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Comparison of gelatine matrix–thrombin sealants used during laparoscopic partial nephrectomy

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OBJECTIVE

To compare haemostasis and other outcomes after the use of bovine-derived or porcine-derived gelatine matrix-thrombin sealants (GMTS) in a continuous series of patients during and for 6 months after laparoscopic partial nephrectomy (LPN).

PATIENTS AND METHODS

Between October 2006 and September 2007, a consecutive sample of 35 patients with renal tumours underwent LPN by a single surgeon at a referral centre. Group 1 (25 patients) received a bovine-derived GMTS and Group 2 (10 patients) a porcine-derived GMTS. All patients underwent LPN and received one of the two GMTS, applied to the resected bed before sutured renorrhaphy over oxidized nitrocellulose bolsters. Surgical and pathology variables, including ischaemia time, blood loss, tumour size, and serum creatinine values before and after LPN, were measured. Glomerular filtration rates were calculated before and after LPN. Haemostasis was ascertained by visual examination.

RESULTS

Intraoperative haemostasis was achieved in all cases. No associated complications occurred within 3 weeks of LPN. The two groups were comparable in age (median, 65 vs 69 years, $P = 0.62$), gender, tumour number and location, median ischaemia time (34 vs 28 min, $P = 0.148$), and blood loss (200 vs 150 mL, $P = 0.518$). One patient in Group 1 developed a urinary fistula. One patient in Group 2 experienced self-limited gross haematuria.

CONCLUSIONS

Both the porcine- and bovine-derived agents provided acceptable haemostasis without adverse events during LPN and in the early postoperative period. Occurrences of delayed haemorrhage and urinary fistula were not likely to be related to the choice of prothrombotic agent.

KEYWORDS

complications, haemostasis, kidney cancer, laparoscopic, partial nephrectomy, thrombin

INTRODUCTION

Over the past decade there has been a per capita increase in cases of kidney cancer, with nearly 70% diagnosed incidentally as clinical T1 lesions [1]. Preferred management for these tumours includes nephron-sparing surgery (NSS) when possible and laparoscopic partial nephrectomy (LPN) may be offered as a minimally invasive option in selected cases [2,3]. Like open techniques, LPN is a complex surgical procedure that requires adequate tumour resection, renal reconstruction, and durable haemostasis, while optimally preserving renal function.

Control of bleeding after tumour excision remains a central concern for both open and minimally invasive nephron-sparing procedures, prompting several innovations focused on achieving durable haemostasis [4–6]. Obtaining haemostasis is perhaps most challenging in LPN, where space and access can be limited. In LPN, limitations in ischaemia time also necessitate the use of agents or materials that work quickly and do not potentiate the risk of renal damage or fistula formation.

Haemostatic agents, such as gelatine matrix thrombin (GMT), oxidized cellulose, microfibrillar collagen, and fibrin glue have been in use since 1979 and adapted for NSS [7]. More recently, GMT sealants (GMTS) have been increasingly used [8]. Approved by the Food and Drug Administration in 1999, they consist of two components: thrombin and a granular gelatine matrix derived from purified animal cross-linked collagen. GMTS can provide immediate, durable haemostasis, and their use in surgical applications has become routine, although they have not been adequately studied for comparative efficacy for various procedures [9]. Studies of the use of porcine-derived collagen GMTS for PN have not been previously published.

Collagen substrate for GMTS obtained from bovine (FloSeal, Baxter Healthcare; Deerfield, IL, USA) and porcine (Surgiflo, Johnson & Johnson; New Brunswick, NJ, USA) tissue sources represent the two most used commercially available materials. Both preparations are admixed with thrombin solution before use to create a colloidal paste. This can be applied through a syringe-driven applicator onto the surface where a thrombogenic seal is desired.

Herein we describe our experience using commercially available bovine- (FloSeal) or porcine-based (Surgiflo) GMTS in a cohort of patients undergoing LPN by a single surgeon. GMTS groups are compared for perioperative

TABLE 1 The patients' preoperative clinical characteristics

Variable	Total	Group 1	Group 2	*P*
Number of patients (%)	35	25 (71)	10 (29)	
Median (range) age, years	65 (40–85)	64 (40–85)	70 (42–85)	0.6
N (%):				
Gender,				
Female	12 (34)	10 (40)	2 (20)	
Male	23 (66)	15 (60)	8 (80)	0.3
Side of mass,				
Right	18 (51)	10 (40)	8 (80)	
Left	17 (49)	15 (60)	2 (20)	0.033
Location,				
Upper pole	10 (29)	8 (32)	2 (20)	
Middle	6 (17)	4 (16)	2 (20)	
Lower pole	19 (54)	13 (52)	6 (60)	0.8
Median (range) size, cm	2.7 (0.9–8.7)	2.7 (0.9–8.7)	1.9 (1.3–3.5)	0.01

outcomes and short-term haemostatic efficacy.

