Endourology
Transurethral Use of Evicel® Fibrin Sealant
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Abstract
Transurethral resection of bladder tumor remains the most common procedure for the diagnosis, management, and treatment of bladder cancer. Deep resection of the detrusor muscle for the correct staging of bladder cancer can increase the risk of hemorrhage that can be difficult to control with standard transurethral surgical maneuvers. Evicel® Fibrin Sealant was applied transurethrally to manage difficult hemorrhage following transurethral resection of bladder tumor in two surgically complex bladder cancer patients. Our early experience suggests Evicel® can be an effective tool in managing difficult to control hemorrhage associated with TURBT. Further clinical investigation is to be encouraged.

Introduction
Transurethral resection of bladder tumor (TURBT) remains the standard for both the initial diagnosis and treatment of bladder cancer. The aims of TURBT include: (1) establishing the histology of the tumor; (2) identifying the depth of tumor invasion; (3) determining important prognostic factors; (4) achieving complete removal of all visible tumors.

While TURBT is a common procedure, on any individual case a surgeon may not always achieve these desired goals. In particular, deep resection of the detrusor muscle (DM) is essential for correct staging. The absence of DM in resection specimens from published series ranges from 30–50% and is associated with a higher risk of residual disease in pT1 tumors, with up to 40% of tumors staged to pT2. Trials investigating re-TURBT have reported detection rates of residual tumor cells of 30–75% across all tumor stages.

This clinical need to perform deeper TURBT to secure DM in the specimen exposes the patient to a greater risk of perioperative complications. A recent analysis of TURBT complications demonstrated that patients who experienced a complication were older, presented with a lower hemoglobin level, more tumors, larger tumors and more co-morbidities. Several studies have confirmed that postoperative bleeding is the most common complication associated with TURBT.

Current maneuvers to deal with persistent TURBT hemorrhage are limited to cauteryization techniques. Endoscopic cautery tools include monopolar and bipolar loops, roller ball, “Button,” and Bugbee electrodes. In the event these maneuvers fail, persistent bleeding from vascular channels following TURBT that includes DM can be a source of significant morbidity.

Case presentation
Patient A is a male patient currently 72 years old with a history of aortic valve replacement on Warfarin and requires coverage with Lovenox for surgical procedures. He underwent Holmium laser enucleation of the prostate on 1/26/12 and suffered an embolic event despite anticoagulant coverage.

He began experiencing intermittent gross hematuria in May 2013 that he attributed to his Warfarin use. Eventually, contrast enhanced CT scan revealed a large right sided bladder mass and UroVysion was positive for malignant cells. He agreed to proceed with TURBT with the assurance that anticoagulant coverage would be continued.

Warfarin was held, Lovenox was started, and he returned to the operating room on 10/24/13. Cystoscopy revealed the right trigone replaced by a large, actively bleeding, sessile mass. Monopolar TURBT was performed resecting deep through the detrusor to expose perivesical fat. Actively bleeding tumor that could not be completely resected was exposed posterior to the bladder. Hemorrhage remained brisk despite all standard surgical maneuvers.

The decision was made to apply Evicel® Fibrin Sealant transurethrally in an effort to secure adequate hemostasis. Consent was secured from appropriate family members. Irrigation was slowed to allow visualization while minimizing disruption of this hemostatic
agent. The Evicel® 5 ml kit was prepared, and a flexible, dual-lumen catheter was passed through the resectoscope and into the deepest extent of the resection site (Fig. 1). Both components of Evicel® were slowly injected through this catheter, mixing at the tip, and completely filled the resection site. The Evicel® was allowed to set for 10 minutes. Cystoscopy revealed an opaque, fibrin plug filling the resection cavity and no further active bleeding. A 3-way catheter was placed to gravity drainage without continuous irrigation.

Lovenox was restarted postoperatively and Warfarin was restarted on postoperative day 2. Intermittent gross hematuria persisted without clots and continuous bladder irritation was never needed. Urine remained clear and the catheter was removed on postoperative day 10. Pathology documented high-grade transitional cell carcinoma with muscularis propria invasion.

He elected to proceed with radiation and chemotherapy, which he completed without any episodes of gross hematuria. He agreed to surveillance cystoscopy on 3/7/14, which revealed a deep, necrotic ulcer on the right trigone without active bleeding. Repeat TURBT was performed on 7/17/2014 for recurrent gross hematuria and pathology revealed necrosis, and no malignancy. He is currently being treated for metastatic disease without gross hematuria.

Patient B is a female patient currently 88 years old who elected not to report gross hematuria over a 12-month period. Cystoscopy on 3/18/15 revealed a large right lateral wall bladder tumor, TURBT was performed 4/9/15 with resection exposing perivesical fat. A very thin detrusor wall, an extremely lateral extent of gross tumor, and obturator nerve stimulation, all complicated efforts at resection. Hemorrhage from extravasal venous channels remained troublesome despite standard surgical maneuvers.

