Successful Restoration of Arteriovenous Dialysis Access Patency after Late Intervention

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Background: Arteriovenous dialysis access may be lost due to stenosis and thrombosis. Patency may be restored by thrombectomy or thrombolysis, but this is often not undertaken when the presentation is delayed. The success rate of delayed intervention is largely unknown.

Methods: In this single centre study, we identified all instances of arteriovenous vascular access failure treated with angioplasty, thrombectomy or thrombolysis between August 2010 and July 2013. Patency rates immediately after intervention, and after 3 months, were assessed using multilevel mixed effects logistic regression.

Results: Sixty failures occurred in 41 accesses (38 patients). The access age at failure was 495 (316 – 888) days. Intervention was carried out after more than 48 hours in 19 failures (32%). Immediate patency was achieved in 46 failures, of which 32 remained patent after 3 months. Delaying intervention increased the likelihood of achieving immediate patency (OR 0.55, 95%CI 0.31 – 1.0, p=0.05). Having lost arteriovenous accesses previously increased the risk of immediate failure (OR 4.0, 95%CI 1.07 – 14.95, p=0.04). There was no association between failure-to-intervention-time and 3-month patency rates (p=0.23). Effect estimates did not differ between arteriovenous fistulae and synthetic arteriovenous grafts.

Conclusion: Delayed intervention for failed arteriovenous vascular access may result in superior early patency rates, and yields equivalent 3 month patency rates.

Keywords: Arteriovenous, Dialysis, Fistula, Salvage, Thrombosis

Summary

Current treatment guidelines recommend that percutaneous intervention to restore arteriovenous vascular access patency be carried out within 48 hours. This is often not possible, and where significant delay has already occurred, intervention may not be attempted on the assumption of futility. Here, we explored the efficacy of delayed intervention by multilevel logistic regression in 60 dialysis access failures, and identified significantly greater immediate, and comparable 3-month, patency rates when interventions were carried out between 3 and 7 days after failure. Our results strongly support intervention to restore patency even after delayed presentation.

Introduction

The introduction of the arteriovenous fistula by Brescia more than half a century ago(1) allowed the practical and safe delivery of chronic haemodialysis. Today, dialysis is delivered via arteriovenous fistulae (AVFs), synthetic arteriovenous grafts (AVGs) or central venous dialysis catheters (CVCs). However, CVCs are associated with increased infection rates, venous stenoses and mortality, leading the Kidney Disease Dialysis Outcomes Quality Initiative (K/DOQI) to introduce the *fistula first* initiative in 2004.(2) Since then, other international treatment guidelines have ubiquitously recommended the preferential use of AVFs and AVGs to CVCs for haemodialysis access. However, AVFs and AVGs commonly fail due to stenosis and thrombosis, and vascular access continues to be described as the Achilles' heel of dialysis.(3) Preservation of vascular access has therefore become a key aim of haemodialysis programmes worldwide.(4)

Given the high complication rates associated with the use of central venous catheters,(5,6) healthcare providers and organisations have encouraged and incentivised the use of non-catheter access via AVFs, or AVGs where an AVF is not feasible.(4) Once successfully created, an AVF or AVG may not remain patent. Failure due to stenosis and or thrombosis may occur before first use (primary) or after access has been successfully utilised for dialysis (secondary). A recent systematic review including data on 12,383 haemodialysis patients placed patency rates at 60% after 1 year if primary failures were included, and at 71% and 64% after 1 and 2 years respectively when primary failures are excluded.(7) Over a dialysis career of many years or even decades, multiple access failures lead to the creation of AVFs or AVGs at multiple sites and, in some cases, the cumulative loss of access may result in a catastrophic inability to provide dialysis. Against this background, much focus has been placed on surveillance programmes to allow early identification of signs of impending vascular access failure;(8) where failure does occur (most commonly through thrombosis), the

use of percutaneous intervention (thrombectomy, thrombolysis and or angioplasty) has become widespread, and is now universally included in dialysis treatment guidelines. (9-11)

