Thrombolytic therapy for central venous catheter occlusion

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ABSTRACT

Background
Long-term central venous catheters have improved the quality of care for patients with chronic illnesses, but are complicated by obstructions which can result in delay of treatment or catheter removal.

Design and Methods
This paper reviews thrombolytic treatment for catheter obstruction. Literature from Medline searches using the terms "central venous catheter", "central venous access device" OR "central venous line" associated with the terms "obstruction", "occlusion" OR "thrombolytic" was reviewed. Efficacy of thrombolytic therapy, central venous catheter clearance rates and time to clearance were assessed.

Results
Alteplase, one of the current therapies, clears 52% of obstructed catheters within 30 min with 86% overall clearance (after 2 doses, when necessary). However, newer medications may have higher efficacy or shorter time to clearance. Reteplase cleared 67-74% within 30-40 min and 95% of catheters overall. Occlusions were resolved in 70 and 83% of patients with one and 2 doses of tenecteplase, respectively. Recombinant urokinase cleared 60% of catheters at 30 min and 73% overall. Alfimeprase demonstrated rapid catheter clearance with resolution in 40% of subjects within 5 min, 60% within 30 min, and 80% within 2 h. Additionally, urokinase prophylaxis decreased the incidence of catheter occlusions from 16-68% in the control group to 4-23% in the treatment group; in some studies, rates of catheter infections were also decreased in the urokinase group.

Conclusions
Thrombolytic agents successfully clear central venous catheter occlusions in most cases. Newer agents may act more rapidly and effectively than currently utilized therapies, but randomized studies with direct comparisons of these agents are needed to determine optimal management for catheter obstruction.

Key words: central venous catheter, thrombolytic agents, obstruction, occlusion.

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Introduction

Long-term central venous catheters (CVC) facilitate medical care for children with chronic illness, particularly those with cancer by providing easy venous access for blood tests, chemotherapy administration, parenteral nutrition (PN), and other necessary intravenous medications. However, potential CVC complications include infection, mechanical dysfunction, thrombosis, and catheter occlusion, which can increase morbidity, interrupt treatment, and require catheter removal.

The most frequent CVC complication is occlusion, which occurs in 14-36% of children with cancer within 1-2 years of insertion.[1-6] Occlusion can be classified as partial (inability to aspirate blood but ability to infuse through the catheter) or complete (inability to aspirate or infuse via the catheter). Although CVC obstruction is considered to be a clinically important issue according to 80% of pediatric oncology centers surveyed in the United Kingdom, differences in prevention, diagnosis, and treatment practices persist due to lack of evidence-based management guidelines.[7] This paper reviews thrombolytic treatment for catheter obstruction based on the current literature from Medline searches using the terms "central venous catheter", "central venous access device" OR "central venous line" associated with the terms "obstruction", "occlusion", "treatment", or "thrombolytic". Efficacy of thrombolytic therapy, CVC clearance rates, time to clearance, and the need for a second dose of thrombolytic were assessed and side effects of thrombolytic therapy reviewed. The emphasis of this review is management of long-term CVCs, so articles that focused on short-term CVCs or hemodialysis catheters were excluded. All original articles from the literature search that analyzed the treatment of long-term CVC occlusions with the thrombolytics discussed in this manuscript were included in the review.

Types of catheter obstruction

CVC obstruction can occur from mechanical causes, precipitation of a medication or PN, or as the result of a thrombotic process. Mechanical obstructions include problems such as a kink in the catheter or tubing, a tight suture, a catheter tip blocked by the vessel wall, a clamp left in the closed position on an external catheter or a needle dislodged or occluded when using implantable ports. An uncommon cause of mechanical obstruction that should be considered is the 'pinch-off syndrome', a condition in which the catheter is compressed between the clavicle and the first rib. While the 'pinch-off syndrome' only occurs in about 1% of patients with a CVC, up to 40% of these cases develop fragmentation and subsequent embolization of the catheter tip into the central vascular system.[8,9]