Evicel® use was discussed and consent was secured from appropriate family members. Evicel® Fibrin Sealant was applied transurethrally into the resection site using the technique outlined above to secure adequate hemostasis. Cystoscopy after application revealed a well-formed fibrin plug filling the resection cavity and no further active bleeding. Patient B was monitored postoperatively without continuous bladder irritation. Her catheter was removed on postoperative day 10. Pathology was reported as low-grade urothelial carcinoma negative for muscularis propria invasion.

She refused additional treatment other than surveillance cystoscopy, which revealed a visible, stable fibrin plug within the resection site and no gross tumor on 5/20/15. On 8/19/15 Urovysion was negative, and cystoscopy demonstrated intact bladder mucosa with typical scar formation and no visible tumor. She has not experienced any further episodes of gross hematuria since her initial resection.

Discussion

Fibrin sealants have been utilized in the United States to achieve surgical hemostasis for two decades. Although these products contain human-derived thrombin and fibrinogen there have been no reported cases of hepatitis or AIDS transmission. Typically, the thrombin and fibrinogen components are delivered to the bleeding tissue to achieve hemostasis. Some products also contain antifibrinolytic agents, but these have been associated with adverse outcomes.

Evicel® Fibrin Sealant (Ethicon, Inc.) is packaged as a kit containing one frozen vial of human fibrinogen and one frozen vial of human thrombin. There are no antifibrinolytic components in Evicel®. This product is indicated as an adjunct to hemostasis when control of bleeding by standard surgical techniques is ineffective or impractical.

Evicel® has been demonstrated to be safe, effective, and superior to Surgicel® absorbable hemostat in achieving hemostasis for mild to moderate bleeding in soft tissue during urologic surgery. Fibrin clots formed with Evicel® have also demonstrated a stronger and more resistant fibrin clot than that formed by Tisseel® (Baxter), an aprotinin–containing fibrin sealant. While Evicel® is now commonly utilized in both laparoscopic and open urologic surgery, we report the first transurethral use of Evicel® to control significant hemorrhage following deep TURBT.

Conclusion

Evicel® Fibrin Sealant is FDA approved for topical use and its transurethral application should be considered an appropriate off-label medical use. It is not expected to be efficacious for brisk arterial bleeding due to rapid wash off. Evicel® should not be injected directly into the circulatory system due to the risk of a thromboembolic event. Evicel® emulates the last phase of physiologic blood coagulation. Thrombin activates the conversion of fibrinogen into fibrin, which occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated by thrombin, crosslinks the fibrin monomers into an even stronger clot. Fibrin sealants like Evicel® are metabolized by fibrinolysis and phagocytosis in the same way as endogenous fibrin. As wound healing progresses fibrinolytic activity is induced by plasmin and the decomposition of fibrin-to-fibrin crosslinked monomers proceeds.

Evicel® Fibrin Sealant has been demonstrated to be a safe and effective hemostatic sealant in a wide variety of laparoscopic and open urologic operations. Our patients document a bene

Conflict of interest

Author declares no relevant conflicts of interest of any type.

References

1. Babjuk M. Transurethral resection of non-muscle-invasive bladder cancer. Eur Urol Suppl. 2009;8:542–548.
2. Mariappan P, Finney AM, Head E, et al. Good quality white-light transurethral resection of bladder tumors (GQ_WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early

Figure 1. Evicel® Fibrin Sealant (Human) (Ethicon, Inc.) and proprietary endoscopic application catheter.
recurrence in new non-muscle invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int. 2011;109:1666–1673.
3. Richterstetter M, Wullich B, Amann K, et al. The value of extended transurethral resection of bladder tumor (TURBT) in the treatment of bladder cancer. BJU Int. 2012;110:E76–79.
4. De Nunzio C, Franco G, Cindolo L, et al. Transurethral resection of the bladder (TURB): analysis of complications using a modified Clavien system in an Italian real life cohort. Eur J Surg Oncol. 2014;40:90–95.
5. Albala DM, Riebman JB, Kocharian R, et al. Hemostasis during urologic surgery: fibrin sealant compared with absorbable hemostat. Rev Urol. 2015;17(1):25–30.
6. Martin Lee M, Provost D, Jones DB. Use of fibrin sealant in laparoscopic gastric bypass for the morbidly obese. Obes Surg. 2004;14:1321–1326.
7. Hickerson WL, Nur I, Medler R. A comparison of the mechanical, kinetic, and biochemical properties of fibrin clots formed with two different fibrin sealants. Blood Coagul Fibrinolysis. 2011;22(1):19–23.