The optimal interval from failure to intervention (hereafter *failure-to-intervention-time*) is not well defined, as only a small number of studies have assessed the impact of failure-to-intervention-time on short and longer-term patency rates. In a series of 47 access failures, Rabin and colleagues failed to identify any association between patency rates and the failure-to-intervention-time, even though 22 interventions were carried out after more than 5 days, and 10 of these after 10 days.(12) In contrast, Kakkos and colleagues reported superior patency rates after early (≤ 2days) compared to late (≥ 3 days) intervention in 285 access failures, although the vast majority (261) were AVGs,(13) and Sadaghianloo *et al* reported improved patency rates after surgical thrombectomy if carried out early (3.6 ± 1.2 hours) versus late (10.3 ± 5.4 hours).(14) Although these data refer predominantly to AVGs and are therefore poorly representative of contemporary European dialysis cohorts, the studies by Kakkos and Sadaghianloo are congruent with international treatment recommendations to intervene as early as possible, or within 48 hours.(9,11,15) In practice, however, such guidelines may be counter-productive by unintentionally discouraging intervention where significant delay has already occurred. Indeed, delays often occur through late presentation, lack of available facilities or interventionists, or an immediate requirement for dialysis through temporary central venous catheter access. There is an urgent need to determine the success rates of later intervention, and to determine the optimum interventional window for the restoration of vascular access patency.

We hypothesised that failure-to-intervention-time was associated with increased probability of loss of post-intervention patency, and with lower 3-month patency rates, after percutaneous intervention for arteriovenous vascular access failure. We therefore performed a single-centre retrospective cohort study of dialysis access failures at the Norfolk and Norwich University

Hospital, United Kingdom, to determine the effect of failure-to-intervention-time on patency rates, and to assess factors contributing to the post-intervention loss of patency.

Subject and Methods

Vascular access failure episodes between August 2010 and July 2013 were identified from electronic hospital records. All adult patients aged 18 years or older were included. Vascular Access (VA) was defined as either a native arteriovenous fistula (AVF) or synthetic arteriovenous graft (AVG). Catheter vascular access was excluded. Acute VA failure was defined as 1) the absence of a clinically detectable bruit or thrill, or 2) inability to obtain any flow from the access, due to thrombosis or critical stenosis. Only cases with 3-month follow-up data were included in the analysis.

Data were abstracted from electronic health records, radiology records and case notes, and included demographics, type, site and age of access, date of access creation, date of failure, previous interventions, type of intervention, and subsequent VA performance. The time from the diagnosis of to intervention (in days) was recorded.

At our institution, a vascular access surveillance program monitors the status and performance of VA in line with international guidelines.(11) All newly created access is monitored by 1) examination by a qualified professional at every in-centre dialysis initiation, 2) review of VA performance at monthly multi-disciplinary meetings, and 3) monthly flow rate recordings using ultrasound flow dilution (Transonic). Surveillance is continued for a period of three years, after which it is discontinued in the absence of complications. AVG flow rates < 600ml/min and AVF flow rates < 400ml/min are considered evidence of failure risk, and result in continued surveillance and or further investigation. Surveillance programme status of failed accesses was captured from an electronic database.

After a clinical diagnosis of access failure, patients were referred for angiography (following Doppler ultrasound confirmation if required). If immediate dialysis was indicated prior to intervention, this was undertaken through placement of a temporary dialysis catheter. All interventions were carried out in the radiology department by one of four interventional radiologists. The decision regarding the type of intervention depended on the responsible radiologist. Interventions consisted of percutaneous angioplasty, thrombolysis using local tissue plasminogen activator (t-PA), mechanical thrombectomy (aspiration and dilatation, including angiojet), or a combination of these procedures. Patients were managed in a high-dependency setting post-procedure, and a lack of high dependency beds commonly resulted in delays in carrying out interventions.

