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Dialysis

Original Article

Successful restoration of arteriovenous dialysis access patency after late intervention

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Abstract

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 (VA) 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 >48 h 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 VA may result in superior early patency rates and yields equivalent 3-month patency rates.

Keywords: arteriovenous; dialysis; fistula; salvage; thrombosis

Introduction

The introduction of the arteriovenous fistula (AVF) by Brescia more than half a century ago [1] allowed the practical and safe delivery of chronic haemodialysis. Today, dialysis is delivered via AVFs, synthetic arteriovenous grafts (AVGs) or central venous catheters (CVCs) dialysis. However, CVCs are associated with increased infection rates, venous stenoses and mortality, leading the Kidney Disease Dialysis Outcomes Quality Initiative 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 (VA) 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 CVCs [5, 6], healthcare providers and organizations have encouraged and incentivized 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 utilized 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 VA 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 long-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 >5 days, and 10 of these after 10 days [12]. In contrast, Kakkos and colleagues reported superior patency rates after early (≤ 2 days) compared with 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 h) versus late (10.3 ± 5.4 h) [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 h [9, 11, 15]. In practice, however, such guidelines may be counterproductive 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 CVC 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 VA 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 VA failure. We therefore performed a single-centre retrospective cohort study of dialysis access failures at the Norfolk and Norwich University Hospital, UK, to determine the effect of failure-to-intervention-time on patency rates, and to assess factors contributing to the post-intervention loss of patency.

Subjects and methods

Vascular access failure episodes between August 2010 and July 2013 were identified from electronic hospital records. All adult patients aged 18 or older were included. VA was defined as either a native AVF or synthetic AVG. Catheter VA was excluded. Acute VA failure was defined as (i) the absence of a clinically detectable bruit or thrill or (ii) 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 intervention (in days) was recorded.

At our institution, a VA surveillance programme monitors the status and performance of VA in line with international guidelines [11]. All newly created accesses are monitored by (i) examination by a qualified professional at every in-centre dialysis initiation, (ii) review of VA performance at monthly multi-disciplinary meetings and (iii) monthly flow rate recordings using ultrasound flow dilution (Transonic). Surveillance is continued for a period of 3 years, after which it is discontinued in the absence of complications. AVG flow rates <600 mL/min and AVF flow rates <400 mL/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 (i) immediate (post-intervention) failure and (ii) failure at 3 months post-intervention. Data are presented as means $\pm$ 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 (≤ 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 α 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 VA 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 eight patients (22%). The 60 failures occurred in 41 accesses; three patients had failures in two separate accesses during the study period (Table 1). Failure occurred only once during the study period in 29 of 41 accesses (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 VA studied, almost half of the 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).

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	1 (*n* = 35)
during study interval	2 (*n* = 3)
Access type	
AVF	28 (68)
AVG	13 (31.7)
Under surveillance at first failure (%)	19 (46)
Number of interventions per access (%)	
1	29 (71.7)
2	9 (22)
3	1 (2.4)
4	1 (2.4)
6	1 (2.4)

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 of 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 of 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 VA 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,
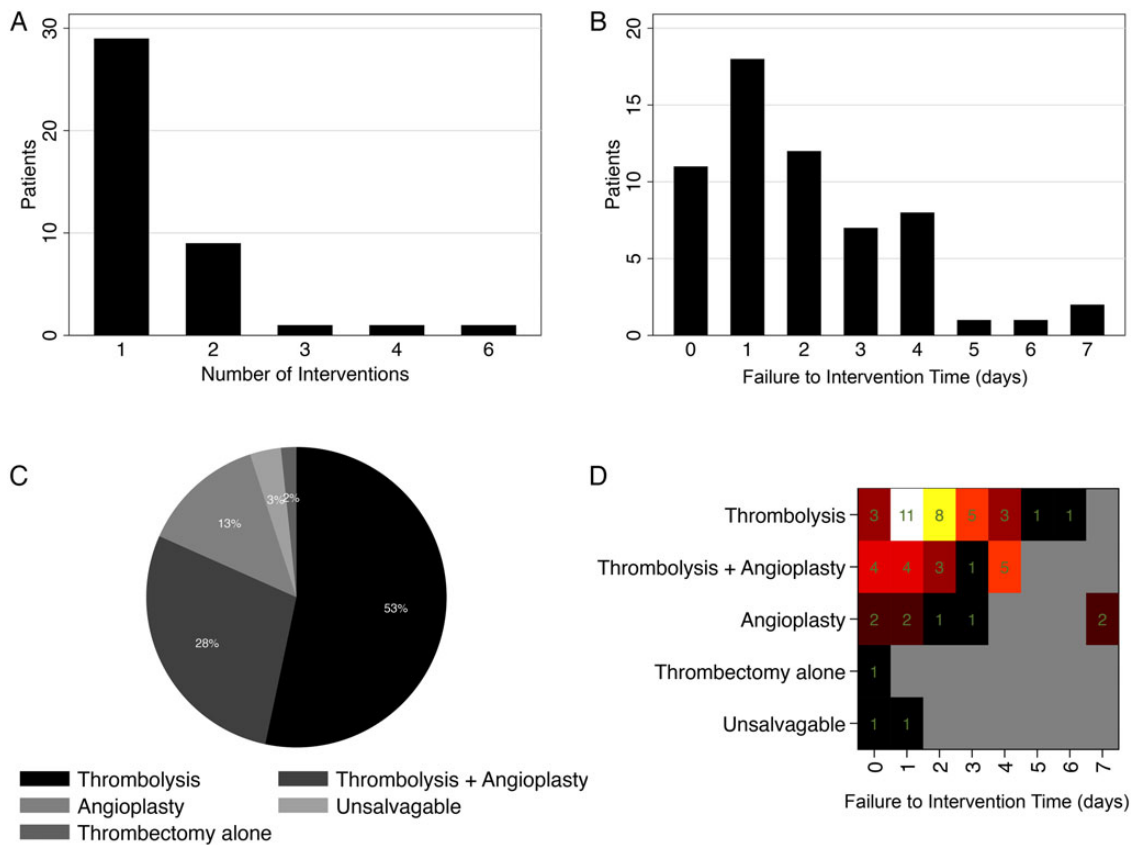
Fig. 1. (A) Number of interventions during the study period. Although most patients received only one intervention, 12 patients received multiple interventions. (B) Interval from failure to intervention, ranging from 0 to 7 days (median 2 days). In 19 cases, intervention was delayed beyond 2 days. (C) 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.