PATIENTS AND METHODS

Between December 2006 and August 2007, 35 consecutive patients with kidney tumours underwent LPN by a single surgeon (J.C.), using GMTS and using similar technique. The selection of GMTS for each patient was determined by the availability of each sealant on the day of the procedure rather than by a systematic process of randomization. The study period occurred during a specific period when the hospital was assessing these products. The supply of these products was not uniform across the time period reviewed. Clinical data were collected through the institutional prospective kidney cancer database, and retrospective review was approved by the Institutional Review Board.

Patients were divided into two groups based on GMTS used: Group 1 comprised 25 patients who received bovine collagen GMTS (FloSeal) and Group 2 comprised 10 patients receiving porcine collagen GMTS (Surgiflo). Surgical technique for renorrhaphy was uniform across the series. Choice of transperitoneal or retroperitoneal approach was based on tumour location. Renal ischaemia was performed by main renal artery or branch artery occlusion with laparoscopic bulldog clamp as necessary to obtain a clear operative field. Attempted renal cooling during ischaemia was used in two patients with solitary kidney by cold retrograde intraureteric perfusion. Ultrasonography was used in all cases to evaluate tumour localization and depth. Lesions were sharply excised using cold scissors. Recognized pelvicalyceal entry was reconstructed with absorbable 3/0 polyglactin suture. Suturing for haemostasis was performed with 2/0 or 3/0 polyglactin suture when necessary, using figure-of-eight sutures when larger transected vessels were repaired. A suspension of ≈10 mL of GMTS was prepared according to the manufacturer's instructions and applied with a volume sufficient to cover the cut surface. A flat section of oxidized cellulose was positioned covering the GMTS followed by rolled bolsters of oxidized cellulose. Capsular renorrhaphy was performed with interrupted zero polyglactin sutures. No ureteric catheters were used. Closed suction drains were placed in cases of collecting system entry or risk for urinoma.

Measurements from preoperative cross-sectional imaging studies were used to identify the number, diameter, and location of tumours. Perioperative complications were defined as any adverse event of grade ≥2 occurring within 30 days of the procedure. The serum creatinine values before and after LPN were evaluated. Estimated glomerular filtration rate (eGFR) was calculated with the abbreviated Modification of Diet and Renal Disease study equation [10]. Abnormal renal function was defined as an eGFR of <60 mL/min/1.73 m^2. A change in eGFR was expressed as a percentage change from the level before LPN to level at the time of the last follow-up after LPN.

A perinephric drain was used in 34 (97%) patients at the time of surgery. Drain fluid creatinine level was measured before hospital discharge in 30 (88%) patients with drains. Urinary fistula was defined as an elevated drain creatinine level necessitating a continuation of the drain for >7 days after LPN. Adequate haemostasis was defined as no visible sign of bleeding from the surgical site during 20 min of intraoperative observation after completion of renorrhaphy in the fully perfused kidney. Haemostasis was classified as delayed if additional steps (i.e. sutures, pressure, and additional GMTS application) were required after vascular reperfusion and as immediate if no additional steps were needed.

Demographic, laboratory, radiographic, operative, perioperative, pathological, and postoperative data were recorded. Variables, including blood loss, ischaemia time, length of stay, intraoperative complications, and dynamic changes in eGFR, were analysed and compared. A clinical database of baseline, perioperative, and follow-up data was maintained prospectively.

For statistical analysis, chi-square or the Mann–Whitney *U*-test were used as appropriate for comparisons of data between groups, with a $P \leq 0.05$ considered to indicate statistical significance.

RESULTS

Preoperative imaging studies identified 32 solid and four complex cystic renal masses in 35 patients. LPN was completed with no intraoperative complications in all patients. The demographic and preoperative data are listed in Table 1. Procedures were electively performed in all but two patients who had solitary kidneys. These two patients, one in each group, had previously undergone radical nephrectomy because of renal cancer. Groups 1 and 2 had no significant differences in median age, gender, indication of the procedure, and number and location of tumours. The median tumour size, measured preoperatively, was larger in Group 1 (2.7 vs 1.9 cm, $P = 0.01$). Right-sided tumours were more prevalent in Group 2 (80% vs 40%, $P = 0.033$).

