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Human gelatin thrombin matrix with rifampin for the treatment of prosthetic vascular graft infections

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ABSTRACT

We aim to describe and report on a novel graft preservation technique using a human gelatin thrombin matrix with rifampin for the treatment of vascular graft infections. Eight patients with vascular graft infections were included, one with bilateral infections, for a total of nine cases from January 2016 through June 2021. All the patients underwent wound exploration and placement of human gelatin thrombin matrix with rifampin. No deaths or allergic reactions had been reported at the 30-day follow-up, with only one major amputation. The graft and limb salvage rates were 77.8% at the 1-year follow-up. The mean time to a major amputation was 122 days, and the mean time to graft excision was 30 days. (J Vasc Surg Cases Innov Tech 2024;10:101365.)

Keywords: Bioabsorbable antibiotics; Expanded polytetrafluoroethylene grafts; HGTM; Human thrombin-gelatin matrix; Prosthetic graft infections; Rifampin; Vascular graft infection; VGI

Approximately 450,000 prosthetic vascular grafts are placed in the United States annually. The autogenous vein is preferred but is not suitable in ≤30% of patients.[1,2] Of the available prosthetic materials for bypass grafting, expanded polytetrafluoroethylene is the most widely used due to its physiologic characteristics.[1-3] Vascular graft infection (VGI) is the most feared complication, with an incidence rate of 1% to 6%.[4-7]

Failure of graft preservation techniques is most commonly due to persistent VGIs.[4-13] Muscle flap coverage has been reported to have mortality rate of 20% to 25% and limb salvage rate of 80%.[12] In addition, PMMA [*poly(methyl methacrylate)*] beads are associated with an intense local inflammatory response and kinked grafts and require reintervention for removal.[14] However, bioabsorbable beads have shown good results in two case series.[8,10,13,15]

We developed a novel technique to treat VGIs using human gelatin thrombin matrix (HGTM) with rifampin (HGTM+R). Rifampin's mechanism of action is through inhibition of bacterial transcription, which allows it to be effective against biofilms.[16,17] We aim to report the outcomes with our initial results.

METHODS

In this retrospective study, all the patients with VGI treated with HGTM+R by two vascular surgeons at San Luke's Memorial Hospital from January 2016 through June 2021. The patients were identified using Current Procedural Terminology codes after institutional review board approval. Informed consent was not required. Patients who underwent wound debridement and instillation of HGTM+R for localized, extracavitary VGIs were included. Patients with bacteremia, nonbiodegradable bead insertion, arteriovenous graft infections, or intracavitary graft infections were excluded. The primary outcomes included limb and graft salvage at 1 year. The secondary outcomes included reintervention, reinfection, and death. Freedom from infection was defined as resolution of clinical signs and symptoms and normalization of laboratory parameters (eg, white blood cell count, neutrophil count) before discharge. Demographic, clinical, procedural, and follow-up data were retrieved from the electronic health records. Follow-up data at 30 days and 1 year after index operation were retrieved. Statistical analysis was performed using descriptive statistics.

Surgical technique. All patients were admitted and received broad-spectrum antibiotics and an infectious disease consultation. Cleansing and debridement was done in the operating room. Debridement continued until healthy, pink, and viable tissue was clinically evident. Wound cultures were taken. The wound bed was thoroughly irrigated with chlorhexidine solution. In back-table preparation, 1200 mg of rifampin powder

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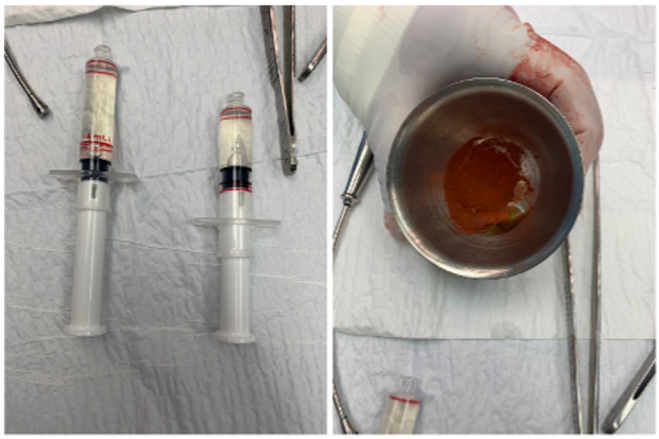

Fig 1. Photographs showing back-table preparation of human gelatin thrombin matrix with rifampin (HTGM+R), which was created by mixing 4 mL of human gelatin thrombin matrix (FloSeal) with 600 mg of crushed rifampin antibiotic powder.