Catheter obstructions can also be due to a non-thrombotic internal occlusion, such as precipitation of medications or parenteral nutrition constituents. Obstructions caused by precipitation of medications with a low pH and those due to calcium phosphate crystals can be treated with 0.1% hydrochloric acid (HCl). Obstructions caused by medications with a high pH can be effectively treated with sodium bicarbonate or sodium hydroxide. Lastly, parenteral nutrition preparations can leave a lipid residue that can obstruct the catheter but that can be successfully cleared with a 70% ethanol solution.[10-12]

Thrombosis can lead to catheter obstruction, including a fibrin sheath around the catheter tip or an intraluminal, mural, or venous thrombosis. A fibrin sheath forms around most CVCs within two weeks after their insertion.[13,14] One autopsy study showed that 100% of CVCs had developed a fibrin sheath encasing the tip of the catheter.[15] These fibrin sheaths usually do not affect catheter function and do not predict the occurrence of a deep vein thrombosis, but they may pose a small risk of partial catheter obstruction or embolization.[16] In contrast to fibrin sheaths, other types of CVC-associated thrombosis frequently lead to occlusion. An intraluminal clot often causes complete catheter obstruction and accounts for 5-25% of catheter occlusions. A mural thrombus may occlude the tip of the catheter and cause partial venous obstruction or progress into a venous thrombosis that leads to complete occlusion of the vein.[16] Moreover, there is some evidence demonstrating an increased risk of post-thrombotic syndrome associated with a history of CVC occlusion, with an odds ratio of 3.7 (95% confidence interval [CI], 1.1 to 12.5) in one study.[17] This may indicate the presence of an underlying asymptomatic deep vein thrombosis that had remained undetected.

There are multiple risk factors associated with development of a CVC occlusion, including location of the tip of the CVC, number and size of the catheter lumens, and the type of CVC. Catheter occlusions occur less frequently in ports when compared to external catheters, such as Broviac and Hickman catheters, with an even lower frequency in peripherally inserted central catheter (PICC) lines.[1-3,5,18-20] CVCs with more than one lumen are associated with an increased risk of clot. The location of the tip of the CVC is also important: the more distal the location of the CVC tip, the higher the risk of obstruction. For example, CVCs with the tip in the superior vena cava obstruct more frequently than those with the tip in the superior vena/right atrium junction or right atrium itself.[18]

Management of thrombotic CVC obstruction

Urokinase

Prior to 1998, urokinase was the only FDA-approved medication used to treat thrombotic catheter occlusions. Urokinase is a naturally occurring serine protease, harvested from neonatal human kidneys, that acts on plasminogen to activate the fibrinolysis cascade (Figure 1 and Table 1). Secondary to concerns about potential risks of transmitting infectious agents, urokinase was removed from the United States market in 1998,[25] although it is still in use in some European countries. Streptokinase, isolated from beta-hemolytic *streptococci*, was also used for catheter clearance, despite the lack of FDA approval for this indication; however, anaphylaxis in an unacceptably high proportion of cases restricted its use.[26]

Alteplase

Alteplase, also known as tissue plasminogen activator (t-PA), catalyzes the conversion of clot bound plasminogen to plasmin, which then activates the fibrinolysis cascade (Figure 1 and Table 1). Already approved for treating acute myocardial infarctions, alteplase was studied to determine its efficacy as a means to clear catheter occlusions (Table 2). In one of the initial studies, alteplase was found to be superior to urokinase for the treatment of radiographically proven thrombotic occlusion of a CVC (59% of catheters cleared by urokinase *vs*. 89% by alteplase P=0.0013).[27]

Considering the favorable results from this trial and the temporary removal of urokinase from the market, alteplase was investigated further as an alternative method for catheter clearance (Table 2). A pivotal study was the COOL (Cardiovascular thrombolytic used to Open Occluded Lines) trial which demonstrated resolution of CVC obstruction in 74% of treatment patients *versus* only 17% of placebo after 120 min ($P<0.0001$).[28] Additional studies demonstrated an overall catheter clearance rate of 87%, with 52% being cleared after the first 30 min and even higher rates in treated peripherally inserted central catheters (PICC) line.[29,30]

