

Cryopreserved venous allograft is an acceptable conduit in patients with current or prior angioaccess graft infection

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ABSTRACT

Objective: The durability of cryopreserved allograft has been previously demonstrated in the setting of infection. The objective of this study was to examine the safety, efficacy, patency, and cost per day of graft patency associated with using cryopreserved allograft (vein and artery) for hemodialysis access in patients with no autogenous tissue for native fistula creation and with arteriovenous graft infection or in patients at high risk for infection.

Methods: Patients implanted with cryopreserved allograft for hemodialysis access between January 2004 and January 2014 were reviewed using a standardized, multi-institutional database that evaluated demographic, comorbidity, procedural, and outcomes data.

Results: There were 457 patients who underwent placement of cryopreserved vein (femoral: n = 337, saphenous: n = 11) or artery (femoral: n = 109) for hemodialysis access at 20 hospitals. Primary indications for allograft use included high risk of infection in 191 patients (42%), history of infected prosthetic graft in 169 (37%), and current infection in 97 (21%). Grafts were placed more frequently in the arm (78%) than in the groin, with no difference in allograft conduit used. Mean time from placement to first hemodialysis use was 46 days (median, 34 days). Duration of functional graft use was 40 ± 7 months for cryopreserved vein and 21 ± 8 months for cryopreserved artery ($P < .05$), and mean number of procedures required to maintain patency at follow-up of 58 ± 21 months was 1.6 for artery and 0.9 for vein ($P < .05$). Local access complications occurred in 32% of patients and included late thrombosis (14%), graft stenosis (9%), late infection (9%), arteriovenous access malfunction (7%), early thrombosis (3%), and early infection (3%). Early and late infections both occurred more frequently in the groin ($P = .030$, $P = .017$, respectively), and late thrombosis occurred more frequently with cryopreserved artery ($P < .001$). Of the 82 patients (18%) in whom the cryopreserved allograft was placed in the same location as the excised infected prosthetic graft, 13 had infection of the allograft during the study period (early: n = 4; late: n = 9), with no significant difference in infection rate ($P = .312$) compared with the remainder of the study population. The 1-, 3-, and 5-year primary patency was 58%, 35%, and 17% for cryopreserved femoral vein and 49%, 17%, and 8% for artery, respectively ($P < .001$). Secondary patency at 1, 3, and 5 years was 90%, 78%, and 58% for cryopreserved femoral vein and 75%, 53%, and 42% for artery, respectively ($P < .001$). Mean allograft fee per day of graft patency was \$4.78 for cryopreserved vein and \$6.97 for artery ($P < .05$), excluding interventional costs to maintain patency.

Conclusions: Cryopreserved allograft provides an excellent conduit for angioaccess when autogenous tissue is not available in patients with current or past conduit infection. Cryopreserved vein was associated with higher patency and a lower cost per day of graft patency. Cryopreserved allograft allows for immediate reconstruction through areas of infection, reduces the need for staged procedures, and allows early use for dialysis. (J Vasc Surg 2017;■:1-6.)

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As the number of patients requiring long-term hemodialysis increases, the management of patients with infected hemodialysis conduits remains one of the greatest challenges in vascular surgery.¹⁻³ The United States Renal Data System reported that in 2014, there were 120,000 new cases of end-stage renal disease (ESRD), associated with an 8% mortality rate due to infection in patients with ESRD and dialysis.⁴

The management of dialysis access graft infection has varied by surgeon and institution, but is most commonly managed by removing the infected graft and placing a new graft in a noninfected site in the same or another limb, either at the same operative procedure or using a staged approach. There has been widespread use of polytetrafluoroethylene (PTFE) when no autogenous

conduit is available because of its theoretical resistance to infection and cost, although recent studies suggest its use in the setting of infection continues to be associated with significant rates of infection and thrombosis.⁵ Cryopreserved allograft has been used in the setting of aortic graft infection and reported to be associated with lower reinfection rates and increased survival than PTFE or other synthetic grafts.^{6,7} Recent evidence has also suggested that cryopreserved vein allografts are better alternatives to PTFE in infected access situations and should be considered in patients with no available autogenous tissue.⁸

The objectives of this study were to (1) examine the safety and efficacy of using cryopreserved vein or artery for immediate, same-site reconstruction of infected hemodialysis access conduits when no autogenous vein is available, (2) evaluate primary, primary assisted, and secondary patency rates for cryopreserved vein and artery, and (3) determine the expense of using cryopreserved vein or artery for arteriovenous access in the setting of infection by using a novel calculation unit of allograft fee per day of patency.