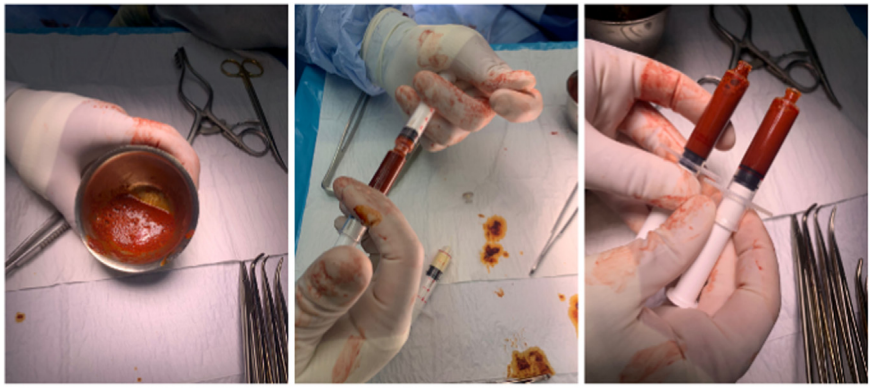

Fig 2. Photographs showing thorough manual dilution of the rifampin powder with human gelatin thrombin matrix and transfer of the mixture to syringes. The mixture is then directly applied to the affected area (not shown).

(Lupin Pharmaceuticals) was mixed with thrombin from an HGTM packet (FloSeal; Baxter BioSurgery) until minimal solid residue was visualized (Fig 1). Next, the rifampin-thrombin solution was mixed with gelatin matrix from the HGTM packet (FloSeal; Fig 2). This was transferred to syringes and applied directly to the exposed graft. Finally, the was wound closed in layers without drains. Nylon sutures were used to approximate the skin edges. One patient required incisional negative pressure wound therapy (NPWT). The patients continued receiving systemic anticoagulation and broad-spectrum intravenous antibiotics until their sensitivity report was available.

RESULTS

A total of 27 patients were identified with VGIs. However, 19 were excluded due to dialysis graft infections (n = 9), nongraft infections (n = 5), and intracavitary graft infections (n = 5). Thus, eight patients with VGIs were included, for a total of nine cases. One patient had bilateral groin wound infections associated with bilateral femoropopliteal bypass grafts placed at different times. Five patients were current smokers, and 50% were chronic steroid users (Table).

Of the nine cases of VGIs, five were early infections (<3 months after implantation). The symptoms from early infection included purulent drainage (n = 2), local signs of inflammation (n = 2), and infected hematoma (n = 1). The symptoms of the four cases of late infection included local signs of inflammation, hematoma, and wound sinus tracts. All VGIs were located in the groin area, except for a single infected popliteal surgical wound. The bypass characteristics are summarized in Table.

Three patients required either graft excision or major amputation, with one patient requiring both. One

Table. Demographic variables, bypass characteristics, vascular graft infection description, and major outcomes

