CME Article

Managing venous stenosis in vascular access for haemodialysis

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ABSTRACT

The prevalence of end-stage renal disease in Singapore is high and rising with some 2,700 patients requiring haemodialysis in the year 2004. In tandem with the increasing prevalence of diabetes mellitus, the number of dialysis patients is projected to rise to nearly 6,000 in the year 2010, adding to the national healthcare costs. Diabetic nephropathy accounts for about 40 percent of patients starting dialysis in Singapore. There have been few studies regarding vascular access for haemodialysis, despite its great demand in the local population. These vascular access channels are far from perfect, and provide great challenges for the vascular surgeons, nephrologists and interventional radiologists on a constant basis. The concomitant vasculopathies in diabetic patients also increase the risk of morbidity related to vascular access interventions. This paper will review the current state of interventions and research associated with managing venous stenosis in renal vascular access for haemodialysis.

Keywords: angioplasty, haemodialysis, renal failure, stenosis, surveillance

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INTRODUCTION

The prevalence of end-stage renal disease in Singapore is high and rising with some 2,700 patients requiring haemodialysis in the year 2004[1]. In tandem with the increasing prevalence of diabetes mellitus, the number of dialysis patients is projected to rise to nearly 6,000 in the year 2010, adding to the national healthcare costs[1]. Diabetic nephropathy accounts for about 40% of patients starting dialysis in Singapore[2]. Vascular access for haemodialysis is in great demand in Singapore and obtaining vascular access is often complicated by concomitant vasculopathies in diabetic patients and multiple problems of restenosis and thrombosis. Maintaining the patencies of the vascular access channels form the day-to-day problems faced by the vascular surgeons, nephrologists and interventional radiologists.

The first successful haemodialysis was performed in 1945 by Dr Willen Kolff, and by the 1960s, vascular access was obtained through an exteriorised Schribner shunt which consisted of a loop of Silastic tubing on the volar part of the forearm connecting rigid Teflon catheters in the radial artery and wrist vein. However, this was associated with frequent problems of infection, restricted patient activity, frequent thrombosis, stenosis, occlusions and aneurysm formation. Since the first Brescia-Cimino autologous arteriovenous fistula was created in 1966, connecting the radial artery to the cephalic vein, there have been significant developments in the field of permanent vascular access for haemodialysis.

TYPES OF PERMANENT VASCULAR ACCESS

The two most widely-used forms of permanent vascular access for haemodialysis are the native arteriovenous fistulas and arteriovenous grafts.

(i) Native arteriovenous (AV) fistulas/grafts. The native arteriovenous fistulas/grafts are currently the first line option, whenever possible, in Singapore, and are usually in the form of a radiocephalic arteriovenous fistula/graft, brachiocephalic arteriovenous fistula/graft, or a brachiobasilic arteriovenous fistula/graft at the wrist, elbow and upper arm, respectively. Such fistulas/grafts require time to mature before they can be utilised, and there is currently no standardised definition or objective criteria to determine if maturation has occurred. The USA National Kidney Foundation Disease Outcomes Quality Initiative (K/DOQI) Guidelines recommend a maturation period of three to four months[3], while local practice suggests a six-week time frame. Probably due to widely variable subjective assessment worldwide, data suggests failure-to-mature rates ranging from 11% to 53%. The long-term primary patency of a mature fistula is reported at 85% at one year and 75% at two years[4, 5]. It has also been shown that patients who are obese, elderly and have concomitant peripheral vascular disease tend to do poorly with native arteriovenous fistulas/grafts and often require other alternatives when their veins are used up. In the local context, such patients make up a large percentage of

those requiring haemodialysis, due to the high prevalence of diabetes mellitus and its associated peripheral vascular disease. Furthermore, with their late presentation, patients often require a concomitant central venous catheter.

(ii) Arteriovenous synthetic grafts. The next best choice of permanent haemodialysis vascular access is the use of arteriovenous grafts, usually made of polytetrafluoroethylene (PTFE) and placed in a forearm loop. They have the benefit of a shorter maturation time and a larger cannulation area[6], but are known to have a poorer long-term primary patency of 50% at one year and 25% at two years. This is usually due to neointimal hyperplasia at the anastomoses[4]. A multicentre randomised controlled trial done by Rooijens et al demonstrated that significantly more interventions were needed for access salvage in those with PTFE grafts compared to those with native arteriovenous fistulas/grafts[7]. In addition, PTFE grafts were more prone to infection, with infection rates reported to be as high as 14%[8]. However, this technique may be beneficial to patients with poor forearm vessels.