METHODS

Patients who underwent placement of cryopreserved vein or artery for hemodialysis access between January 1, 2004, and 2014 were included in the study. All patients were currently undergoing hemodialysis at the time of cryopreserved allograft placement. Cryopreserved vein used by investigators was femoral or saphenous vein; cryopreserved artery was femoral artery. All cryopreserved grafts used by each institution were obtained from CryoLife, Inc (Kennesaw, Ga). Only patients with no prior use of cryopreserved allograft for hemodialysis access were considered for study inclusion. Patients undergoing placement of cryopreserved allograft as a patch to an existing prosthetic or autogenous graft were not included in the study. Invitations to participate were sent to institutions who had previously published on cryopreserved allograft, prior Vascular Low-Frequency Disease Consortium (VLFDC) participants, and institutions with a high volume of cryopreserve allograft usage. They were encouraged to participate in a multi-institutional retrospective study of cryopreserved allograft in the setting of infection.

Definition of patency used the Society for Vascular Surgery and American Venous Forum reporting standards for patients with hemodialysis access.⁹ Primary study end points were (1) time to first use of the graft for hemodialysis, (2) need for intervention, and (3) graft failure. Patients considered "high risk" included those with concurrent systemic infections, infection at a remote location, patients on immunosuppression, patients on steroids, and those who had a previous vascular access graft infection.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of multi-center data enrolled in the Vascular Low-Frequency Disease Consortium database
- **Take Home Message:** In 457 patients, cryopreserved allografts were placed for angioaccess after removal of an infected graft or in patients with high risk for infection, when an autogenous conduit was not available. All allografts performed very well, but cryopreserved veins had higher patency and lower cost per day of graft patency.
- **Recommendation:** The authors suggest that cryopreserved vein grafts should be used for angioaccess in infected fields when autogenous conduit is not available.

VLFDC and database management. The methodology of the VLFDC process has been described and published in detail.^{6,10,11} In brief, a standardized, multi-institutional database was created by the originating authors at the University of California, Los Angeles, which evaluated demographic, comorbidity, procedural, follow-up, and outcomes data. It was the responsibility of the principal investigator at each participating site to ensure that Institutional Review Board approval was obtained; in this study, all Institutional Review Boards approved the study protocol and database, and all waived patient consent due to the minimal risk associated with this retrospective study. In addition, each participating site's principal investigator was responsible to ensure that implant lists of those meeting inclusion criteria were complete and included all patients and to ensure the validity of all deidentified data submitted to the VLFDC team at the University of California, Los Angeles. All VLFDC participating investigators reviewed the collective data before abstract submission, meeting presentation, and manuscript submission.

Statistics. The Excel 16.0 database (Microsoft Corp, Redmond, Wash) was used for collecting and maintaining the data. Statistical analysis was performed using SPSS Statistics 24.0 software (IBM Corp, Armonk, NY). Continuous variables are presented as mean \pm standard deviation. Differences between two or more groups were compared using the Student *t*-test, analysis of variance, Kruskal-Wallis test, and Mann-Whitney *U* test. Unless total group (N) is stated, the percentages reported are not inclusive. Differences between groups for noncontinuous variables were analyzed using the χ^2 test and the Fisher exact test. Multivariable analysis was performed with a 95% confidence interval using binary and multivariable logistic regression models. Time-dependent variables were analyzed using Kaplan-Meier life tables. Significant differences were identified with a *P* value

Table I. Most frequently used arterial inflow and venous outflow sites in implantation of cryopreserved vein and artery for hemodialysis access (N = 457)