The primary outcomes were 1) immediate (post-intervention) failure, and 2) failure at 3 months post-intervention. Data are presented as means ± SD or median (IQR) as appropriate, or as counts (%) for numerical data. Since our data included multiple failures per access, and multiple accesses per patient, we accounted for intra-access dependence and intra-individual dependence respectively by assessing the primary outcomes using multilevel mixed effects logistic regression. Patients and accesses were considered random intercepts, and time from failure to intervention as random coefficient. Diabetic status, gender, access age, patient age, access type (fistula versus graft) and the number of previous interventions were considered fixed effects predictors. Regression coefficients are presented as odds ratios (95% CI). Since a considerable number of interventions occurred after several days, we arbitrarily divided failures into early ($\leq$ 2 days) or late ($>$ 2 days) failures. For comparisons between early and late groups, events were viewed as independent within subject, and demographic data included for each presentation such that multiple events for the same patient would be associated with entries at each presentation.

Comparisons of continuous variables were made by student's T-test or Mann-Whitney U-test as appropriate, and comparisons of proportions by Fisher's exact test. For all analyses, a two-

sided alpha of ≤ 0.05 was considered statistically significant. No adjustment was made for multiple comparisons. Data were analysed using Stata SE release 13.1 (StataCorp, College Station TX).

Results

We identified 60 acute vascular access failures in 38 patients (21 (55%) male) during the study period (Table 1). The age at first presentation was 65 ± 16 years, and diabetes was present in 8 patients (22%). The 60 failures occurred in 41 accesses; 3 patients had failures in two separate accesses during the study period (Table 1). Failure occurred only once during the study period in 29/41 acceses (71.7%), with multiple failures and interventions occurring in 12 accesses (Figure 1A). The age of access at the time of failure was 495 (316 – 888) days, and the median interval from failure to intervention (failure-to-intervention-time) was 2 (1 – 3) days (range 0 – 7, Figure 1B). Consistent with the high age of vascular accesses studied, almost half of accesses had been subject to previous intervention (25 (42%) angioplasty, 28 (47%) thrombolysis).

Of 60 interventions, 32 (53%) consisted of thrombolysis, 17 (28%) of thrombolysis and angioplasty, 8 (13%) of angioplasty alone, and 1 of thrombectomy. Two were deemed unsalvageable at the time of intervention (Figure 1C). There was no clear association between the failure-to-intervention interval and the type of intervention undertaken (Figure 1D).

Immediate patency was restored in 46 cases (77%). After 3 months, 14 of these had again failed, yielding a patency rate of 0.53. Cases were divided into early (≤ 2 days, n=41) and late (n=19) intervention (Table 2). The age of the early intervention group was significantly lower (60 ± 17 years) compared with the late intervention group (70 ± 15 years, p = 0.04), and the age of access at the time of failure was also significantly shorter (460 (235 – 790) versus 664

(450 – 1472) days, p = 0.04). There were no differences in gender, diabetic status, type of access, number of previous interventions or inclusion in the surveillance programme between groups. Overall, delays in achieving intervention had been noted in 50/60 (83%) cases. The reasons for delay are shown in table 2, and were similar in both groups. The leading causes for delay were a lack of interventional radiology unit availability (63%) and a requirement for emergency dialysis due to hyperkalaemia (15%). Failure was due to thrombosis in 59/60 cases; one failure in the late intervention group was due to severe flow-limiting stenosis without thrombosis (table 2).

In a multilevel mixed effects regression model including age, gender, diabetic status, previous thrombolysis and previous angioplasty as fixed effects predictors, the number of previous vascular access sites was associated with increased odds of immediate failure (OR 4.0, 95%CI 1.07 – 14.95, p=0.04). Rather than increasing the risk of post-intervention failure, increasing failure-to-intervention-time appeared to reduce the risk of failure (OR 0.55, 95%CI 0.31 – 1.0, p=0.05). Importantly, the type of intervention undertaken (whether thrombolysis, angioplasty, thrombectomy or some combination of these) was not associated with immediate failure (p=0.24), and was removed from the final model (Table 3A). Concerning patency at 3 months after intervention, the number of previous vascular access sites was again associated with increased odds of failure (OR 0.68, 95%CI 0.99 – 37.5), although this did not reach statistical significance (p=0.051). There was no association between failure-to-intervention-time and 3-month failure (p=0.23) (Table 3B).