VENOUS STENOSIS

The major cause of haemodialysis vascular access dysfunction is venous stenosis as a result of venous neointimal hyperplasia. Histologically, this is characterised by an increase in the proliferation of smooth muscle cells, increased production of extracellular matrix and angiogenesis (microvessel formation). Immunohistochemical studies also show the involvement of various pro-inflammatory cytokines and matrix proteins[9]; e.g., macrophages, vascular endothelial growth factors, platelet derived growth factor. Various initiating factors have been found to be associated with these biochemical and cellular changes:

(i) Haemodynamic stress. The most significant initiating factor in venous neointimal hyperplasia occurring in arteriovenous fistula/grafts is probably haemodynamic stress. The venous neointimal hyperplasia is known to occur in regions of either abnormally high or low shear stress over a chronic course[10]. Such regions occur in the course of an arteriovenous fistula/graft due to the disruption of physiological parameters of blood flow, typically very close to regular puncture sites, where very high flows and pressure changes during dialysis may be an inciting factor.

(ii) Polytetrafluroethylene grafts. Insertion of a foreign body can cause a cellular inflammatory reaction and production of macrophages and pro-inflammatory cytokines that increase smooth muscle cell and endothelial cell activation[11]. These cytokines can also travel downstream of the graft to cause stenosis in the downstream vein. The region of stenosis is usually at the anastomosis with the native vein.

(iii) Dialysis needles. Repeated thrombi formed by insertion and removal of dialysis needles in the blood vessels produce cytokines, including platelet-derived growth factor, leading to an increase in the pro-inflammatory cytokines and venous stenosis[5].

(iv) Uremia. There is strong evidence to suggest that uremia, frequently occurring in patients with end-stage renal disease, leads to endothelial dysfunction and may predispose to venous neointimal hyperplasia[12, 13]. Venous stenosis can occur centrally secondary to insertion of a permanent catheter, or peripherally due to the fistula or graft. This leads to reduced access flow rates downstream of the stenotic lesions, signs of venous hypertension, and failure of the arteriovenous fistulas, which is arbitrarily assigned as flow rates of less than 500 ml/min, as measured by a Transonic device (Transonic Systems Inc, Ithaca, USA). However, practice varies from institution to institution.

ANGIOPLASTY

Haemodialysis patients are often referred to vascular surgeons and interventional radiologists because of reduced access flow rates. Attempts are usually made to repair the stenotic lesions before considering the final option of creating a new access route. There is a role for venous duplex scanning and magnetic resonance angiography in these cases, but a diagnostic angiogram is the most useful when considering intervention.

Percutaneous transluminal angioplasty (PTA) is a useful option for stenotic lesions in arteriovenous fistulas/grafts. This technique was initially described by Dotter and Judkins in 1964 and later modified by Grüntzig, who introduced the angioplasty balloon. The procedure involves crossing the stenosis with a guidewire. The angioplasty balloon is then inflated within the lesion, usually for 30–60 seconds, then deflated and withdrawn. Multiple trials have been done to evaluate the efficacy of this procedure and the potential long-term patency rate following PTA is well established[14–18]. Published series consistently report 40% to 50% six-month unassisted patency rates from PTA[3].

Many variables in the use of PTA have been studied, including the type of balloons used, the PTA balloon inflation pressures, and the time the balloon is kept inflated. However, there have been no major changes in the medium-term outcome of restenosis despite advances in balloon technology and technique.

(i) Cutting balloon angioplasty. A newer modification is the cutting balloon, which was first designed by Barath

et al[19]. Cutting balloon angioplasty (CBA) features three or four atherotomes, mounted longitudinally on the outer surface of a noncompliant balloon. With the inflation of the balloon, it expands radially and delivers longitudinal microsurgical incisions in the vessel wall, thus facilitating its dilatation with a lower balloon inflation pressure. With conventional balloon angioplasty, the high pressures used cause great trauma to the vein walls, thus initiating a reparative process – intimal hyperplasia. The lower balloon inflation pressures (recommended from 4–8 atm) used with the cutting balloons are thought to reduce pressure to the wall, thus reducing trauma, intimal hyperplasia and restenosis.

To date, few studies have been done to compare the use of cutting balloon angioplasty against its conventional counterpart. However, a randomised control trial done by Vesely and Siegel on 340 patients with stenotic or thrombosed haemodialysis grafts revealed that there was no difference in the six-month primary patency rates in the target lesion or the entire vascular access circuit[20]. The concept underlying this technology appears to be flawed.