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 (%)	16 (39)	11 (58)	27 (45)	0.27
Diabetic (%)	11 (27)	6 (32)	17 (28)	0.76
AVF	20 (49)	13 (68)	33 (55)	0.18
AVG	21 (51)	6 (32)	27 (45)	
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	41 (100)	18 (95)	59 (98)	–
Stenosis only	0 (0)	1 (0)	1 (2)	
Delay in achieving intervention	31 (76)	19 (100)	50 (83)	
Delay reason (%)				0.11
Delayed consent	1 (2)	0 (0)	1 (2)	
Radiology availability	23 (56)	15 (78)	38 (63)	
Hyperkalaemia	6 (15)	3 (16)	9 (15)	
Retinopathy treatment	0 (0)	1 (5)	1 (2)	
Delayed clinical decision	1 (2)	0 (0)	1 (2)	
Anticoagulation before procedure				0.816
Pre-existing	4 (10)	1 (5)	5 (8)	
Heparin	5 (12)	2 (10)	7 (12	
Not anticoagulated	32 (78)	16 (84)	48 (80)	

Table 3. Multilevel mixed effects logistic regression models

	OR	95% CI		P-value
A: Immediate failure				
Failure-to-intervention interval	0.55	0.31	0.999	0.05
Diabetes	0.2	0.2	2.0	0.17
Male	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
B: Failure at 3 months				
Failure-to-intervention interval	0.68	0.36	1.27	0.23
Diabetes	1.09	0.95	12.29	0.95
Male	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

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 VA 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 VA failure is a serious complication, resulting in increased CVC 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 VA 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 VA loss had occurred.

Current national and international guidelines recommend early intervention in the case of VA failure, ideally within 48 h [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: (i) 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, (ii) conversely, less severe or incompletely occluded accesses may have more likely been deferred, (iii) given the relatively small sample size, these differences may have been purely stochastic, and (iv) patient-level factors that may not have been captured within the limits of this analysis.

In terms of selection bias, our data do not suggest that this was a significant contributing factor. Patient characteristics did not materially differ between groups; the cause for access failure was thrombosis (rather than non-thrombosed stenosis) in 59 of 60 cases; a similar number of cases in both groups received anticoagulation, and the causes for delayed intervention did not differ between groups. It is however possible that clinical decisions were influenced by factors not captured by our data. In contrast, the modest sample size in our study is an important limitation. 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 clinical measure of success. However, in order for the direction of the effect to be reversed (i.e. for the late group to demonstrate statistically significantly worse immediate patency rates), the unlikely scenario of a further 12 immediate failures would have had to occur in the late intervention group. Taking together these considerations, our data should therefore not be taken as evidence to support a deliberate delay in intervention, but instead should provide strong evidence against a nihilistic approach to VA in those cases where inevitable delays had already occurred.

Patients with previous VA 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, randomized trial compared warfarin with 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 h, 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 fully account for selection bias in terms of the time to intervention and were unable to capture those patients in whom intervention may not have been undertaken on the basis of perceived futility; we did not have sufficient data on blood pressure in the post-procedure period to determine whether this contributed to failures; 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 VA placement for emergency dialysis, pressures on services and high-dependency level bed space and the availability of appropriate interventional radiology expertize 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, randomized trials are necessary to definitively determine whether delayed intervention is harmful or beneficial.

However, our data provide support for intervention even when the 48-h window has been missed, and suggest that decisions for conservative management on the basis of futility after this period are unfounded.

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