Operative data are summarized in Table 2. After GMTS application and renal reperfusion, haemostasis was adequate and immediate in all patients. No statistically significant

TABLE 2 Operative and renal function data

Variable	Total	Group 1	Group 2	*P*
Mean (range) operative time, min	198 (113–349)	195 (113–349)	207 (130–307)	0.6
N (%):				
Approach,				
Retroperitoneal	8 (23)	6 (24)	2 (20)	
Transperitoneal	27 (77)	19 (76)	8 (80)	0.8
Ischaemia,				
Hypothermic	2 (5.7)	1 (4)	1 (10)	
Normothermic	30 (85.7)	23 (92)	7 (70)	
None	3 (8.6)	1 (4)	2 (20)	0.2
Median (range) ischaemia time, min				
Hypothermic	46 (45–47)	45	47	
Normothermic	34 (18–91)	34 (18–91)	28 (21–47)	0.1
Pelvicalyceal entry, *n* (%)	15 (43)	11 (44)	4 (40)	0.8
Median (range) blood loss, mL	200 (25–1500)	200 (25–650)	150 (50–1500)	0.5
Blood transfusions (<7 days), *n*	0	0	0	1
Intraoperative complications, *n*	0	0	0	1
Renal function				
Median (range):				
eGFR, mL/min/1.73 m^2				
Preoperative	58.8 (44.8–89.3)	59.7 (44.8–89.3)	55.2 (45.4–69.8)	0.2
Postoperative	53.0 (36.6–87.5)	57.5 (36.6–87.5)	49.3 (37.1–84.3)	0.6
% change eGFR	–7.7 (–33.1–39.4)	–7.7 (–30.1–39.4)	–9.65 (–33.1–8.3)	0.7
Follow-up, weeks	30 (1–61)	29 (1–61)	35 (3–56)	0.6

differences in operative time, approach, ischaemia time, measured blood loss, or pelvicalyceal entry were identified. One patient in Group 1 had multiple lesions resected, necessitating complex reconstruction, and a prolonged ischaemia time of 91 min. Pathology findings were similar in both groups. Tumour size, measured after LPN, was larger in Group 1 patients (3.5 vs 2.0 cm, $P = 0.029$), consistent with the preoperative imaging data, although this difference does not appear to be clinically relevant. Of 36 lesions in all, 29 (83%) were primary renal cancers, five (14%) were benign neoplasms, and one (3%) was a metastatic breast lesion associated with angiomyolipoma.

The mean (SD; range) length of stay was 3.2 (2.5; 2–14) days in Group 1 and 2.8 (1.6; 1–7) days in Group 2 ($P = 0.61$). One patient in Group 1 with solitary kidney developed urinary fistula managed with perinephric drain removed after 40 days. One patient in Group 2 developed spontaneous gross haematuria at 24 days after LPN, requiring re-admission and blood transfusion alone. One patient in Group 2 with a solitary kidney developed pulmonary embolus, as determined by ventilation/perfusion scan on postoperative day 4; he received full anticoagulation and had no further sequelae. There was no statistical difference in the occurrence of complications between the groups.

Renal function data are summarized in Table 2. The median (range) preoperative eGFR was 59.7 (44.8–89.3) mL/min/1.73 m^2 in Group 1 and 55.2 (45.4–69.8) mL/min/1.73 m^2 in Group 2. No patients required haemodialysis after LPN. At a median (range) follow-up of 30 (1–61) weeks there was no difference in eGFR percentage change from baseline between the groups.

DISCUSSION

LPN appears to be an acceptable approach for select renal masses, offering the opportunity for curative resection with smaller incisions and the potential for minimal postoperative convalescence. Gill *et al.* [3] have reported retrospectively on LPN in comparison with open surgical techniques for NSS. While the oncological outcomes with LPN appear equivalent to open surgical techniques in their study, perioperative complications were more prevalent with LPN; most notably, postoperative haemorrhage and urinary fistula occurred in 4.2% and 3.1% of patients, respectively. These complications occurred with similar frequency in the present study, both with an occurrence of 2.9%.

As with open surgical approaches for NSS, vascular control, adequate visualization for excision and reconstruction, and techniques for obtaining durable haemostasis are of critical importance during LPN. Vascular occlusion to provide a bloodless operative field is commonly used for NSS. Many haemostatic agents such gelatines, thrombin, oxidized cellulose, microfibrillar collagen, and fibrin have been used for this purpose [7]. Of these agents, the evidence favours GMTS for providing haemostasis [8]. A recent survey reported that half of urologists who perform LPN use bovine GMTS as a haemostatic agent, together with oxidized nitrocellulose bolsters [11].

