A prospective, randomized, pilot trial of a polyethylene glycol (PEG)-coated collagen patch (Hemopatch®) for intraoperative hemostasis during deceased donor renal transplant

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Abstract

Introduction: The objective of this study was to evaluate the safety and feasibility of using a polyethylene glycol (PEG)-coated collagen patch (Hemopatch®) in patients undergoing deceased donor renal transplant. The primary outcome was the amount of intraoperative estimated blood loss in those patients receiving the patch compared to without. Secondary outcomes were the subjective achievement of hemostasis, perigraft collection, and drop in hemoglobin 48 hours postoperatively.
Methods: We performed a single-center, prospective, randomized trial. Patients scheduled to undergo deceased donor renal transplant surgery were randomized to receive the PEG-coated patch or standard hemostasis (i.e., electrocautery and clips).
Results: A total of 30 patients were enrolled over 15 months and randomized to receive the PEG-coated patch (n=15) or standard hemostasis (n=15). The mean age was 62.5 years. As determined by the operating surgeon, hemostasis was successfully achieved in all 15 cases using the PEG-coated patch. In the PEG-coated patch group, there was a trend towards less estimated blood loss (237 cc vs. 327 cc; p=0.11) and a lower drop in hemoglobin 48 hours postoperatively (22.27 g/L vs. 29.53 g/L; p=0.09) compared to the standard hemostasis group. Perigraft collection was similar between groups (27% vs. 40%; p=0.43). Subgroup analysis on patients who received anticoagulation therapy revealed no significant difference in blood loss between groups.
Conclusions: Based on our single-center experience, the PEG-coated patch (Hemopatch®) is a safe and feasible option to aid hemostasis during deceased donor renal transplant surgery. Hemostasis was successfully achieved in all cases using the PEG-coated patch.

Introduction

Kidney transplant is the optimal treatment for end-stage renal disease (ESRD) and is associated with lower morbidity and mortality compared to dialysis.[1] Patients with ESRD often have impaired hemostasis due to platelet dysfunction or coagulation defects and have cardiovascular comorbidities requiring anticoagulation therapy.[2,3] These factors may increase the risk of developing hemorrhagic complications such as thrombosis and bleeding during surgery, potentially affecting graft function.[4] While creatinine clearance is the optimal predictor of graft function, anemia is also associated with poor graft outcomes.[5,6] Postoperative fluid collection around the transplanted kidney can also have considerable influence both on outcome and on functional recovery of the graft.[7] Therefore, achieving hemostasis during renal transplant is particularly important in this patient population.

Deceased donor renal transplant poses a particular challenge due to the lack of detailed preoperative vascular assessment of the allograft, which can make hemostasis more difficult to achieve. For instance, following revascularisation of the allograft, surface oozing may arise from vascular branches of the perinephric fat.[8]

While intraoperative interventions such as sutures, clips and electrocautery are commonly used, other adjunctive methods may be used to aid hemostasis. Several studies have demonstrated a shorter time of hemostasis and surgery with the use of biomaterials.[7] While these biomaterials differ in their composition, all are applied directly to the site of action and trigger the coagulation cascade or form a mechanical barrier to prevent effusion. Synthetic agents act independently of the coagulation cascade and use a monomer cross-linker to bind to tissue.[9]

Recently, topical hemostatic agents have played a vital adjunctive role in many types of surgery including urologic tumour resection of the kidney, bladder and prostate and in various procedures for genitourinary trauma and reconstruction.[9] However, no studies to date have evaluated its role in renal transplant surgery.[10–17] The polyethylene glycol-coated (PEG-coated) collagen patch (Hemopatch®, Baxter Healthcare Corporation) is a promising new synthetic hemostatic agent with a dual mechanism of action. The PEG coating rapidly adheres to the tissue surface while the collagen layer facilitates platelet activation and adhesion. The PEG-coated patch is potentially more convenient to apply than other adjunctive hemostatic agents, which may require warming and mixing.[7,9,16,17] Nevertheless, its use in renal transplant surgery remains to be established as no previous studies have been reported. Herein, we report the findings of a prospective randomized pilot trial that assessed the safety and feasibility of a PEG-coated patch on achieving hemostasis in deceased donor renal transplant surgery.

