Creation, cannulation and survival of arteriovenous fistulae:
Data from the Dialysis Outcomes and Practice Patterns Study

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Background. An arteriovenous (A-V) fistula is the optimal vascular access for hemodialysis. The National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) recommends that fistulae should mature for at least one month before cannulation, but this recommendation is not evidence-based. Cannulation within 14 days of creation is associated with reduced long-term fistula survival. Fistulae ideally should be left to mature for at least 14 days before first cannulation.

Methods. Prospective observational data were analyzed for a random sample (N = 3674) of incident patients at the time of initiating hemodialysis, hemofiltration or hemodiafiltration in 309 facilities in France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States, taking part in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Results. Although the proportion of patients who had predialysis care by a nephrologist differed little between countries, there were large variations in the proportion of patients who commenced hemodialysis via an A-V fistula, A-V graft or central venous catheter. The usual time interval between referral and creation of an A-V fistula also differed greatly between countries. For new hemodialysis (HD) patients initiating HD with an A-V fistula (N = 894) the following results were observed: (1) median time to first cannulation varied greatly between countries: Japan and Italy (25 and 27 days), Germany (42 days), Spain and France (80 and 86 days), UK and US (96 and 98 days). (2) No association was found between cannulation ≤28 days versus >28 days for patient characteristics of age, gender, and fifteen different classes of patient co-morbid factors. (3) Risk of A-V fistula failure was increased for incident patients who had a prior temporary access [relative risk (RR) = 1.81, P = 0.01] or who were female (RR = 1.52, P = 0.02). (4) Cannulation ≤14 days after creation was associated with a 2.1-fold increased risk of subsequent fistula failure (P = 0.006) compared to fistulae cannulated >14 days. (5) No significant difference in A-V fistula failure was seen for fistulae cannulated in 15 to 28 days compared with 43 to 84 days.

Conclusion. Significant differences in clinical practice currently exist between countries regarding the creation of A-V fistulae prior to starting hemodialysis and the timing of initial cannulation. Cannulation within 14 days of creation is associated with reduced long-term fistula survival. Fistulae ideally should be left to mature for at least 14 days before first cannulation.

Long-term hemodialysis was made possible initially by the Quinton-Scribner shunt. Subsequently, the Brescia-Cimino arteriovenous fistula facilitated reliable vascular access. The original report of this arteriovenous (A-V) fistula in 1966 describes fourteen patients aged between 28 and 54 years with a maximum period of use being 15½ months [1]. Notably, the fistulae were cannulated the day after creation. Since 1966, the profile of patients starting hemodialysis has changed considerably, the majority of new patients now being more elderly and having greater comorbidity and poorer peripheral circulation. Synthetic vascular grafts have been developed as a further type of permanent A-V access.

If A-V access cannot be created or used, uncuffed and tunneled cuffed catheters in a central vein offer the main alternatives for hemodialysis. These have reduced the immediate imperative to cannulate A-V fistulae immediately after surgery. It is now common practice for initial cannulation to be delayed so that the fistula can “mature,” that is, the vein can become larger in diameter and its wall “arterialize.” The intention of this delay is to permit adequate blood flow through the fistula and to reduce the risk of local hemorrhage at the cannulation site due to tearing of the vein wall, which may result in occlusion of the fistula. The current National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) guidelines endorse this practice and recommend that initial cannulation be delayed for at least four weeks following surgery [2]. However, this guidance is based

Key words: arteriovenous fistula, vascular access, hemodialysis, end-stage renal disease, cannulation practice, fistula survival, DOPPS.

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upon opinion and the workgroup was unable to reach a consensus on the ideal maturation period.

A proportion of patients with end-stage renal disease presents late and requires urgent dialysis [3]. This is associated with increased morbidity and mortality, some of which can be attributed to the temporary access required [4]. However, the majority of patients are known to a nephrologist before dialysis is started. Keeping the times between referral for access surgery, fistula creation and first cannulation to a minimum will substantially enhance the possibility that these patients begin hemodialysis with a permanent vascular access.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international prospective observational study of hemodialysis practice and patient outcomes being carried out at a random sample of dialysis facilities in North America, Europe, Japan, Australia, and New Zealand [5]. Data for this article have been taken from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. We have compared A-V fistula practice between these countries, identified factors associated with the time between surgery and initial A-V fistula cannulation for new ESRD patients when starting hemodialysis (HD), and studied the association between time to cannulation and subsequent fistula survival.