Discussion

Non-catheter dialysis vascular access failure is a serious complication, resulting in increased central venous catheter use and increased infection rates and mortality.(3) Finding an association between increasing failure-to-intervention-time and probability of failed intervention would have important implications for service delivery, healthcare costs and patient outcomes. In this single-centre study, we describe vascular access failures, interventions and outcomes in 38 patients receiving haemodialysis. Unexpectedly, we identified a greater primary success rate with increasing failure-to-intervention time and, although not statistically significant, the direction of the effect was similar for 3-month patency. Second, we identified a significant increase in the risk of failure if previous vascular access loss had occurred.

Current national and international guidelines recommend early intervention in the case of vascular access failure, ideally within 48 hours.(15) Our finding of an increased success rate with delayed intervention is surprising. Given that acute thrombosis is associated with vessel wall inflammation and endothelial damage, and such early active inflammation may be pro-thrombotic, it is biologically plausible that some delay in intervention may in fact be beneficial. However, these data should be interpreted with caution, as there are several possible explanations for this result: 1) selection bias may have resulted from greater pressure from the responsible clinicians to intervene in cases where access was deemed at "higher risk" of failure, or where access was more precarious, 2) conversely, less severe or incompletely occluded accesses may have more likely been deferred, 3) given the relatively small sample size, these differences may have been purely stochastic, or 4) patient-level factors that may not have been captured within the limits of this analysis.

Selection bias appears unlikely given that patient characteristics did not materially differ between groups; the cause for access failure was thrombosis in 59/60 cases; a similar number of cases in both groups received anticoagulation; and the causes for delayed intervention did not differ between groups.

Although the odds ratio for failure after late intervention is 0.55, the point estimates are wide and only narrowly reaches statistical significance. Further, despite a similar directional effect, there was no significant reduction in the odds of failure with delayed intervention after 3 months, and this is arguably a more meaningful measure of success. Our data should therefore not be taken as evidence to support a deliberate delay in intervention, but instead should argue against a nihilistic approach to vascular access in those cases where inevitable delays had already occurred.

Patients with previous vascular access loss may have a greater propensity to thrombosis. In the present study, every additional previously failed fistula increased the risk of initial failure and 3 month failure 4- and 6-fold respectively, indicating that some patients may be predisposed to fistula failure, perhaps due to anatomical or thrombophylic factors, or to pre-existing venous intimal hyperplasia.(3) Many have studied the use of anti-platelet agents or vitamin K anatagonists to maintain patency in patients with recurrent events. A Cochrane review concluded that the use of anti-platelet agents was associated with increased patency rates.(16) One small, randomised trial compared warfarin to placebo for AVF patency maintenance, and was terminated prematurely due to increased haemorrhagic events in the intervention group. Further, warfarin was associated with an increased risk of failure (OR 1.76).(17) We were unable to assess the use of warfarin and anti-platelet agents in our cohort, as drug data were not consistently captured.

Our study has several notable strengths. First, we report single-centre real-world data on 60 contemporary failed accesses. Established patient pathways drive management of such patients in our centre, and interventions are carried out by one of four interventional radiologists. Second, the study population is demographically representative of the contemporary UK dialysis population. Third, given the wide distribution of failure-to-intervention-times, and number of cases where this exceeded the guideline recommendation

of 48 hours, we were able to assess the impact of late intervention on patency. Finally, we accounted for intra-individual dependence by multilevel mixed effects regression. These strengths should be viewed against the limitations of our study, which is open to the weaknesses inherent in the analysis of retrospective data. We are unable to account for selection bias in terms of the time to intervention, and were unable to capture those patients in whom intervention my not have been undertaken on the basis of perceived futility; the factors determining late intervention were not recorded in the majority of cases; and data on the use of anti-platelet agents were not consistently available.