Methods

Patient eligibility

Eligible patients were at least 18 years of age and scheduled for deceased donor renal transplant surgery at our institution. Patients were excluded if they were scheduled for living donor renal transplant surgery, had uncorrectable bleeding diathesis or hypersensitivity to bovine proteins or brilliant blue (FD&C Blue 1). Further, if patients in the standard hemostasis group received additional hemostatic agents (e.g. topical or absorbable hemostats), they were also excluded. All included patients provided informed consent.

Study design

This was a prospective randomized trial conducted at a single institution. Over 15 months, 30 patients were enrolled and randomized to receive the PEG-coated patch (n=15) or standard hemostasis, defined as electrocautery and clips (n=15). Randomization was completed using computer randomization software in the operating room at the time of transplant surgery. The trial was approved by the Hamilton Integrated Research Ethics Board and registered on ClinicalTrials.gov under the identifier: NCT0263367. Hemopatch® was provided by Baxter Healthcare Corporation.

Outcomes and assessment

Preoperative baseline data was collected. The primary outcome was the amount of intraoperative estimated blood loss. Blood loss was estimated from the drain output and the volume of blood absorbed by the PEG-coated patch. Secondary outcomes included the achievement of hemostasis, perigraft collection and drop in hemoglobin 48 hours postoperatively compared to baseline. Hemostasis was assessed intraoperatively by the operating surgeon two minutes after the PEG-coated patch was applied. A Doppler ultrasound was required 48 hours postoperatively to assess the presence of perigraft collection. Renal function, hemoglobin level and drain output (if a drain was placed intraoperatively), was assessed on postoperative day 2, 7 and 30.

Statistical analysis

All study data was captured and managed using REDCap software hosted at St. Joseph's Healthcare Hamilton. Data was compared using independent samples t-test and chi-squared test. Data was analyzed using IBM® SPSS Statistics version 25.0.

Procedure

All deceased donor renal transplantation surgeries were performed by three transplant surgeons at St. Joseph's Healthcare Hamilton. A standard surgical approach was used by all three surgeons. Randomization was performed prior to the initiation of the transplant procedure. After back table preparation of the allograft, extra-peritoneal access was achieved using a modified Gibson's incision. Iliac vessels were mobilized and overlying lymphatics were clipped and divided. The renal artery and vein were anastomosed end-to-side to the iliac vasculature followed by unclamping of the vessels.

In the PEG-coated patch group, after initial hemostatic control with clipping of all active bleeders and electrocoagulation of surface oozers, a 4.5 x 4.5 cm sized PEG-coated patch was applied over the renal hilum and sinus fat of the kidney. Dry gauze was used to hold the PEG-coated patch in place and gentle, uniform pressure was applied over the entire pad surface for two minutes. The gauze was then removed from the pad and the PEG-coated patch was left in situ once hemostasis was achieved. After achieving hemostasis, reconstruction of the urinary tract was done with uretero-vesical anastomosis (Lich-Gregoir technique).

In the standard hemostasis group, hemostasis was achieved using surface electrocoagulation and clipping of bleeders. Patients requiring additional agents for hemostatic control were excluded from the study.

Results

A total of 30 patients (17 men and 13 women; mean age [SD], 62.5 [10.5]) were randomized between June 2016 and September 2017 to receive the PEG-coated patch (n=15) or standard hemostasis (n=15). All patients were followed for 30 days postoperatively. Demographic and baseline characteristics were similar between groups (Table 1). In each group, 10 patients (20 in total, 67%) were on anticoagulation therapy. There were no major intraoperative complications and postoperative recovery of all patients was uneventful. One patient in the PEG-coated patch group died two weeks after transplant surgery of causes unrelated to transplant surgery.