The high efficacy and low risk of alteplase for treating CVC occlusions in adults prompted studies in children. Several trials found that alteplase administered for 1-4 h produced catheter clearance rates of 85-95% (Table 2).[31-36] In a subset analysis of pediatric patients in the COOL trials and a multicenter trial using a dosing regimen and dwell times identical to those in the COOL trials, alteplase was confirmed to be safe and effective with overall catheter clearance rates of 83-87% and no adverse outcomes documented.[35,36]

New medications for thrombotic catheter occlusion

As illustrated by the preceding studies, alteplase produces a high rate of clearance of thrombotic catheter occlusions after relatively short dwell times of up to 2-4 h. However, even this amount of time can cause delays in patient care and in critically ill patients can increase morbidity when venous access is needed urgently. Furthermore, catheters that do not regain patency require removal, exposing the patient to additional risks. New thrombolytics show promise of higher clearance rates and faster onset of action that may further improve patient safety and the efficiency of care. Reteplase, tenecteplase, recombinant urokinase (r-UK), and alfimeprase have been evaluated for CVC occlusions and will be discussed below. Anistreplase is another type of thrombolytic medication that so far has only been studied as treatment for cardiovascular disease in adults (Table 1).[21]

Reteplase

Reteplase is a variant of the tissue plasminogen activator that differs from alteplase in that it lacks several structural domains normally found in alteplase. These alterations may allow reteplase to bind less tightly to the clot and allow for increased diffusion, leading to an increased half-life and thrombus penetration (Figure 1 and Table 1).[37] Studies analyzing the efficacy of reteplase indicate catheter clearance of 67-74% after 30-40 min with overall clearance rates ranging from 80-95% (Table 2).[37-39] A maximum dose of 0.4 U was found to be safe with no increased risk of hemorrhage or treatment related side effects reported.

Tenecteplase

Tenecteplase is also a recombinant form of tissue plasminogen activator with a similar mechanism to alteplase. There are three amino acid changes that contribute to changes in the characteristics associated with this medication, such as increased specificity for plasmin, a half-life four times longer than alteplase, and an increased resistance to plasminogen activator inhibitor (Figure 1 and Table 1). [40] Studies demonstrated resolution of the occlusion in 81-87% of patients and maintenance of patency in 80-81% of subjects after at least seven days following administration (Table 2).[40,41] This newer medication was also found to be safe with only 6 serious adverse events noted in the subsequent seven days, none of which were attributed to the therapy.[40]

Recombinant urokinase

Another option to manage CVC occlusions that has been explored in adults is the recombinant form of urokinase (r-UK) that directly cleaves plasminogen into plasmin to catalyze the fibrinolysis pathway (Figure 1 and Table 1). Recent studies have demonstrated that r-UK, at a dose of 5000 IU/mL, was effective and safe, with 54-75% of occlusions cleared after up to 2 treatments, each lasting 30 min, and minimal adverse events in the subsequent 72 h (Table 2).[42,43] In a dose-range study, it was found that higher doses do not improve rates of catheter clearance but do increase the risk of adverse effects, such as hemorrhage (Table 2).[44]

Alfimeprase

Alfimeprase is a truncated form of the metalloproteinase fibrolase, isolated from the Southern copperhead snake and reconstructed via recombinant DNA technology. Alfimeprase has direct proteolytic activity against fibrin by binding to its Aα chain. This causes direct degradation of the thrombus, independently of the plasminogen acti-