Delays in intervention after access failure are often inevitable, and may be driven by late presentation, the need for temporary vascular access placement for emergency dialysis, pressures on services and high dependency level bed space, and the availability of appropriate interventional radiology expertise outside office hours. Nevertheless, our findings challenge the widely held view, implied in contemporary clinical practice guidelines, that late intervention is likely to be futile. Our data are restricted to a 7-day interventional window; we cannot infer from our analyses what the optimal interventional window should be, but it is likely that this may vary depending on the type of access (with later intervention feasible for AVG). Prospective, randomised trials are necessary to definitively determine whether delayed intervention is harmful or beneficial. However, our data provide support for intervention even when the 48-hour window has been missed, and suggest that decisions for conservative management on the basis of futility after this period are unfounded.

Conflict of Interest Declaration

The authors declare no conflict of interest. The contents of this manuscript have not been published whole or in part, except in abstract format.

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Table 1: Baseline Patient and Access Characteristics

PATIENTS	
n	38
Male (%)	21 (55)
Age (years, at first failure during study period)	65 ± 16
Diabetes (%)	8 (22)
ACCESSES	
n	41
Number of distinct accesses intervened upon during study interval	1 (n = 35) 2 (n = 3)
Access type AVF (68) AVG	 28 (68) 13 (31.7)
Under surveillance at first failure (%)	19 (46)
Number of interventions per access (%) 1 2 3 4 6	 29 (71.7) 9 (22) 1 (2.4) 1 (2.4) 1 (2.4)

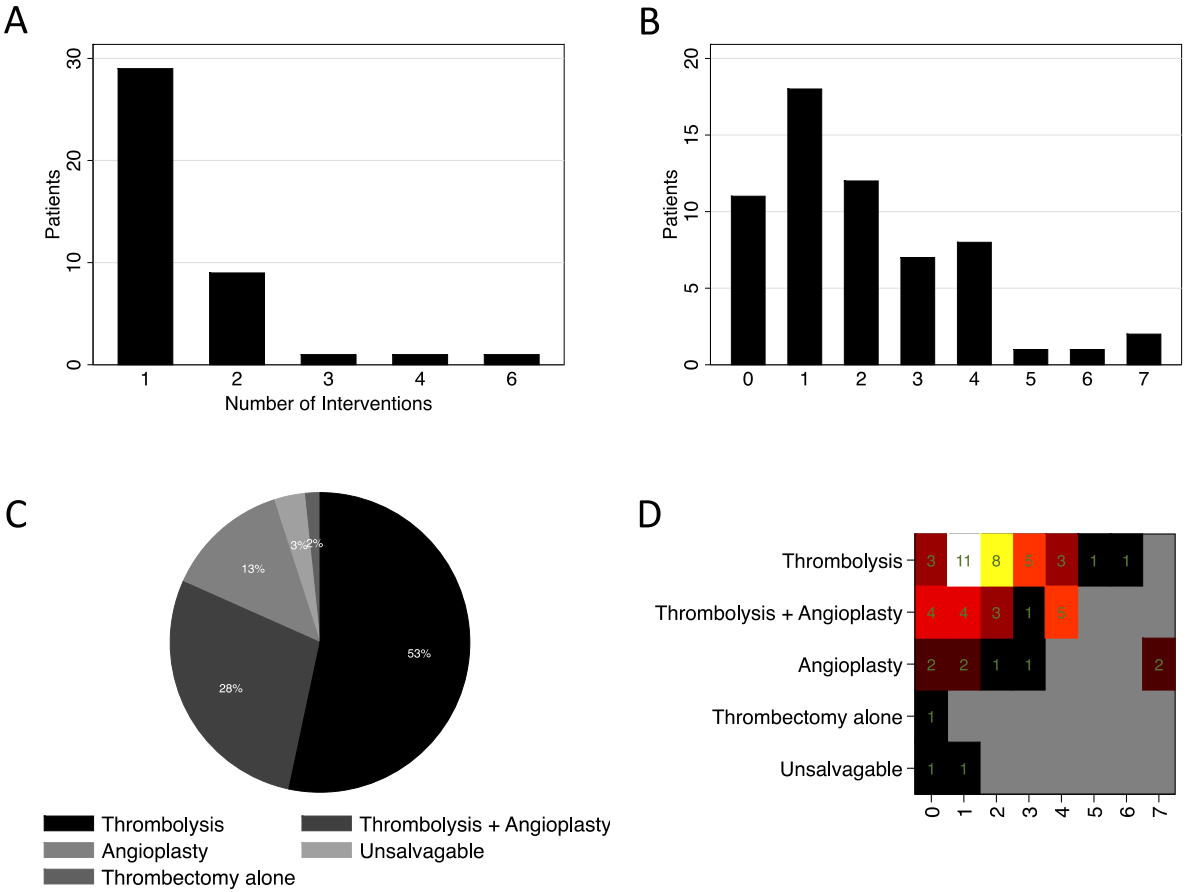
Table 2: Characteristics of Early versus Late Intervention Groups