Arterial inflow site	No. (%)	Venous outflow site	No. (%)
Brachial	283 (62)	Axillary	178 (39)
Radial	41 (9)	Cephalic	87 (19)
Axillary	23 (5)	Basilic	69 (15)
Subclavian	9 (2)	Subclavian	23 (5)
Femoral	96 (21)	Femoral	78 (17)
Iliac	5 (1)	Saphenous	18 (4)
		Iliac	5 (1)

of $<.05$. The value of “allograft fee per day of graft patency” was calculated by dividing the mean allograft fee (processing fee charged to the hospital or institution by CryoLife Inc for processing) by the mean number of days of graft patency, expressed as dollars per day graft of patency.

RESULTS

A total of 457 patients were identified at 20 hospitals across the United States, and 348 cryopreserved vein and 109 cryopreserved artery allografts were placed; of these, there were 337 femoral vein allografts (97%) and 11 saphenous vein; all 109 artery allografts were femoral artery.

Demographics and comorbidities. The mean age at time of cryopreserved allograft placement for arteriovenous access was 62 ± 15 years, with more women than men (3:2). Comorbidities of patients included hypertension (83%), diabetes mellitus (65%), current or prior tobacco use (43%), current or prior intravenous drug use (7%), and serology positive for human immunodeficiency virus (2%). Mean body mass index was 27.6 ± 7.7 kg/m². Before placement of the cryopreserved allograft for hemodialysis access, patients had a mean of 2.6 ± 1.1 prior failed hemodialysis grafts or fistulas, or both.

Location and indications. The most frequent site of implantation was in the arm ($n = 356$ [78%]), followed by the groin ($n = 101$ [22%]; Table I). Looped grafts were most frequently used (61%). Indications for use of cryopreserved allograft, in addition to all patients having no autogenous tissue available, included high risk of infection ($n = 191$ [42%]), history of infected prosthetic graft ($n = 169$ [37%]), and current hemodialysis graft infection ($n = 97$ [21%]). Thirty-one patients (7%) were on immunosuppression medication, and in 82 patients (85% of patients with current graft infection; 18% of total grafts implanted), the cryopreserved allograft was placed adjacent to or through an infected field. The most common organisms reported from operative cultures

Table II. Local access and remote complications^a

Complication	No. (%)	Significant difference	P
Local access complications			
Early thrombosis	14 (3)		
Late thrombosis	64 (14)	Increased with artery allograft	$<.001$
Graft stenosis	41 (9)		
Early infection	14 (3)	Increased with grafts placed in groin	.030
Late infection	37 (9)	Increased with grafts placed in groin	.017
AV access malfunction	32 (7)		
Pseudoaneurysm at needle stick site	18 (4)		
Remote complications			
Steal syndrome	30 (7)	Increased with vein allografts	.028
Venous hypertension	29 (6)		
AV, Arteriovenous. ^a Early complication, ≤ 30 days; late complication, >30 days.			

were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and polymicrobial.

Complications. Complications occurred in 32% of patients, with late thrombosis and late infection being the most frequently reported (Table II). Late thrombosis occurred more frequently when arterial conduits were used, and early and late infection occurred more frequently in the groin. Of the 82 patients (18%) in whom the cryopreserved allograft was placed in the same location as the excised infected prosthetic graft, infection of the allograft occurred in 13 during the study period (early: $n = 4$; late: $n = 9$), with no significant difference in infection rate ($P = .312$) compared with the remainder of the study population; 8 of the allografts were femoral artery, 4 were femoral vein, and 1 was saphenous vein ($P = .418$). The most common site of graft stenosis was at the venous outflow site, and pseudoaneurysms occurred most frequently with femoral vein grafts (13 of 18 [72%]) at the needle stick site. Remote complications occurred in the same limb in 13% of patients and included steal syndrome and venous hypertension (Table II). Steal syndrome more frequently occurred in patients when venous allografts were used.