METHODS

Data sources

Data for these analyses were restricted to end-stage renal disease (ESRD) patients, greater than 17 years of age, receiving in-center hemodialysis, hemofiltration, or hemodiafiltration at 145 dialysis facilities in the United States (US), 63 facilities in Japan, 21 facilities in Germany, and 20 facilities each in France, Italy, Spain, and the United Kingdom (UK). The five European countries are collectively referred to as Europe (EUR) in this paper. Although these five European countries do not represent all European HD practice, they accounted for approximately 84% of all HD patients in the European Union in 1995 [6].

Data for these analyses were collected from July 1996 to May 2001 in the US, from June 1998 to November 2000 in EUR, and from February 1999 to March 2001 in Japan. Nationally representative samples were obtained using randomized selection of dialysis facilities and of their patients with ongoing longitudinal data collection as described previously [7]. Patient level data were collected from patients’ medical records. Information regarding the typical time from surgery referral to access placement was obtained from a survey completed by the unit’s nurse manager and, if unavailable, survey responses from the unit’s medical director were used. There was a strong correlation between these two sources (data not shown).

Vascular access data were collected for each patient at entry into the study and updated whenever a vascular access-related event occurred. Vascular access information included type of access, placement location, and dates of creation, first use and failure. Vascular access-related infections and procedures also were recorded.

Description of patient sample and calculation of A-V fistula cannulation time

Analyses were confined to new hemodialysis (HD) patients using an A-V fistula at the time of study entry, and with the requirement that the study entry date was within 14 days of the patient’s first-ever HD treatment for ESRD (N = 894). Eighty percent of patients in the analysis entered DOPPS on their date of first-ever dialysis, and eighty six percent entered DOPPS within two days of their first-ever dialysis treatment. Therefore, the study entry date was used as a close approximation for the date of first A-V fistula use. Time to first A-V fistula cannulation was calculated as the time from the A-V fistula creation date until patient’s study entry date. This will slightly overestimate the time to first cannulation in a small number of patients. Hence, a sensitivity analysis was performed using a stricter requirement that the study entry date had to be within five days of the patient’s first-ever HD treatment. Analyses were confined to new ESRD patients when starting hemodialysis (HD), and studied the association between time to cannulation and subsequent fistula survival.

Statistical analysis

Predictors of “early versus late” first A-V fistula cannulation. Logistic regression was used to investigate the relationship between patient characteristics and whether A-V fistulæ were first cannulated in a short time interval (<28 days) versus a longer time interval (>28 days). Patient characteristics included as predictor variables within the logistic regression analyses (N = 694) were: age, gender, diabetes mellitus, peripheral vascular disease, diagnosis of dementia or depression, coronary heart/artery disease, angina, chronic obstructive pulmonary disease, pulmonary edema, dyspnea, malnourishment, whether the patient had seen a nephrologist more than one month prior to ESRD, A-V fistula placement in upper versus lower arm, hospitalization within the three-month period prior to starting HD, whether the patient had a prior temporary access, country of residence, and facility clustering effects.

Access survival analyses. Cox proportional hazards regression was used to model time to first failure of the A-V fistula as a function of different categories of A-V fistula cannulation time. Time to failure was calculated
as the time from first use of the A-V fistula until first failure. Failure was defined as any reported event (such as thrombosis) resulting in an A-V fistula being non-functional for HD, even though the access may be usable at a later time if successfully salvaged by subsequent de-clotting or revision procedures. Observations were censored when a patient departed from the facility or the last day of known access follow-up. Models were adjusted for the following covariates: age, gender, diabetes mellitus, peripheral vascular disease, whether patient had seen a nephrologist more than one month prior to ESRD, whether A-V fistula was placed in the upper versus lower arm, and country of residence. This adjustment for country provides for consistency in effects across all countries instead of allowing a relationship in one country to dominate the overall results.

All statistical analyses were performed using SAS version 8. Logistic regression analyses employed the GENMOD procedure with a binomial error distribution and logit link function. Facility clustering effects in logistic regression models were accounted for using variance estimates based on generalized estimating equations (GEE) assuming an exchangeable correlation structure and using a “repeated” statement specifying facility-level clustering. Cox regression analyses employed the PHREG procedure. Facility clustering effects in these analyses were addressed using robust standard error estimates based on the sandwich estimator [8] with an independence working correlation.

