Journal of Nephrology & Therapeutics

Teoh et al., J Nephrol Ther 2014, 4:3
DOI: 10.4172/2161-0959.1000161

Research Article Open Access

Recombinant Tissue Plasminogen Activator is Safe and Effective in Increasing Haemodialysis Catheter Longevity in Paediatric Haemodialysis Patients

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Rec date: Mar 22, 2013, **Acc date:** May 02, 2014, **Pub date:** May 07, 2014

Abstract

Background: Haemodialysis catheter (HDC) occlusion is a common cause of poor blood flow, inadequate dialysis and HDC loss. From Jan 2009, our unit used infusions of recombinant tissue plasminogen activator (rtPA), Alteplase 0.1-0.2 mg/kg/hour over 1-2 hours for thrombolysis of occluded catheters.

Methods: Retrospective review of outcomes of all patients who were treated with rtPA infusion for HDC occlusion in our unit between Jan 2009 to Dec 2012. Twenty patients underwent 5,407 sessions of catheter-directed haemodialysis in our unit (mean age 7.4 years, range 0.3-15.8 years).

Results: Ten patients accounted for 339 episodes of rtPA infusions (median 12, range 1-115). Thirty-three radiographic contrast studies were performed – 21 (64%) confirmed presence of thrombus. The immediate success rate, defined as return of manual aspiration and infusion capabilities to both ports was 100%. No patients required exclusion from thrombolytic therapy due to contraindications. One patient had rtPA infusion discontinued after 9 infusions due to spontaneous bruising despite normal fibrinogen levels. The remainder of patients tolerated the treatment well. All patients had normal coagulation profile. No HDC were surgically changed due to occlusion by thrombus.

Conclusion: Low dose Alteplase infusion is safe and efficacious in the management of HDC occlusion. It provides a means for improving the long-term survival of HDC catheters in patients with limited available options of vascular access for haemodialysis.

Keywords: Recombinant tissue plasminogen activator; Haemodialysis; Central venous catheter; Thrombus; Haemodialysis catheter

Introduction

Haemodialysis requires repeated, secure access to the bloodstream whilst ensuring an adequate rate of blood flow. Tunnelled central venous catheters/haemodialysis catheters (HDC) provide a means of permanent vascular access, which provides sufficient blood flow to allow adequate haemodialysis and can be used immediately once inserted. HDCs are the most common means of vascular access in paediatric haemodialysis as connection to the dialysis circuit is straightforward and needle-free [1].

Disadvantages and shortcomings of prolonged catheter use include thrombotic occlusion (either by thrombus or fibrin sheath) [2,3], catheter-related infection [4], malposition and/or migration [5]. Management approaches of catheter occlusion include fibrin sheath stripping and surgical revision. In children, these procedures require general anaesthesia which creates significant anxiety for patient and their parents, particularly when multiple, repeated procedures are required. Moreover, a repeated catheter insertion increases the risk of central venous stenosis [6].

rtPA intra-catheter locks and infusions are increasingly being used for thrombolysis of occluded haemodialysis catheters [7-9]. Intracatheter locks of rtPA is efficacious and safe, but optimal patency rates (80-90%) are often seen only after several boluses have been administered, which may require up to 48 hours [10,11]. Short intracatheter infusions of rtPA have been used in interventional radiology units and on paediatric haematology-oncology patients [10-16], proving to be safe [8], convenient and cost-effective [17-18]. Thus from January 2009, our tertiary unit elected to use infusions of low-dose rtPA as an alternative method for thrombolysis of occluded haemodialysis catheters in our paediatric haemodialysis patients.

Methods

All children on haemodialysis in our tertiary nephrology unit with HDC occlusion who were treated with recombinant tissue plasminogen activator (rtPA) between January 2009 and December 2012 were identified from our hospital database. In our practice, haemodialysis catheter occlusion by thrombus/fibrin sheath was empirically diagnosed when there was no blood return on manual

aspiration, or failure to achieve minimum blood flows on haemodialysis of at least 3 ml/kg/min, in the absence of other potential causes of catheter occlusion such as kinking and/or malposition. HDC thrombus was defined by echocardiography or contrast studies depending on service availability.

All children in our unit are haemodialysed thrice weekly via a HDC. Children are treated with 20-50 iu/kg/hr unfractionated heparin (UFH) infusion during HD, following a loading dose of 10 iu/kg, and HDCs are locked with 5000 iu/ml UFH following dialysis. Inadequate flows during dialysis, or reversal of flows, are managed initially with alteplase (rtPA) line locks. Failure to respond is investigated by a contrast study of the catheter, echocardiography, or both, depending on service availability. Haemodialysis catheter access is restricted to a small team of specialist nurses who meticulously adhere to a strict, sterile, non-touch technique when accessing these catheters to reduce the risk of infection.