(ii) High pressure balloons. High pressure (>15 mmHg rated burst pressure) and ultra-high pressure (>20 mmHg rated burst pressure) angioplasty balloons have been a new addition to the field of angioplasty. Studies show that more than 50% of venous stenoses require at least high angioplasty balloon inflation pressures of 10–15 atm to achieve dilatation of the stenosis, with up to one-third requiring ultra-high pressures exceeding 20 atm. High pressures are commonly needed for PTA in the native outflow veins while ultra-high pressures are more frequently needed in native fistulas, in particular, venous anastomotic stenoses. The few small studies that have been done show that, despite the close to 100% technical success obtained, the primary patency rates are not significantly improved as compared to the use of conventional angioplasty.

(iii) Balloon inflation time. There is a lack of published studies regarding modifications to balloon inflation time and most interventional radiologists and product recommendations agree on a 30–60 second inflation time. Preliminary studies by Vesely and Siegel are awaited and there might be some suggestion that prolonging the balloon inflation time may improve the efficacy of the procedure.

(iv) Cryoplasty. A novel variation to conventional angioplasty involves the use of cryoballoons. A liquid form of nitrous oxide enters the balloon and becomes a gas, which simultaneously inflates the balloon and freezes (-10 °C) the adjacent vascular tissue. Although in vitro studies suggest that smooth muscle cells exhibit reduced viability after freezing, the exact mechanisms involved are not well known[21]. In a study done by Rifkin et al, five patients with rapidly recurrent venous lesions at the graft-vein anastomosis showed an increase in the time to stenosis or thrombosis in the arteriovenous grafts, from a mean of three weeks to more than 16 weeks[22]. Gray also presented with results of a primary patency of 57% and 28% at three months and six months, respectively, using the PolarCath Peripheral Balloon Catheter System[23]. It is of note that all patients complained of significant pain during the procedure, which may result in cryoplasty being one of the least preferred methods.

STENTS

For patients with multiple PTA, attempts to salvage vascular access, including those with complications of venous rupture, are possible through placement of metallic stents in the peripheral outflow veins. Endovascular stents vary in their deployment methods and material used. Those available in the market include those made of stainless steel or nitinol, and different deployment methods used include the self-expanding or balloon-expanding type. Self-expanding nitinol stents (shape memory alloy recoverable technology [SMART] stents [Cordis, Johnson and Johnson, NJ, Warren, USA]) are found to be ideal due to their flexibility and resistance to crushing, especially important properties for their use in superficial locations of the veins. In a Taiwanese study done by Pan et al, the stainless steel self expandable Wallstent or Jostent (Jomed, Abbott Laboratories, Abbott Park, IL, USA) was chosen for use in arteriovenous fistula haemodialysis patients with a need to restore vascular access after insufficient balloon dilatation. Results showed a primary patency of 81% and 31% at six and 12 months post-procedure, respectively[24]. A similar study done by Turmel-Rodrigues et al showed that, for native fistulas, primary patency rates were 47% at six months and 20% at one year. Slightly better results were obtained for patients with polytetrafluoroethylene grafts, with primary patency rates of 58% at six months and 23% at one year, respectively[25]. In a study done by Vogel et al using the SMART stent, primary patency rates of 67% and 41% were obtained at six months and 12 months, respectively[26]. Complications reported in the above studies were mainly due to malpositioning of the stent. Subsequent failure of the stents occurred due to the development of venous neointimal hyperplasia, which occurred through the holes in the mesh. Severe fractures of the stent were also reported.

STENT GRAFTS

An improvement to conventional endovascular stents is the stent graft, comprising a tubular synthetic graft supported by an internal stent. It is believed to have the benefit of reducing the incidence of venous neointimal

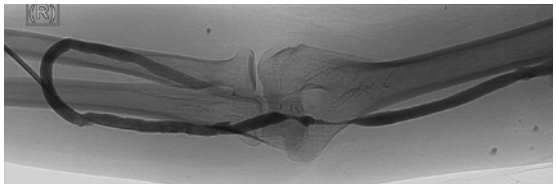

Fig. 1a Angiogram shows a long segment of stenosis in the basilic vein after creation of a right brachio-basilic arteriovenous graft.

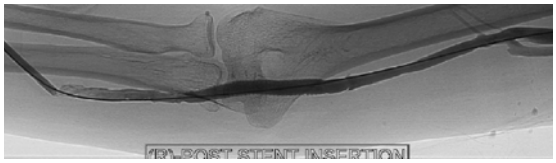

Fig. 1b Post-stent angiogram shows a Viabahn stent graft inserted in the same patient.

hyperplasia, the most common cause of failure of vascular access. There is a lack of published studies regarding the use of stent grafts. An unpublished arteriovenous access stent graft trial showed primary circuit patency of 38% at six months follow-up. Early experience by Vesely with the Viabahn (WL Gore, Flagstaff, AZ, USA) has demonstrated that a stent graft made of expanded polytetrafluoroethylene and nitinol can successfully exclude a pseudoaneurysm from a haemodialysis graft, and may prevent further enlargement and decrease the likelihood of rupture[27]. Masuda et al also reported that endoluminal stent-grafts can be successfully inserted into the axillary vein for creation of an AV fistula and remain patent for two years or more[29]. The latest development in this arena includes drug-coated stents which have proven to be useful in preventing venous neointimal hyperplasia in animal models[28]. This method may be most useful in patients with very small, unusable arm veins or multiple failed AV grafts[29] (Fig. 1).