The mean intraoperative estimated blood loss was similar between groups, although there was a non-significant trend towards lower blood loss with the PEG-coated patch compared to standard hemostasis (237 [165] cc vs. 327 [128] cc, p=0.107). Compared to baseline, the mean drop in hemoglobin 48 hours postoperatively was similar between groups, with a non-significant trend towards a lower drop with the PEG-coated patch (22.27 [11.85] g/L vs. 29.53 [10.76] g/L, p=0.09) (Table 2). Transfusion rates were similar between groups (27% vs. 40%, p=0.44). Based on the operating surgeon's assessment, hemostasis was achieved in all patients of the PEG-coated patch group. In most cases, three PEG-coated patches were used (73%). All patients received a Doppler ultrasound after surgery and the incidence of perigraft collection was similar between groups (27% vs. 40%, p=0.43). Renal function and hemoglobin level on postoperative day 2, 7 and 30 were similar between groups. As a drain was only placed intraoperatively in three patients, comparison of drain output was not done. A subgroup analysis was conducted for patients on anticoagulation therapy and no significant difference in blood loss was found between groups.

Discussion

In this randomized pilot trial, the use of a PEG-coated patch to achieve hemostasis in patients undergoing deceased donor renal transplant surgery was safe and demonstrated equivalence with no hemostatic agent use. The estimated intraoperative blood loss and drop in hemoglobin 48 hours postoperatively was similar between groups and trended favourably towards the PEG-

coated patch group. Hemostasis was achieved in all patients who received the PEG-coated patch. The incidence of perigraft collection was similar between groups. No intraoperative or postoperative complications occurred. These findings may suggest that the PEG-coated patch is a safe adjunctive hemostatic agent in deceased donor renal transplant surgery.

There is limited evidence available informing the use of adjunctive hemostatic agents in clinical practice. This requires further attention in the renal transplantation setting given the increased risk of hemorrhagic complications in patients with ESRD, with bleeding rates reported as high as 40-50% in this patient population.[18] Further, hemostasis can potentially be more challenging during deceased donor renal transplantation as the operating surgeon is usually unfamiliar with the vascular anatomy of the allograft. Nevertheless, the importance of achieving hemostasis in this setting poses an opportunity for the investigation of novel agents to aid hemostasis.

The PEG-coated patch is a ready to use topical hemostatic agent that has a unique dual mechanism of action by initiating the coagulation cascade and facilitating platelet adhesion via PEG monomer cross-linkage. The combination of these two independent mechanisms can create rapid and lasting hemostasis by sealing the bleeding surface and accelerating the body's clotting mechanism.[19] The unique mechanism of the PEG-coated patch to achieve hemostasis in combination with its ready to use design presents a safe and feasible option as an adjunctive hemostatic agent. Other agents used to aid hemostasis are composed of oxidized cellulose (Surgicel®), fibrin-thrombin collagen patches (TachoSil®) and gelatin-thrombin glue (Floseal®).[20] A multi-institutional study conducted across 18 centres by Breda *et al.* demonstrated that among 1,347 surgical cases, 77% had utilized a hemostatic agent.[21] This relatively high rate of hemostatic agent usage reflects a trend favouring its use among surgeons. Further, several studies have found that these hemostatic agents are integral for achieving hemostatic control during partial nephrectomy.[22–24] However, no studies to date have evaluated the use of a PEG-coated patch in deceased donor renal transplant surgery.

While we found a trend towards lower estimated intraoperative blood loss in the PEG-coated patch group compared to the standard hemostasis group, this could be attributed to the initial control of bleeding from the renal hilum and renal sinus area. Further, we did not find a significant difference in blood loss among patients who received anticoagulation therapy.