Recombinant tissue plasminogen activator (Alteplase) was administered at an initial dose of 0.1 mg/kg/hour, infused into the occluded catheter port over 1 hour, prior to dialysis. Depending on response, dose increases are made by the patient's attending nephrologist, up to a maximum dose of 0.2 mg/kg/hour, infused over 2 hours, prior to dialysis. Treatment was continued until resolution of the HDC thrombus. No loading doses of rtPA were given prior to the infusion. Vital signs were monitored every 15 min during treatment and patients were observed for at least 1 hour post infusion. Coagulation profile comprising of prothrombin time, activated partial thromboplastin time and fibrinogen levels, were checked pre- and post-infusion of rtPA. Exclusion criteria for rtPA infusion included active bleeding, thrombocytopaenia (platelet count less than 50,000) and/or abnormal coagulation profile.

Immediate success was defined as the return of manual aspiration and infusion capabilities to the affected port and successful restoration of blood flow was defined as the ability to re-establish the same blood flow that had been present prior to catheter thrombosis. Inability to restore catheter function after three consecutive infusions of rtPA was considered primary failure requiring surgical intervention.

The following information was collected from the notes: the patient's age at commencement of HD and at diagnosis of thrombus, underlying diagnosis, number of HDCs, number of HD sessions prior to diagnosis of HDC thrombus, dose of rtPA, duration of treatment, time to resolution of thrombus, and any adverse effects.

Results

Over a 4-year period from January 2009 to December 2012, 20 children underwent 5,407 sessions of catheter-directed haemodialysis in our centre via 20 HDCs. Ten children were diagnosed with HDC thrombus, accounting for 339 episodes of rtPA infusions (median 12, range 1 – 115). A total of 33 diagnostic interventions were performed when there was a clinical suspicion of a HDC thrombus. A diagnosis of HDC thrombus was confirmed on 21 (64%) occasions. No children were excluded from rtPA infusion. All 10 patients had HDCs placed in the right internal jugular vein.

The mean (range) age of all children at commencement of HD in the 4-year period was 7.4 (0.3–15.8) years. The mean (range) age of the 10 children was 6.3 (0.3–14.8) years at commencement of HD and was 7.1 (0.9–14.9) years at time of first rtPA infusion. Mean (range) duration of HD at time of first rtPA infusion was 0.8 (0.1–2.5) years and mean (range) sessions of HD at time of first rtPA infusion was 134 (15–390) sessions.

n	Diagnosis	Age (years) @ start of HD	At time of first rtPA infusion			No of rtPA				Outcomes (as of 31 Dec 2012)
			Age (years)	Duration of HD (years)	HD Sessions	0.1 mg/kg/h over 1 hour	0.1 mg/kg/h over 2 hours	0.2 mg/kg/h over 1 hour	0.2 mg/kg/h over 2 hours	
1	Renal Dysplasia	2.4	4.9	2.5	390	3	4	2	0	Line remained in-situ x 2.5 years
2	Bilateral Wilm's Tumour	2.0	3.1	1.1	171	6	4	30	5	Line remained in-situ x 2 years until transplant
3	Nephrotic syndrome	10.5	10.8	0.3	47	108	0	0	1	Line remained in-situ x 3.2 years
4	Posterior Urethral Valves	5.6	6.3	0.7	109	1	0	0	0	Line remained in-situ x 2.1 years until transplant
5	Renal Dysplasia	14.8	14.9	0.1	15	115	0	0	0	Line remained in-situ x 2.8 years
6	Primary Hyperoxalosis	0.3	1.7	1.4	218	10	0	22	1	Line remained in-situ x 1.2 years
7	Prune Belly Syndrome	8.5	9.6	1.1	172	2	0	0	0	Line remained in-situ x 0.75 years until transplant
8	Renal Dysplasia	0.5	0.9	0.4	62	1	2	10	1	Line remained in-situ x 0.2 years until transplant

9	Renal Dysplasia	13.9	14.5	0.6	94	2	0	0	0	Line remained in-situ x 0.3 years until transplant
10	Cystic Kidney Disease HNF1B	4.3	4.7	0.4	63	4	1	4	0	Line remained in-situ x 1 year until transplant

Table 1: Patient age (years) at commencing HD and at time of first rtPA infusion, underlying diagnoses, duration and HD sessions prior to thrombus, doses of rtPA and outcomes.

One patient had rtPA infusion discontinued after the 9th infusion due to spontaneous bruising, despite normal platelet, prothrombin time, activated partial thromboplastin time and fibrinogen levels. Two patients had very mild, self-resolving bleeding from gum and site of gastrostomy tube insertion while on infusion with rtPA. The remaining patients tolerated the infusions well without any adverse effects. Vital signs during and after the rtPA infusions were stable in all patients. All patients had normal pre- and post-infusion coagulation profile (PT, APTT and fibrinogen levels).

All 10 patients who had HDC thrombotic occlusions had successful restoration of normal flows during dialysis and line function. Immediate success rate was 100%. Seven patients had repeated episodes of re-occlusion throughout their duration on HDC-delivered haemodialysis warranting repeated use of rtPA therapy. Of these patients, restoration of adequate blood flows for dialysis were achieved after each repeated course of rtPA infusions. No HDCs were lost due to thrombosis or required surgical replacement due to thrombosis. Six patients had functioning HDCs when they were removed at time of renal transplantation. Of the remaining 4 patients, median HDC survival was 967 days (IQR 557 - 1132) as of 31st December 2012.