Pt. No.	Age, years; sex	BMI, kg/m^2	Comorbidities	Bypass type	Infection site	Early vs late infection	Organism	Alive	Major amputation	Graft salvage
1	65, M	30.5	Ex-smoker, steroid use, diabetes, hypertension, COPD, CHF	Fem-Pop (ePTFE)	Left	Late	*Proteus penneri*	Yes	No	Yes
				Fem-Pop (ePTFE)	Right	Late	*P. penneri, Klebsiella pneumoniae*	Yes	Above knee	No
2	88, M	29.4	Steroid use, hypertension	Fem-Fem (ePTFE)	Left	Early	*Citrobacter koseri, Proteus mirabilis, Clostridium perfringens, Enterococcus faecalis*	Yes	–	No
3	79, F	25.6	Ex-smoker, steroid use, hypertension, COPD	Fem-Pop (ePTFE)	Right	Late	*Pseudomonas aeruginosa, K. pneumoniae*	Yes	Above knee	No
4	67, M	31.6	Current smoker, CKD, hypertension	Fem-Pop (ePTFE)	Right	Late	Escherichia *coli, Enterococcus faecium* (MRSA)	Yes	No	Yes
5	79, M	23.5	Ex-smoker, steroid use, diabetes, hypertension	Fem-Pop (Dacron)	Right	Early	*K. pneumoniae*	No	No	Yes
6	77, F	27.6	Diabetes, CKD, hypertension	Fem-Pop (ePTFE)	Left	Early	*K. pneumoniae* (ESBL)	No	No	Yes
7	61, F	20.0	Diabetes, hypertension	Fem-Pop (ePTFE)	Left	Early	MSSA	Yes	Above knee	Yes
8	56, F	27.4	Current smoker, hypertension	Fem-Fem (ePTFE)	Right	Early	*Morganella morgagnii*	No	No	Yes

BMI, Body mass index; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *COPD,* chronic obstructive pulmonary disease; *ePTFE,* expanded polytetrafluoroethylene graft; *ESBL,* extended spectrum beta-lactamase; *F,* female; *Fem-Fem,* femoral–femoral bypass; *Fem-Pop,* femoropopliteal bypass; *M,* male; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *MSSA,* methicillin-sensitive *S. aureus*; *Pt. No.,* patient number.

patient had severe asthma requiring high-dose steroids, diabetes mellitus, hypertension, and congestive heart failure and was a previous smoker. A muscle flap graft and incisional NPWT were placed during the index operation after implantation of HGTM+R. However, the graft was excised 11 days later, and the patient required a major amputation at 22 days due to worsening ischemia. Another patient had rheumatoid arthritis requiring low-dose steroids and hypertension. Wound reexploration with debridement occurred at 7 days after HGTM+R application, with graft excision and ipsilateral axillofemoral bypass creation performed at 49 days. Wound culture revealed a polymicrobial infection with a rifampin-resistant *Enterococcus faecalis,* in addition to *Citrobacter koseri* and *Proteus mirabilis.* Computed tomography angiography revealed that the extra-anatomic bypass was patent at 1 year of follow-up. The third patient had asthma requiring low-dose steroids, hypertension, and diabetes mellitus and was a previous smoker. Wound reexploration was performed with additional HGTM+R and conventional NPWT placement at 125 days of follow-up. The patient required amputation at 222 days due to an occluded bypass and severe ischemia without any other infectious process present in the graft.

The wound cultures from the first and third patients described in the previous paragraph grew, exclusively, gram-negative bacilli (ie, *Proteus penneri, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*). These organisms were resistant to penicillin and first-, third-, and fourth-generation cephalosporin. Home infusion antibiotics were prescribed for all polymicrobial infections, and oral antibiotics were prescribed for three cases with a single organism reported from the wound culture in accordance with the infectious disease service recommendations. The bacterial isolates for all nine cases are summarized in Table.

The mean hospital length of stay was 15.2 days after the index procedure. At 30 days, no patient had died or experienced an allergic reaction and one patient had required a major amputation. The graft salvage and limb salvage rates were 77.8% at a median follow-up of 1 year. Of the cohort, 77% were deemed free of infection. A total of 12 total reinterventions were performed during the follow-up period. The mean time to reintervention

due to persistent infection was 7 days. The average time to graft excision was 30 days. The mean interval to a major amputation was 122 days.

Two patients were lost to follow-up at 118 and 135 days. The initial postoperative visit of both patients at a mean of 12.4 days revealed adequate healing of the surgical site without overt signs of inflammation or infection.