Blood transfusion given to renal transplant recipients often leads to broad sensitization. Both leukocytes and erythrocytes carry a significant HLA antigen load. Prevention of sensitization requires efforts to avoid unnecessary blood transfusions.[25] Although there are multiple variables on which the decision to transfuse blood products depends on, in our study, the transfusion rates were similar between groups, which provides evidence for the safety of the PEG-coated patch. This was supported by the trend towards a lower drop in hemoglobin observed 48 hours postoperatively in the PEG-coated patch group.

Perigraft collections after renal transplant are common and are reported as high as 50% in some series.[15] Hematomas are the most common type of perigraft collection, usually occurring

soon after transplant. Significant perigraft collections (>50 cc) can have considerable influence both on outcome and on functional recovery of the allograft.[14] In our study, patients received a Doppler ultrasound on postoperative day 2 to evaluate if perigraft collection occurred. Interestingly, the incidence of perigraft collection was similar between groups (27% vs. 40%, p=0.43) and lower than expected based on previous series. However, we were unable to compare the amount of perigraft collection as only three patients had a drain placed intraoperatively. Nevertheless, this finding may suggest that the PEG-coated patch can be used without additional postoperative morbidity in this patient population.

The first clinical study of the PEG-coated patch on the genitourinary system was conducted by Imkamp *et al.* who investigated the performance of the PEG-coated patch in laparoscopic, zero-ischemia partial nephrectomy.[20] This was a seven patient case series demonstrating the hemostatic efficacy of a PEG-coated patch following enucleation of the renal mass. Hemostasis was achieved in all cases and the median tumour size was 3.0 cm. In four of the seven patients, no hemostatic undersuture was used. This may suggest that in select patients, particularly those with small exophytic tumours, a PEG-coated patch may be effective for hemostasis without the need for undersuture. The postoperative period was uneventful and the investigators did not find any significant drainage or bleeding on ultrasound. In the study, a PEG-coated patch was applied at the renal parenchyma which could be a more active site for bleeding compared to the renal hilum and renal sinus fat, where it was applied in our study.

Several limitations exist in our study. This was a prospective randomized control trial conducted at a single center, recruiting a total of 30 patients over 15 months. As this was a pilot trial evaluating the initial experiences of using a PEG-coated patch in deceased donor renal transplant surgery, blinding was not done. Assessment of hemostasis was subjectively determined by the operating surgeon, which may be a source of bias. Although drain output is an important indicator of graft function, we were unable to evaluate this parameter as only three patients had a drain placed intraoperatively. As our study was unpowered with a small sample size, larger multicenter trials are required to validate our findings and establish efficacy. Future prospective trials should evaluate the reliability and long-term effects of using a PEG-coated patch with direct comparison to other hemostatic agents. Due to the limited scope of our study, we were unable to evaluate the potential advantages of the PEG-coated patch on long-term graft function. To address this, future studies should have a longer follow-up and evaluate the cost-utility profile of the PEG-coated patch. However, to the best of our knowledge, this is the first study to investigate the safety and efficacy of a PEG-coated patch to achieve hemostasis in patients undergoing renal transplant surgery. Therefore, the use of a PEG-coated patch may be used to aid hemostasis in renal transplant surgery.

Conclusions

The PEG-coated patch is a novel hemostatic agent with a dual mechanism of action. We demonstrated its safety and feasibility in controlling intraoperative bleeding as an adjunct to

traditional surgical methods for hemostasis in deceased donor renal transplant surgery. In our study, hemostasis was achieved in all cases utilizing the PEG-coated patch. Compared to standard hemostatic methods, the PEG-coated patch group demonstrated similar intraoperative blood loss, incidence of perigraft collection and rate of blood transfusion. Our data suggests that the PEG-coated patch is a safe and feasible adjunctive hemostatic agent in renal transplant surgery.