Patency. The primary patency rate for cryopreserved vein allografts at 5 years was significantly higher than artery ($P < .001$), at 17% and 8%, respectively (Fig). Primary assisted patency rates were not significantly different for vein and artery allografts (50% and 35% at

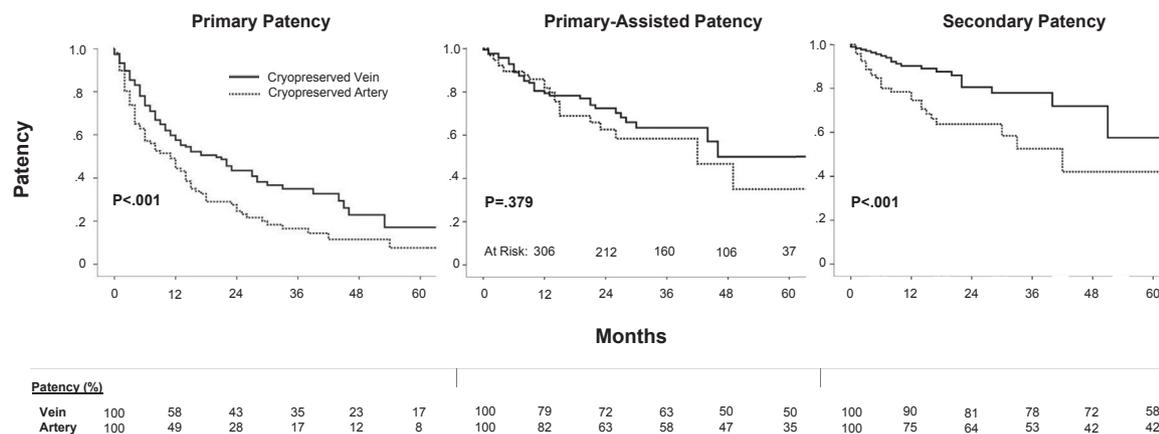


Fig. Primary, primary assisted, and secondary patency for cryopreserved artery and vein allografts placed for hemodialysis access in patients with no autogenous tissue available.

5 years, respectively). The secondary patency rate for vein allograft was significantly higher than artery at 5 years (58% and 42%, respectively; $P < .001$).

Follow-up. Mean follow-up for all patients was 58 ± 21 months; mean time from placement of the cryopreserved graft to first hemodialysis use for both artery and vein was 46 ± 14 days (median, 34 days), 51 ± 15 days for artery allografts and 42 ± 13 days for vein allografts ($P = .173$). Eleven patients died before first use, and 22 patients required reintervention before first hemodialysis use. Mean duration of functional hemodialysis use was 40 ± 7 months for cryopreserved vein and 21 ± 8 months for cryopreserved artery ($P < .05$). The mean number of procedures required to maintain graft patency was 1.6 for cryopreserved artery and 0.9 for cryopreserved vein ($P < .05$). Mean allograft fee per day of graft patency was \$6.97 for cryopreserved artery and \$4.78 for cryopreserved vein ($P < .05$).

DISCUSSION

Replacement of an infected hemodialysis graft has traditionally necessitated a two-stage procedure, with an initial infected graft excision and placement of a central venous catheter, followed by delayed access graft placement.¹ The time required between excision and use of a new graft is often lengthy and increases the patient's risk of a central access catheter infection.¹² In the absence of autogenous tissue being available for arteriovenous fistula creation, alternative conduits composed of synthetic graft material, xenograft, fresh cadaveric allograft, and cryopreserved allograft have been used. Comparing cryopreserved artery and PTFE, Ha et al¹³ found that time from graft placement to first hemodialysis use was significantly shorter for cryopreserved artery (5 vs 34 days; $P < .001$). Matsuura et al² reported successful hemodialysis through implanted cryopreserved vein ≤ 14 days of implantation in 44 patients. Although we

found longer times to first dialysis than those reported by Ha and Matsuura, our mean time to first use was 45 ± 13 days, with no significant difference in time to maturity between artery and vein. Absence of standardization of "first use" criteria across all centers in our study may be responsible for the longer intervals between implantation and first use than previously reported.