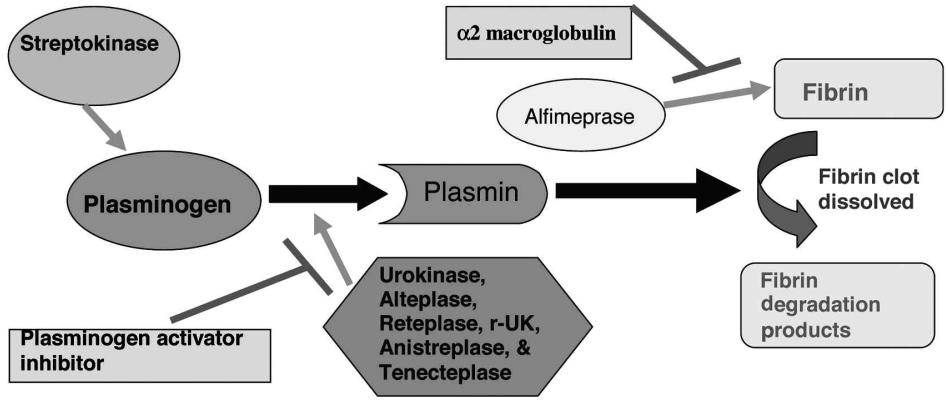

Figure 1. Diagram of the mechanism of action of thrombolytic medications. Streptokinase binds plasminogen, which converts free plasminogen to plasmin. Alteplase, urokinase, recombinant urokinase (r-uk), reteplase and tenecteplase cleave plasminogen to produce plasmin, a process that is inhibited by plasminogen activator inhibitor. Alfimeprase cleaves fibrin directly to produce fibrin degradation products, a process inhibited by α2 macroglobulin.

vation system (Figure 1 and Table 1). When the medication enters the cardiovascular system, it is bound and neutralized by plasma alpha 2-macroglobulin.[22,45] Alfimeprase has been considered for treatment of acute coronary syndrome, stroke, deep vein thrombosis, and, in particular, catheter directed thrombolysis of acute peripheral artery occlusions, for which trials are ongoing to evaluate safety and efficacy.[22] Its activity and pharmacokinetics suggest that it would be a rapid and effective thrombolytic with few systemic side effects, particularly useful for treatment of CVC occlusions. A randomized multicenter study found alfimeprase to be more effective than alteplase at catheter clearance after 15 min with clearance rates of 50% with 3 mg alfimeprase *versus* 0% with 2 mg alteplase

Table 1. Characteristics of thrombolytic medications.[21-24]

	Cells of origin	Method of action	Site of action	Half- life	Metabolic clearance	Dose for CVC	Cost in the USA	Allergic reactions
Urokinase	Physiological thrombolytic from renal parenchymal cells. Synthesized as prourokinase and activated via proteolytic cleavage	Enzyme that directly cleaves plasminogen to produce plasmin	Systemic plasminogen	8-20 min	Hepatic clearance	5000 IU	250,000 U vial: $540 5000 IU dose: $11*	Few allergic reactions
Streptokinase	Enzyme from group C β hemolytic *streptococcus*	Combines with circulating plasminogen to convert free plasminogen to plasmin	Circulating plasminogen	85%: 20 min 15%: 80 min	Hepatic clearance			5-15% allergic reaction; 0.1% anaphylaxis
Alteplase (t-PA)	Tissue plasminogen activator (t-PA) from vascular endothelial cells produced by recombinant DNA technology	Converts clot-bound plasminogen to plasmin	Plasminogen at the clot site	5 min	Hepatic clearance	2 mg/ 2 mL	50 mg vial: $2000*; 2 mg: $80-116**	Rare
Reteplase	A fragment of t-PA enzyme produced in *E Coli* via recombinant DNA technology. Contains the kringle-2 and protease domains	Converts clot bound plasminogen to plasmin. Binds less tightly than t-PA allowing it to diffuse throughout the clot	Plasminogen at the site of the clot	11-19 min	Renal and hepatic	0.4 U/ 2 mL	10.4 U vial: $1500; 0.4 U dose: $58*	Rare
Tenecteplase	A genetically modified version of the tissue plasminogen activator enzyme that is made via recombinant DNA technology.	Converts clot-bound plasminogen to plasmin. Binds more specifically to fibrin than t-PA or reteplase	Plasminogen at the site of the clot	17-24 min	Hepatic clearance		50 mg vial: $2900*	Rare
Recombinant urokinase (r-UK)	Murine hybridoma cell line	Enzyme that directly cleaves plasminogen to produce plasmin		15 min		5000 U/mL		Rare
Alfimeprase	A truncated form of fibrolase, a metalloproteinase isolated from southern copperhead snake, and made via recombinant DNA technology	Direct proteolytic activity against fibrin and directly degrades thrombi, independent of plasminogen activation. Bound and neutralized by plasma α2 macroglobulin	Fibrin Aα chain and to a lesser extent Bβ chain	11-54 min	Hepatic clearance			
Anistreplase	Acylated inactive complex of streptokinase and human lysine-plasminogen	Activated by deacylation. Then, cleaves the Arg/Val bond in plasminogen to form plasmin	Circulating and clot-bound plasminogen	40-90 min			$55.09 per dose***	5% allergic reaction; 0.1% anaphylaxis