RESULTS

Data on the initially used vascular access from DOPPS was based on 3674 HD patients starting ESRD therapy in EUR, Japan, and the US. These data reveal large variations between countries in the proportion of patients who commenced hemodialysis via an A-V fistula, ranging from 83% in Germany to 48% in the United Kingdom and only 15% in the United States (Fig. 1). Conversely, a much higher proportion of patients started dialysis via central venous catheters in the United Kingdom (50%) and the United States (61%) than in Japan (31%) and other European countries (15 to 39%). A further 23% of patients in the United States started dialysis via an A-V graft, a type of access used rarely in European countries (≤5%) and Japan (3%).

Since central venous catheters are inevitably required when patients present to a nephrologist for the first time already in need of urgent dialysis, we evaluated the time interval from first nephrologist visit to ESRD start. The proportion of patients who had more than one month of pre-dialysis care by a nephrologist ranged from 72 to 87%, and 65 to 82% saw a nephrologist more than four months before initiation of dialysis (Fig. 2). The higher use of catheters in the UK and US does not appear to be fully explained by this interval since 76% and 68% of UK and US patients, respectively, had seen a nephrologist for more than four months (Fig. 2).

If the time from surgical referral to access creation is particularly long, then patients require a longer period of nephrological care before ESRD in order to start dialysis using a permanent access. Figure 3 shows the distribution of the time from referral to surgical creation of a permanent A-V access by country as reported by the dialysis unit staff. In the UK, staff at the majority of dialysis facilities (60%) reported intervals of more than four weeks between referral and surgical creation of a permanent access. In contrast, in France, Germany, Italy, Japan and the United States the majority of units (65 to 95%) reported little delay (≤2 weeks) between referral
and surgery. These variations suggest that there are important differences between countries in the clinical pathway along which patients are prepared for dialysis.

Considering only those patients who started maintenance HD via an A-V fistula, there is a wide range of intervals between the creation of the fistula and its first cannulation shown in Figure 4. This interval is less than four weeks in 27% of all patients and more than eight weeks in 43% of patients. The median time to first fistula cannulation differed between countries, ranging from <28 days in Japan and Italy to 96 and 98 days in the UK and US, respectively (Fig. 5). The adjusted odds ratio of an A-V fistula being cannulated more than 28 days versus less than 28 days after creation varied between countries in parallel with the median time to first cannulation (Fig. 5). For all other countries, these intervals were significantly longer than the intervals for Japan or Italy. Prescribed blood flow rates at the time of starting hemodialysis varied between countries (Table 1), being higher in the US than in Japan or the European countries. However, a simple regression analysis adjusted for facility clustering effects indicated an insignificant relationship between patient prescribed blood flow rate and time to first A-V fistula cannulation ($P = 0.47, N = 769$). This relationship remained insignificant after adjustment for patient age, gender, comorbidity, early nephrologic
care, use of a prior temporary access, and hospitalization in the three months prior to study entry ($P = 0.09$, average effect size of a 10 day increase in mean cannulation time per 100 mL/min increase in blood flow rate).

In the multivariate analysis of factors possibly associated with cannulation of A-V fistulae by day 28 (“early cannulation”), only three factors were statistically significant (Table 2). Patients who had been seen by a nephrologist more than one month prior to starting dialysis had a significantly lower chance of their fistula being cannulated ≥28 days after creation. In contrast, patients who had been hospitalized within three months prior to starting dialysis, and those patients who had a prior temporary access, were significantly more likely to have their A-V fistula cannulated ≥28 days of creation. No association was found between cannulation ≥28 days and patient age, gender and fifteen different classes of patient co-morbid factors.

An analysis of A-V fistula failure indicated a substantially increased risk of failure in patients who had had a prior temporary access [relative risk (RR) = 1.81, $P = 0.01$] and in female patients (RR compared to males = 1.52, $P = 0.02$). It was found that the hazards for A-V fistula survival were not proportional in patients with or without a prior temporary access. Therefore, the remaining A-V fistula survival analyses were restricted to patients without a prior temporary access ($N = 642$). For this group of patients, cannulation within the first 14 days after creation was associated with a significantly increased risk of subsequent fistula failure. In this adjusted analysis, there was no significant trend to decreased fistula failure among the cannulation intervals greater than 14 days (Fig. 6) and fistula failure was not significantly different between any of the cannulation interval groups greater than 14 days. A comparison of the survival of fistulae cannulated within 14 days versus more than 14 days showed separation of the two curves within the first few days and perhaps further separation after approximately 200 days (Fig. 7). The relative risk of failure for fistulae cannulated between 0 and 14 days was increased by a factor of 2.1 compared with those cannulated after 14 days ($P = 0.006$).