When Matsuura et al² compared the use of PTFE and cryopreserved allograft, they found that 12% of PTFE grafts became infected during the 2-year study period compared with 0% of cryopreserved femoral vein ($P = .002$). These low infection rates with cryopreserved allograft occurred even though 82% of the total study population was septic or had an infected arteriovenous graft. Similarly, Lin et al¹ reported a 0% infection rate using cryopreserved femoral vein in 36 patients with remote bacteremia or an infected arteriovenous graft. The low infection rates reported by Matsuura et al² and Lin et al¹ correlate with our findings, which showed a low infection rate of 2.4% (2 of 82 patients) in patients with active graft infection.

When examining factors associated with infection of cryopreserved grafts, Bolton et al¹⁴ found that 81% (9 of 11 patients) of graft infections occurred with grafts placed in the thigh or groin. We also found the highest rates of infection, both early and late, were associated with grafts that were placed in the groin ($P = .03$ and $P = .017$, respectively), irrespective of conduit type (vein or artery). Such high rates of infection with grafts placed in the groin are not specific to cryopreserved grafts; infection rates associated with PTFE grafts have also been reported to be as high as 43% in larger series.¹⁵

Several single-center studies have reported patency rates associated with cryopreserved femoral vein, and others have reported on outcomes with cryopreserved artery; however, no other multicenter series in the United States has reported and compared patency rates of cryopreserved artery and vein in patients with current

or prior arteriovenous graft infection. Primary graft patency for cryopreserved femoral vein grafts at 1 year in patients with infection has been reported to be between 49% and 68%.^{1,2,16} In a study examining the use of cryopreserved femoral artery in patients with ESRD, with or without infection, Ha et al¹⁵ reported primary patency >60% at 1 year and >40% at 2 years, rates higher than their prosthetic graft control group. The 1-year primary patency rate in our study was 58% for cryopreserved vein and 49% for cryopreserved artery ($P < .05$). The difference in patency between vein and artery conduits remained significantly different out to 5 years of follow-up ($P < .001$).

A cost analysis performed by Madden et al¹⁷ found that total hospital costs associated with placement and maintenance of PTFE and cryopreserved allografts were similar in patients with noninfectious indications for access. In our analysis, we used a novel approach for comparing the use of cryopreserved vein and artery in patients with infectious causes, concluding that use of cryopreserved vein was significantly less expensive per day of patency than cryopreserved artery (\$4.78 vs \$6.97, respectively; $P < .05$). Although these values only consider the allograft fee and did not include associated interventions to maintain patency, the mean number of interventions was lower with cryopreserved vein, further distinguishing cryopreserved vein as the most cost-effective option. Supporting our quantitative findings, Scher and Katsman¹⁶ have suggested that the benefits of using cryopreserved femoral vein (as an alternative to PTFE) may outweigh the costs in patients requiring replacement of an infected hemodialysis graft.

The main limitation of this study relates to the retrospective methodology, which prevented the elimination of bias from patient selection and treatment. Our follow-up data are based on information collected during follow-up visits, as well as institutional data, if dialysis was performed in-network, but it is possible that interventions performed at another site may have been under-reported. There were also no predefined criteria for reporting the exact location of grafts placed through, as opposed to adjacent to, infected fields, and why artery or vein conduits were used, but surgeon preference may have affected this decision.

CONCLUSIONS

Cryopreserved vein and artery provide an excellent option in patients with active arteriovenous graft infection and those at high risk for infection. Cryopreserved vein is associated with higher primary and secondary patency than artery and has a significantly lower mean allograft fee per day of graft patency. Use of cryopreserved allograft allows for immediate reconstruction adjacent to or through areas of infection, reducing the need for staged procedures, and allows for earlier hemodialysis use.

AUTHOR CONTRIBUTIONS

Conception and design: MHL, PL

Analysis and interpretation: MHL, PL, AA, EB, JK, CA, MR, GL, SP, JH

Data collection: MHL, PL, AA, EB, JK, CA, MR, GL, SP, JH

Writing the article: MHL, PL

Critical revision of the article: MHL, PL, AA, EB, JK, CA, MR, GL, SP, JH

Final approval of the article: MHL, PL, AA, EB, JK, CA, MR, GL, SP, JH

Statistical analysis: MHL

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Overall responsibility: PL

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