References

1. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant*. 2011;11(10):2093-109.
2. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. *Semin Thromb Hemost.* 2004;30(5):579-589.
3. Kaw D, Malhotra D. Hematology: issues in the dialysis patient: platelet dysfunction and end-stage renal disease. *Semin Dial.* 2006;19(4):317-22.
4. Pupka A, Chudoba P, Barć P, et al. Intraoperative hemostasis during kidney transplantation and the use collagen mesh dressing covered by fibrin glue (TachoComb). *Polim Med*. 2003;33(3):27-32.
5. First MR. Renal function as a predictor of long-term graft survival in renal transplant patients. *Nephrol Dial Transpl*. 2003;18(1):3-6.
6. Abou-Jaoude MM, Nasser H, Khalaf AN, et al. Co-morbid factors related to surgical complications in kidney transplant patients. *Am J Med Med Sci*. 2012;2(3):29-35.
7. Tammaro V, Vernillo A, Dumani X, et al. Prevention of fluid effusion in kidney transplantation with the use of hemostatic biomaterials. *Transplant Proc*. 2014;46(7):2203-6.
8. Kakaei F, Nikeghbalian S, Malekhosseini SA. Kidney Transplantation Techniques. Current Issues and Future Direction in Kidney Transplantation 2013 Feb 13. IntechOpen.
9. Pursifull NF, Morey AF. Tissue glues and nonsuturing techniques. *Curr Opin Urol*. 2007;17(6):396-401.
10. Lewis KM, Spazierer D, Slezak P, et al. Swelling, sealing, and hemostatic ability of a novel biomaterial: A polyethylene glycol-coated collagen pad. *J Biomater Appl*. 2014;29(5):780-8.
11. Sageshima J, Ciancio G, Uchida K, et al. Absorbable cyanoacrylate surgical sealant in kidney transplantation. *Transplant Proc*. 2011;43(7): 2584-6).
12. Hilal MA, Underwood T, Taylor MG, et al. Bleeding and hemostasis in laparoscopic liver surgery. *Surg Endosc*. 2010;24(3):572-7.
13. Öllinger R, Mihaljevic AL, Schuhmacher C, et al. A multicentre, randomized clinical trial comparing the Veriset™ haemostatic patch with fibrin sealant for the management of bleeding during hepatic surgery. *Hpb*. 2013;15(7):548-58.
14. Fischer L, Seiler CM, Broelsch CE, et al. Hemostatic efficacy of TachoSil in liver resection compared with argon beam coagulator treatment: an open, randomized, prospective, multicenter, parallel-group trial. Surgery. 2011;149(1):48-55.
15. Berrevoet F, de Hemptinne B. Use of topical hemostatic agents during liver resection. *Digest Surg*. 2007;24(4):288-93.
16. Spotnitz WD, Burks S. Hemostats, Sealants, and Adhesives II: Update As Well As How and When to Use the Components of the Surgical Toolbox. *Clin Appl Thromb Hemost.* 2010;16(6):497.
17. Lewis KM, McKee J, Schiviz A, et al. Randomized, controlled comparison of advanced hemostatic pads in hepatic surgical models. *ISRN Surgery*. 2014.
18. Weltert L, D'Aleo S, Chirichilli I, et al. Prospective Randomized Clinical Trial of HEMOPATCH Topical Sealant in Cardiac Surgery. *Surg Technol Int*. 2016;29.

