially enhance the technique of LPN and help the surgeon to perform the procedure more comfortably.

Further prospective, randomized and controlled studies are required to evaluate the potential role of *FloSeal* in LPN.

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