** Prices are the acquisition costs as per Pharmaceutical Services Department at St Jude Children's Research Hospital; ** $80 is the price when the vial is divided into 2 mg doses. $90 is the price of an individual 2 mg vial as per Cathflo Activase®. The average wholesale price per Cardinal health is $116. *** Average Wholesale Price (AWP) per Cardinal Health.*

Table 2. Studies of thrombolytic treatment of CVC obstruction.[27-45]

Citation	Study Design	Patients	Methods	Restoration of CVC function	Comment
			Alteplase (t-PA)		
Haire *et al.*[27]	Double-blind, randomized trial: urokinase *vs*. t-PA	Adults N=50	Radiographically proven CVC thrombotic occlusions: randomized to 2mg t-PA *vs.* 10,000 U urokinase: CVC assessed at 120 min, repeated if no resolution	Overall CVC clearance: 59% (urokinase) *vs*. 89% (t-PA) *P*=0.0013	
Ponec *et al.*[28]	Double-blind, placebo-controlled, multicenter trial	Adults & Children N=149	Weight < 30 kg: 110% of CVC lumen volume at 2 mg/2mL Weight > 30 kg: 2 mL of 2 mg/2 mL CVC assessed at 120 min, repeated if no resolution; Administered up to 3 doses (if in the placebo group, 2nd dose was t-PA and if in the treatment group, 3rd dose was placebo)	120 min: 74% (treatment) *vs.* 17% (control) *P*<0.0001; overall CVC clearance 89.9%	Success: clearance of only 1 CVC lumen
Deitcher *et al.*[29]	Phase III, open-label, single-arm, multicenter trial	Children and adults N=995	Weight < 30 kg: 10% of CVC lumen volume at 2 mg/2 mL Weight > 30 kg: 2 mL of 2 mg/2 mL; CVC assessed at 30 & 120 min, repeated if no resolution; up to 2 doses	1st 30 min: 52% 1st 120 min: 78% 2nd 30 min: 84% Overall CVC clearance: 87%	No major adverse effects
Ng *et al.*[30]	Subset analysis: phase III, open-label, single-arm, trial: PICC lines	Children and adults N=240	Weight < 30 kg: 110% of CVC lumen volume with 2 mg/2 mL Weight > 30 kg: 2 mL of 2 mg/2 mL; CVC assessed at 30 & 120 min; procedure repeated if no resolution, with maximum 2 doses	1st 30 min: 59% 1st 120 min: 81% 2nd 30 min: 89% Overall CVC clearance: 93%	
Choi *et al.*[31]	Prospective consecutive cohort	Children N=34	Weight < 10 kg: 0.5 mg placed in CVC lumen Weight > 10 kg: 1-2 mg placed in CVC lumen Dwell time 2-4 h	Overall CVC clearance 85% (up to 120-240 min)	
Chesler *et al.*[32]	Single-center review	Children N=42	0.5 mg placed in CVC to dwell for 30-60 min; Repeated if no resolution, with maximum 2 doses	30-60 min: 69% Overall CVC clearance: 88% (up to 60-120 min)	
Fisher *et al.*[33]	Retrospective review	Children N=22	Between 0.22 mg and 2 mg placed in CVC lumen, with dwell time of 25-120 min; If no resolution, 2nd dose administered, with dwell time of 30-60 min	1st dose (up to 120 min): 86% 2nd dose (up to an additional 60 min): 95%	
Jacobs *et al.*[34]	Prospective data collections	Children N=228	110% of CVC lumen filled with 1 mg/mL t-PA with dwell of 20 min; repeated if no resolution; up to 3 doses	20 min: 71%; 40 min: 87%; Overall CVC clearance 91%	
Blaney *et al.*[35]	Prospective, open-label, single-arm, study	Children N=310	Weight < 30 kg: 110% of CVC lumen volume with 2 mg/2 mL Weight > 30 kg: 2 mL of 2 mg/2 mL; CVC assessed at 30 and 120 min; repeated if no resolution, maximum 2 doses	1st 30 min: 54% 1st 120 min: 75% 2nd 30 min: 80% Overall CVC clearance 83%	
Shen *et al.*[36]	Subset analysis of phase III, open-label, single-arm, multicenter trial	Children N=122	Weight < 30 kg: 110% of CVC lumen volume with 2 mg/2mL Weight > 30kg: 2 mL of 2 mg/2 mL; CVC assessed at 30 and 120 min; repeated if no resolution, maximum 2 doses	1sr 30 min: 56% 1sr 120 min: 81% 2nd 30 min: 84% Overall CVC clearance: 87%	
			Reteplase		
Terrill *et al.*[37]	Single-institution, dose-escalating study	Children N=15	Started with dose 0.1 U/0.1 mL; if 3 patients tolerated dose without side effects, dose increased to 0.2 U and then 0.3 U and 0.4 U; CVC was assessed every 15 min up to 60 min and then at 120 min	1st 60 min: 73% Overall CVC clearance 80%	Average dwell time 31 min
Owens[38]	Retrospective chart review	Adults; N=98	0.4 U administered to CVC lumen, dwell time of at least 30 min; 2nd dose given to some patients if no resolution	1st dose: 74% Overall CVC clearance: 96%	Variety of CVCs Ave dwell time 40 min
Lui *et al.*[39]	Open-label, single-arm, prospective study	Adults; N=139	0.4 U/2 mL - CVC lumen filled with maximum 2 mL; CVC assessed at 30 & 60 min; repeated if no resolution after 60 min	1st 30 min: 67% 1st 60 min: 89% Overall CVC clearance: 95%	
			Tenecteplase		
Tebbi *et al.*[41]	Phase III open-label single arm trial	Children and adults N=246	Weight < 30 kg: 110% of CVC lumen volume with 2 mg/2 mL Weight > 30 kg: 2 ml of 2 mg/2 mL; CVC assessed at 15, 30, and 120 min; repeated if no resolution, maximum of 2 doses	1st 120 min:72% 2nd 120 min:81% 81% maintenance of patency after 7 days	