19. Lutz J, Menke J, Sollinger D, et al. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2013;29(1):29-40.
20. Lewis KM, Kuntze CE, Gulle H. Control of bleeding in surgical procedures: critical appraisal of HEMOPATCH (Sealing Hemostat). *Med Devices (Auckl).* 2016;9:1.
21. Imkamp F, Tolkach Y, Wolters M, et al. Initial experiences with the Hemopatch® as a hemostatic agent in zero-ischemia partial nephrectomy. *World J Urol*. 2015;33(10):1527-34.
22. Breda A, Stepanian SV, Lam JS, et al. Use of haemostatic agents and glues during laparoscopic partial nephrectomy: a multi-institutional survey from the United States and Europe of 1347 cases. *Eur Urol*. 2007;52(3):798-803.
23. Richter F, Schnorr D, Deger S, et al. Improvement of hemostasis in open and laparoscopically performed partial nephrectomy using a gelatin matrix-thrombin tissue sealant (FloSeal). *Urology*. 2003;61(1):73-7.
24. Gill IS, Ramani AP, Spaliviero M, et al. Improved hemostasis during laparoscopic partial nephrectomy using gelatin matrix thrombin sealant. *Urology*. 2005;65(3):463-6.
25. Siemer S, Lahme S, Altziebler S, et al. Efficacy and safety of TachoSil® as haemostatic treatment versus standard suturing in kidney tumour resection: a randomised prospective study. *Eur Urol*. 2007;52(4):1156-63.
26. Scornik J, Meier-Kriesche HU. Blood transfusions in organ transplant patients: mechanisms of sensitization and implications for prevention. *Am J Transplant*. 2011;11(9):1785-91.

Figures and Tables

Table 1. Baseline characteristics			
Characteristic	**PEG-coated patch (n=15)**	**Standard hemostasis (n=15)**	**p**
Mean age (SD)	63.7 (11.1)	61.3 (10)	0.54
Sex, n (%)			
Male	8 (53.3%)	9 (60%)	0.713
Female	7 (46.7%)	6 (40%)	
Type of deceased donor			0.256
Donation after cardiac death	4 (26.7%)	7 (46.7%)	
Neurologically deceased donor	11 (73.3%)	8 (53.3%)	
Comorbidities			
Hypertension	14 (93.3%)	14 (93.3%)	1.0
Coronary artery disease	7 (46.7%)	5 (33.3%)	0.456
Diabetes mellitus	9 (60%)	4 (26.7%)	0.065
Asthma	1 (6.7%)	2 (13.3%)	0.543
Chronic obstructive pulmonary disease	0 (0%)	2 (13.3%)	0.143
Renal replacement therapy			
Hemodialysis	10 (66.7 %)	13 (86.7%)	0.195
Peritoneal dialysis	5 (33.3%)	2 (13.3%)	
Previous renal transplant	1 (6.7%)	3 (20%)	0.283
Immunosuppresive therapy			
Cyclosporine	2 (13.3%)	0 (0%)	0.143
Mycophenolic acid	14 (93.3%)	15 (100%)	0.309
Glucocorticoids	15 (100%)	15 (100%)	–
Sirolimus	0 (0%)	0 (0%)	–
Tacrolimus	14 (93.3%)	14 (93.3%)	1.0
Azathioprine	0 (0%)	1 (6.7%)	0.309
ATG	3 (20%)	4 (26.7%)	0.666
Basiliximab	11 (73.3%)	9 (60%)	0.439
Simulect	0 (0%)	1 (6.7%)	0.309
Blood thinners	10 (66.7%)	10 (66.7%)	1.0
Past medical or surgical procedures	7 (46.7%)	7 (46.7%)	1.0

SD: standard deviation.

Table 2. Operative characteristics			
Characteristic	**PEG-coated patch (n=15)**	**Standard hemostasis (n=15)**	**p**
Intraoperative complications	0 (0%)	1 (6.7%)	0.309
Blood transfusion or blood products used	4 (26.7%)	6 (40%)	0.439
Number of Hemopatch® used 2 3	 4 (26.7%) 11 (73.3%)	–	–
Location of Hemopatch® application Arterial anastomosis Venous anastomosis Renal sinus	 13 (86.7%) 3 (20%) 15 (100%)	–	–
Intraoperative perigraft drain placement	2 (13.3%)	1 (6.7%)	0.543
Postoperative ultrasound suggestive of perigraft collection	4 (26.7%)	6 (40%)	0.439