A sensitivity analysis viewing additional categories of cannulation time suggested that the highest risk period was during the first 11 days (0 to 11 days RR = 2.75, $P = 0.004$, $N = 57$; 12 to 21 days RR = 1.16, $P = 0.73$, $N = 64$, each compared to the reference group of 43 to 84 days). Due to sample size limitations, it was not feasible to perform fistula survival analysis as a function of different categories of cannulation time for patients having a prior temporary access.

**DISCUSSION**

This international study, using a uniform data collection instrument, demonstrates large differences between countries in the use of vascular access. Focusing specifically on A-V fistulae, this study shows marked variations between countries in the time interval from patients being referred for creation of an A-V fistula to its creation, and from A-V fistula creation to first cannulation in patients new to maintenance HD.

No association was found between initial cannulation time and any of the patient characteristics studied. This suggests that local circumstances and policies of access surgery and fistula cannulation are more important than patient-related factors in determining cannulation time. The blood flow rate prescribed for the first dialysis varied widely between countries (Table 1). This was highest in the US, which had the longest median time between creation and first cannulation.

The percentage of patients presenting to a nephrologist within four weeks of starting dialysis showed moderate differences between the countries included in this study. The percentage of patients starting dialysis via a permanent access, that is, fistula or graft, was highest in Germany, which had the lowest percentage of patients referred to a nephrologist at least four weeks prior to starting dialysis. However, Germany had the shortest usual time between referral and access surgery. As reported previously [9], there is an association between a short waiting time for surgery and a high rate of primary permanent access use for new ESRD patients.

The percentage of patients starting dialysis via a permanent access is similar between France, Italy, Spain and Japan. Spain has the highest percentage of patients referred to a nephrologist at least four weeks prior to ESRD; however, nearly a quarter of Spanish units reported times greater than four weeks between referral and access surgery. The median cannulation time differed markedly between these four countries. This sug-
DOPPS: A-V fistula creation, cannulation and survival

Fig. 5. Median time to first cannulation of A-V fistulae by country (bars), and adjusted odds ratio of an A-V fistula being cannulated ≤28 days versus >28 days after creation relative to Japan (dashed line within bar). The adjusted odds ratio for each country except Italy was significantly different from the adjusted odds for Japan (P < 0.05). Odds ratios are adjusted for age, gender, peripheral vascular disease, diabetes, dementia, depression, malnourishment, coronary heart disease, coronary artery disease, angina, pulmonary edema, COPD, dyspnea, pre-ESRD care, hospitalization within 3 months of study entry, arm location of A-V fistula placement, and were limited to A-V fistulae in which cannulation time was ≤730 days. All results relate to cannulation of A-V fistulae used by incident patients when starting HD; N = 694.

Table 1. Median prescribed blood flow rates at the time of starting hemodialysis using an A-V fistula in Japan, 5 European countries, and the US

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>Median blood flow rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>134</td>
<td>240</td>
</tr>
<tr>
<td>Germany</td>
<td>131</td>
<td>200</td>
</tr>
<tr>
<td>Italy</td>
<td>82</td>
<td>265</td>
</tr>
<tr>
<td>Japan</td>
<td>97</td>
<td>160</td>
</tr>
<tr>
<td>Spain</td>
<td>153</td>
<td>300</td>
</tr>
<tr>
<td>UK</td>
<td>52</td>
<td>250</td>
</tr>
<tr>
<td>US</td>
<td>241</td>
<td>300</td>
</tr>
</tbody>
</table>

suggests that the timing of fistula creation in the predialysis period and subsequent fistula cannulation are coordinated, resulting in a similar percentage of patients starting dialysis via a fistula.

Primary permanent access use was lowest in the UK and USA, which had the longest median cannulation times. In the UK, many units reported long times between referral and access surgery. In fact, 60% of units report waiting times greater than four weeks, a percentage far higher than any other country. This practice would require UK patients to be referred especially early in the predialysis period in order to increase the likelihood of incident patients starting HD with an A-V fistula. The long periods between creation and cannulation seen in the UK may be a consequence of this and/or a deliberate policy of long fistula maturation time.