Discussion

Our study on our paediatric haemodialysis cohort over a 4-year period highlights the efficacy of low-dose, intracatheter rtPA infusion in maintaining patency of haemodialysis catheters and restoration of adequate blood flow for functional dialysis requirements.

Intracatheter dwells/locks of rtPA have been used to restore patency of occluded central venous catheters in various adult and paediatric patient populations with success rates of up to 87% [10,11,15,19-21]. The recently published ALTE-DOSE study which compared 30-minute dwells of rtPA (Alteplase) 1mg vs 2mg in adult haemodialysis patients, found that the mean survival time of haemodialysis catheters were 782 days (1mg group) and 955 days (2 mg group) [20]. It concluded that the administration of a 2 mg dose of rtPA was superior to 1mg with regard to resolving occlusion and prolonging catheter days, with the hazard of catheter removal due to unresolved catheter dysfunction quoted as 2.75 times higher in the 1 mg rtPA group compared to the 2 mg rtPA group [20].

Another method of administering rtPA to restore catheter patency involves forceful application of boluses over 30 min, which resulted in 88.2% success by Zacharias et al. [22] Other studies have suggested that rtPA infusion may be more effective than local instillation in HDC thrombolysis [7,15,23]. In a paediatric haemodialysis cohort, Bamgbola et al. achieved a 100% success rate of de-clotting with rtPA infusion of 2.5 mg infused over 2 hours in 6 of their patients treated for 7 episodes of haemodialysis catheter thrombosis [7]. rtPA has a short half-life and has a strong fibrin-specificity. Infused rtPA dissolves the fibrin-rich clots and maintains a weak fibrinolytic activity in the circulation, leading to a reduction in circulating fibrin and its deposition on the resolving intracatheter thrombus [24]. In addition, rtPA infusion may improve its contact with the intracatheter thrombus (as compared to dwells), increasing its net biological activity [23,25].

The use of rtPA infusions for thrombolysis offers numerous practical advantages: it is non-invasive, can be easily and promptly administered upon detection of catheter occlusion in the dialysis unit, and patients can be monitored by trained nephrology nursing staff should complications arise. At low doses, side effects are rare and its use significantly reduces the risks from hospitalisation, general anaesthesia and surgery [19,26]. Furthermore, rtPA can be infused prior to dialysis, alleviating the need for additional staff, and so long as the patient remains stable with the possibility to delay dialysis, infusions can be scheduled at the convenience of the patient and the dialysis centre.

In our study, no potential patients were excluded due to risk factors for adverse events. The most common effect of rtPA use was bleeding at sites of tissue injury, as occurred in two of our patients during their rtPA therapy [26]. Both were very mild and resolved spontaneously at the end of infusion. One of our patient's did have spontaneous bruising involving his extremities, despite having normal platelet counts, prothrombin time, activated partial thromboplastin time and fibrinogen levels. The remainder of our patients experienced no adverse events with the doses of rtPA infusion that were used. In our opinion, the safety profile and short half-life of rtPA allowed for its use even in the absence of a definitive thrombotic cause of catheter occlusion. Failure to restore catheter function after therapeutic trial of rtPA may serve as a diagnostic clue to a non-thrombotic aetiology.

Adequate central venous access provides a lifeline to patients with end-stage renal failure for adequate haemodialysis and repeated surgical revision requires multiple venous access sites, increasing the risk of central venous stenosis. Several of our patients had many previous central venous access placements and have limited options for future vascular access available. We prioritised maintaining the patency of their haemodialysis catheters by repeated rtPA infusions for recurring episodes of catheter occlusion, which contributed to the increased frequency of rtPA infusions in several of our patients in the study. Our practice of maintaning the patency of HDCs in these patients with repeated rtPA infusions prolonged catheter survival up to more than 3 years (as of 31 December 2012). No patients in our population lost their HDC due to thrombosis or required surgical replacement of thrombosed catheters. Excluding those whose HDC were removed at time of transplant, median HDC survival in our population was 967 days at the end of the data analysis period (as of 31 December 2012). Since the introduction of rtPA use in our population (January 2009), there had been no catheter-related infection. We believe the fibrinolytic effect of rtPA played a contributory role in

reducing the HDC infection rate by preventing the build-up of biofilm protein-fibrin matrix [27].

Limitations of our study are the small sample size, its retrospective design and the lack of a control group.

We believe our findings offer a safe and effective alternative means to improve the long-term survival of haemodialysis catheters especially in patients with limited options for vascular access. We feel it provides an appropriate initial means of catheter thrombolysis prior to more invasive procedures. It has the potential to improve patient care while minimizing cost and morbidity. Our observations would need further confirmation in a prospective study sufficiently powered to examine all relevant variables.

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