GMTS are composed of a granular gelatine matrix derived from collagen cross-linked with glutaraldehyde. FloSeal and Surgiflo only differ in the source of collagen, coming from bovine and porcine derivatives, respectively

[12]. They are mixed with thrombin solution before use, generating a slurry compound that can be applied directly to a bleeding surface to create a thrombogenic plug. Preparation time is ≈2 min, and the mixture remains usable up to 2 h after mixing.

GMTS facilitates the final step of the coagulation cascade through conversion of fibrinogen to fibrin by the use of thrombin. As blood is needed as the fibrinogen source, GMTS must to be applied to a bleeding surface. An additional tamponade effect is produced after contact with blood when granular swelling of ≈20% occurs [12]. Use for haemostasis in neurosurgical, cardiovascular, nose, throat, and spine surgery has been described [9].

Hick *et al.* [13] first described the use of FloSeal in a porcine renal trauma model reporting less blood loss compared with conventional repair. Use in hand-assisted LPN in a survival porcine model without hilar control was investigated by Desai *et al.* [14] showing haemostasis and no evidence of urinary fistula after 30 days. Initial report of GMTS in NSS was described in 2003 by User and Nadler [15], with application in LPN reported by Bak *et al.* [16] in 2004. Richter *et al.* [8] described the use of FloSeal in 15 open PNs and 10 LPNs in which immediate and durable haemostasis was obtained in all patients. Abdominal ultrasonography 10 days after the procedure showed no perirenal haematoma.

In a retrospective investigation, Gill *et al.* [17] evaluated outcomes from 63 LPN patients using FloSeal with oxidized nitrocellulose bolsters compared with 68 patients for whom nitrocellulose bolsters alone were applied. Overall complications decreased from 36.6% to 15.9%, and haemorrhagic events decreased from 11.8% to 3.2% when FloSeal was applied.

The manner of GMTS preparation is similar for both Surgiflo and FloSeal products. Flow characteristics, total volume, and consistency of the products can be altered by modifying the amount of liquid thrombin added. In the present study there were no notable differences in handling or ease of application. Immediate haemostasis was obtained in all patients, and no intraoperative or early perioperative complications directly attributable to the agents were identified.

There were two haematological events in the present series. One case of pulmonary embolus was confirmed with ventilation perfusion scan in a Group 1 patient with asymptomatic tachycardia 4 days after LPN. Pre-existing and postoperative mobility limitations in this patient were felt to contribute to his risk for this complication. Evaluation of the source of the thrombus was not performed at the time, because identifying the source would not have altered clinical management. One case of delayed haemorrhage presenting as gross haematuria 24 days after LPN occurred in a Group 2 patient and was self-limited. The late onset of this event and the absence of perinephric haematoma or pseudoaneurysm on imaging at the time were not consistent with a fibrinolytic event related to the compound.

The preoperative eGFR was <60 mL/min/1.73 m^2 in 18 (51%) patients, which suggests the existence of baseline renal insufficiency. Similar findings were reported by Huang *et al.* [18] in a cohort of 662 patients with kidney cancer with normal preoperative creatinine values in which 26% of patients had an eGFR of <60 mL/min/1.73 m^2. There was no significant difference in the eGFR change from baseline between the two groups during the follow-up interval. This would suggest equivalent or no nephrotoxicity attributable to either compound. Considerable variation in the postoperative eGFR occurred, as indicated by the broad range in percentage change from baseline after LPN, in some cases showing improved renal function. This variation is not well understood and perhaps indicates a limitation of using calculated values of GFR, which are largely a function of dynamic changes in serum creatinine measurements, for longitudinal analysis to gauge response to treatment.

The present study has the limitations of a retrospective analysis in a clinical series. The patient numbers were not comparable between the two groups, and data points were limited to those clinically obtained. While prospective, randomized, comparative studies could be performed, the similarity in mechanism for these agents, their indications for clinical use, and results as reported herein suggest that these agents are equivalent, allowing use to be based on surgeon preference.

In conclusion, retrospective comparative evaluation in the clinical use of GMTS compounds for haemostasis during LPN in the present series indicates equivalent perioperative haemostatic efficacy of commercially available bovine and porcine collagen-based agents when used with oxidized nitrocellulose bolsters.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **GMT(S)**, gelatine matrix-thrombin (sealants); **(L)PN**, (laparoscopic) partial nephrectomy; **NSS**, nephron-sparing surgery; **eGFR**, estimated glomerular filtration rate.