Variables	Early (n=41)	Late (n=19)	Total (n=60)	p-value
Age at failure	60 ± 17	70 ± 15	63 ± 17	0.04
Male gender (%)	16 (39)	11 (58)	27 (45)	0.27
Diabetic (%)	11 (27)	6 (32)	17 (28)	0.76
AVF AVG	20 (49) 21 (51)	13 (68) 6 (32)	33 (55) 27 (45)	0.18
Age of access	460 (235 – 790)	664 (450 – 1472)	495 (316 – 888)	0.04
Previous Thrombolysis	21 (51)	7 (37)	28 (47)	0.40
Previous Angioplasty	15 (37)	10 (53)	25 (42)	0.27
Surveillance program	22 (54)	9 (47)	31 (52)	0.78
Known Access Problem	22 (54)	15 (79)	37 (62)	0.89
Immediate access patency	29 (71)	17 (89)	46 (77)	0.19
Patency after 3 months	20 (49)	12 (63)	32 (53)	0.40
Failure type Thrombosis Stenosis only	 41 (100) 0 (0)	 18 (95) 1 (0)	 59 (98) 1 (2)	 -
Delay in achieving intervention Delay reason (%) Delayed consent Radiology availability Hyperkalaemia Retinopathy treatment Delayed clinical decision	31 (76) 1 (2) 23 (56) 6 (15) 0 (0) 1 (2)	19 (100) 0 (0) 15 (78) 3 (16) 1 (5) 0 (0)	50 (83) 1 (2) 38 (63) 9 (15) 1 (2) 1 (2)	 0.11
Anticoagulation before procedure Pre-existing Heparin Not anticoagulated	 4 (10) 5 (12) 32 (78)	 1 (5) 2 (10) 16 (84)	 5 (8) 7 (12 48 (80)	0.816

Table 3: Multilevel mixed effects logistic regression models

Table 3A: Immediate Failure				
	OR	**95% CI**		**p-value**
Failure-to-intervention interval	0.55	0.31	0.999	0.05*
Diabetes	0.2	0.2	2.0	0.17
Male gender	3.5	0.6	19.6	0.16
Previous fistula sites	4.0	1.07	14.95	0.04
Previous angioplasty to index access	0.98	0.21	4.6	0.98
Previous thrombolysis to index access	0.57	0.09	3.6	0.55
AVG	0.41	0.05	3.10	0.39
Table 3B: Failure at 3 months				
	OR	**95% CI**		**p-value**
Failure-to-intervention interval	0.68	0.36	1.27	0.23
Diabetes	1.09	0.95	12.29	0.95
Male gender	2.52	0.24	26.88	0.44
Previous fistula sites	6.1	0.99	37.5	0.051
Previous angioplasty to index access	3.26	0.35	30.74	0.30
Previous thrombolysis to index access	0.69	0.09	5.39	0.72
AVG	0.93	0.08	11.26	0.42

Figure 1



A. Number of Interventions during the study period. Although most patients received only one intervention, 12 patients received multiple interventions. B. Interval from failure to intervention, ranging from 0 to 7 days (median 2 days). In 19 cases, intervention was delayed beyond 2 days. C. Type of intervention performed. Thrombolysis was performed in 81% of patients (28% with angioplasty). D. Heatmap demonstrating the density of each type of intervention over the failure-to-intervention-time. There was no association between the failure-to-intervention-time and the type of intervention performed.