In the US, no units reported times greater than four weeks between referral and surgery. However, 60% of patients start HD with a catheter, despite 68% seeing a nephrologist for more than four months before ESRD. Three-fourths of patients who started HD with a catheter did not have a permanent access placed during the pre-ESRD period [9]. This suggests that, in the US, referral of patients for vascular access creation does not occur early enough during the pre-ESRD period to ensure that most patients are able to start HD with a permanent access. High catheter use occurs in the US despite substantial use of grafts, which often require shorter time periods for maturation compared to A-V fistulae. The higher proportion of US patients using grafts rather than native fistulae is dependent upon local practice [10–12].

The finding that the A-V fistula failure rate is greater in women than men, independent of other risk factors, has been reported by others [9, 13, 14]. We did not find the significantly poorer fistula survival in elderly and diabetic patients as has been reported in single center studies [13–16], perhaps due to the much wider range of surgical skill and techniques used in this international study.

Arteriovenous fistulae that were cannulated within 14 days of creation had a significantly increased subsequent chance of failure. No significant association was found between fistula survival and first cannulation after 14 days. In a sensitivity analysis, the highest risk period appeared to be within the first 11 days. However, the wide confidence intervals for the early cannulation categories suggest that a recommendation to delay cannulation for at least 14 days would be prudent.

As this is an observational study, it is not possible to make a causal link between cannulation and subsequent fistula failure. Spontaneous fistula thrombosis is also more likely early after fistula creation.

Only limited data are available with which to compare these results. Culp et al have reported an increased risk of thrombosis of A-V fistulae cannulated within 30 days of creation compared to longer than 30 days [17]. How-
Table 2. Factors associated with early cannulation of A-V fistulae

<table>
<thead>
<tr>
<th>Covariate</th>
<th>AOR of early AV fistula cannulation (≤28 days vs. &gt;28 days)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seen by nephrologist ≥1 month prior to ESRD</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0.60</td>
<td>0.10</td>
</tr>
<tr>
<td>AV fistula placed in upper vs. lower arm</td>
<td>0.67</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalized within 3 months prior to starting HD</td>
<td>1.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Had a prior temporary access</td>
<td>2.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted odds ratios (AOR) were adjusted for age, gender, diabetes, peripheral vascular disease, dementia/depression, coronary heart disease, coronary artery disease, angina, chronic obstructive pulmonary disease, dyspnea, and malnutrition, which were not significantly related to the outcome variable (P > 0.05). The model was adjusted also for facility clustering effects and country; 14% of patients had a prior temporary access but started maintenance hemodialysis via an A-V fistula.

ever, a large proportion of the 118 patients studied had previous temporary catheters. Insertion of temporary catheters is associated with a number of local complications [3] and their presence is subsequently associated with a sevenfold increase in risk of infection compared with A-V fistulae [18]. The present and other recent studies show that the use of prior temporary catheters also is associated with shortening of subsequent A-V fistula survival [9, 19].

One may suppose that those A-V fistulae that are sufficiently well developed to be cannulated within 14 days of creation would be those where the artery and vein are of a larger caliber or better quality. Therefore, it is all the more striking that these fistulae have a significantly worse long-term survival. The survival curves of fistulae for those cannulated before and later than 14 days after creation diverge at the start and then again later in the study period. This suggests acute complications in the first one to two weeks after earlier cannulation and perhaps a delayed effect related to cannulation trauma. This hypothesis could be tested in an experimental A-V fistula model, which also would allow interventions aimed at inhibiting such a pathological process. For example, a possible beneficial role of angiotensin converting enzyme inhibiting medications has been suggested (abstract; Young et al, *J Am Soc Nephrol* 12:307A, 2001) [20].

These data suggest that A-V fistulae should be left to mature for at least 14 days before first cannulation. Further studies are required to allow more reliable selection
of those fistulae that are suitable for cannulation after 14 days. Currently, this decision must rely on clinical judgment, perhaps supplemented by measurement of fistula blood flow rate using color Doppler ultrasound [21]. Furthermore, staff training and experience in A-V fistula cannulation also may be an important pre-condition for a successful program in cannulating and maintaining A-V fistulae. This study suggests that urgent placement of an A-V fistula and cannulation after two weeks may be feasible without an added risk of subsequent A-V fistula failure for certain types of patients. This approach may avoid the use of central venous catheters in these patients. Our data fail to substantiate the wisdom of an arbitrary one-month delay before cannulation of A-V fistulae.

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