DISCUSSION

To the best of our knowledge, this is the first case series reporting this novel technique. HGTM is the generic name of FloSeal (Baxter BioSurgery). Gelatin matrix is a well-known topical hemostatic agent that is absorbed within 4 to 6 weeks.[18] The mechanism of action of gelatin matrix is not fully understood, but it is believed to act physically rather than chemically.[19] The foamed solution is associated with a decrease in infection at the site of application and can absorb 40 times its weight, expanding >200% in vivo.[18] The antibiotic rifampin was chosen due to its bacteriostatic properties. It functions by inhibiting bacterial transcription and has a notable effect against biofilm development of gram-positive clinical isolates.[16] We hypothesize that its hemostatic and absorptive properties allow the rifampin antibiotic to remain active in the wound bed for an extended time.

Our population demonstrated outcomes that appear to be consistent with the literature, including that the inguinal site is the most common site for graft infections and that diabetes mellitus, smoking, and steroid use are common risk factors for VGIs.[20,21] Rifampin sensitivity was not determined routinely by the microbiology department. Two organisms were tested for rifampin sensitivity; one was resistant. However, this culture was a polymicrobial wound infection with rifampin-resistant *E. faecalis*. The femoral–femoral graft had to be excised but the extra-anatomic bypass was patent at 1 year of follow-up.

In situ graft reconstruction can be achieved with a venous autologous graft immediately after wound cleansing and debridement. It is usually performed in conjunction with muscle flap coverage and requires long-term antibiotic therapy.[12,22] Muscle flap coverage has the advantage of obliterating dead space, improving local delivery of intravenous antibiotics and white blood cells, controlling serous drainage, and promoting wound healing.[11] Conflicting evidence has been reported, with some studies indicating high rates of survival and graft salvage of 85% at 1 year,[20] and others showing suboptimal graft salvage rates of 50%.[9,23,24] The graft preservation technique with muscle flap coverage has improved since its inception in the 1980s. It provides increased blood flow and nutrients, improves leukocyte function, enhances antibiotic delivery, and obliterates dead space.[12,23,25–27] Recent studies have shown comparable limb and graft salvage results between sartorius muscle flap, gracilis muscle flap, and rectus femoris flap coverage. However, sartorius muscle flap coverage can be too small for large wounds, its proximity to the infected wound could compromise the integrity and effectiveness, and the blood supply could be compromised in patients with critical limb ischemia.[12,27] In addition, rectus femoris flaps have the potential for loss of knee extension and decreased ambulation ability in chronically ill patients.[12,26] Our novel technique is a viable option before considering muscle flap coverage due to its ease of use, decreased operative time, much less morbidity, and comparable limb and graft salvage rates.

PMMA beads have been reported to have a freedom from infection rate of 58% to 90% in some case series and cohort studies.[6,7,14] However, patients required reintervention 1.4 to 2.5 times, on average.[4-6] Moreover, the need for PMMA bead removal is impractical and carries high morbidity. In addition, it can cause mechanical problems, increasing turbulent flow and thrombosis formation.[7,10,15,28] The limb and graft salvage rates with bioabsorbable antibiotic-impregnated beads are comparable those in our study at 77.8%.[9,10,28] There are limited studies on absorbable antibiotic-impregnated material, which has shown acceptable limb salvage and freedom from infection.[8,9] In addition, it is associated with a decreased risk of systemic toxicity and mechanical problems associated with the conduit.[8,9]

This study has limitations due to its small sample size. Furthermore, it was a retrospective review conducted at a single institution, which affects the generalizability of the findings to a broader patient population. Additionally, the patients were empirically treated during the index operation using the described technique. Opening the wound, obtaining a wound culture, and waiting for bacterial isolate reports without proper source control would increase the length of the hospital stay, increase morbidity, and, most likely, decrease the graft salvage rates.

CONCLUSIONS

HGTM+R is a safe and successful alternative for patients with graft infection. To the best of our knowledge, we describe a novel technique for the effective treatment of VGIs. It is a technique that can be applied without compromising future surgical management options, maintaining graft patency, and avoiding complications common to other options for graft and limb salvage. When a localized infection of an already incorporated vascular graft is detected, the described technique should be considered as the first option for the treatment of this disease.

DISCLOSURES

None.

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