ROLE OF SURVEILLANCE

The role of regular access monitoring via ultrasound blood flow measurements has not been shown to be cost-effective. There is a reported increase in the rates of pre-emptive angioplasty procedures and thereby shortened primary patencies of fistulas and grafts[30]. However, this increase in intervention does not seem to decrease the rate of thrombosis or alter cumulative fistula patency[31]. Hence, clinical surveillance or access flow rates may still be the best monitoring option for now.

CONCLUSION

At present, new endovascular intervention techniques have had equivocal results compared to the conventional PTA. However, they increase the options available to patients with lesions resistant to the conventional treatment and may reduce the need for a surgical creation of a new permanent vascular access for haemodialysis. They also increase secondary patency and extend the use of a failing arteriovenous fistula while allowing planning and creation of a new arteriovenous fistula and avoiding central vein cannulation. Although such interventional techniques are minimally invasive and associated with low mortality, larger randomised controlled trials are needed to assess safety, patency and cost-effectiveness. The ultimate aim is to enhance long-term vascular access function and reduce the costs associated with the maintenance of access patency. Newer technology and more clinical research may be useful in improving sensitivity for early detection of stenosis, which will allow early intervention and possibly better outcomes. Until then, clinical surveillance of access flow rates and subsequent intervention planning may still be the most cost-effective approach.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 200701A)

	True	False
Question 1. Native arteriovenous fistulas for dialysis:		
(a) Can be readily salvaged after thrombosis by vascular interventions, including thrombolysis.	☐	☐
(b) Have a long-term patency rate of 75% at one year.	☐	☐
(c) Are the best first-line choice of dialysis access in almost all patients.	☐	☐
(d) Develop neointimal hyperplasia more frequently on the arterial supply side of the fistula.	☐	☐
Question 2. Synthetic PTFE arteriovenous grafts:		
(a) Have the major advantage of immediate usability after implantation.	☐	☐
(b) Have a long term patency rate of 75% at one year.	☐	☐
(c) Are prone to abrupt thrombosis, but can be salvaged even days to weeks later by aggressive vascular interventional methods.	☐	☐
(d) Have a high incidence of stenosis due to neointimal hyperplasia, usually at the venous anastomosis.	☐	☐
Question 3. The development of venous neointimal hyperplasia in dialysis access grafts:		
(a) Is more common in native AV fistulas than synthetic PTFE grafts.	☐	☐
(b) Is predominantly related to shear haemodynamic stresses on the vessel wall due to high flow rates and turbulent flow.	☐	☐
(c) May be at the site of most frequent repeated venous access for dialysis.	☐	☐
(d) May occur remotely from the AV fistula or graft in proximal central veins.	☐	☐
Question 4. Treatment of stenosed dialysis access grafts or fistulas:		
(a) Can be achieved using simple balloon angioplasty without stenting in most cases.	☐	☐
(b) Shows superior long-term patency over balloon angioplasty when stents and intraluminal stent grafts are used.	☐	☐
(c) Usually requires extremely high balloon inflation pressures which may exceed 20 mmHg.	☐	☐
(d) Can be best determined by routine serial Doppler ultrasound.	☐	☐
Question 5. The use of stents and stent grafts for dialysis graft/fistula salvage:		
(a) Is useful for exclusion of pseudoaneurysms.	☐	☐
(b) Is valuable in cases where fistula/graft ruptures occur as a direct result of high pressure balloon angioplasty.	☐	☐
(c) Routinely results in improved long-term patency over balloon angioplasty alone.	☐	☐
(d) May be accompanied by stent fracture, which may lead to occlusion of the graft/fistula.	☐	☐

Doctor's particulars:

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MCR number: _____ Specialty: _____

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SUBMISSION INSTRUCTIONS:
(1) Log on at the SMJ website: **www.sma.org.sg/cme/smj** and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:
(1) Answers will be published in the SMJ March 2007 issue. (2) The MCR numbers of successful candidates will be posted online at **www.sma.org.sg/cme/smj** by 15 March 2007. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers.(5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (January 2007 SMJ 3B CME programme): 12 noon, 25 February 2007