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Gabrail *et al.*[40]	Phase III randomized, double-blind, placebo-control trial, with crossover	Children and adults N=97	Weight < 30 kg: 110% of CVC lumen volume with 2 mg/2 mL Weight > 30 kg: 2 mL of 2 mg/2 mL; CVC assessed at 15, 30, and 120 min; repeated if no resolution with maximum of 2 doses	1st 30 min: 44%-tenecteplase 19%-placebo 1st 120 min: 60% -tenecteplase 23% -placebo	
			Recombinant urokinase		
Haire *et al.*[42]	Phase III double-blind, placebo-controlled	Children and adults N=180	5000 IU/mL at volume to fill CVC lumen; CVC assessed at 5, 15, and 30 min; Repeated if no resolution with max 2 doses	2 doses: 54% (r-UK) *vs.* 30% (placebo), *P*=0.002	
Svoboda *et al.*[43]	Open-label, multicenter study	Children and adults N=878	5000 IU/mL at volume to fill CVC lumen; CVC assessed at 5, 15, and 30 min; Repeated if no resolution, with maximum 2 doses	30 min: 60%; Overall CVC clearance: 75%	
Deitcher *et al.*[44]	Phase II randomized, double-blind, placebo-control, dose-ranging trial	Children and adults N=108	Doses 5,000, 15,000, and 25,000 IU/mL; Given at a volume to fill CVC lumen; CVC assessed at 5, 15, and 30 min; repeated if no resolution with maximum 2 doses	Overall CVC clearance: r-UK *vs.* placebo 5,000 IU: 69% *vs.* 28% 15,000 IU: 70% *vs.* 24% 25,000 IU: 68% *vs.* 28%	Higher risk of bleeding with higher doses
			Alfimeprase		
Moll *et al.*[45]	Phase II randomized, double-blind, multicenter, dose-ranging study	Adults N=55	Alfimeprase 0.3, 1.0, or 3.0 mg *vs.* t-PA 2 mg at volume 2 mL to fill CVC lumen; CVC assessed at 5, 15, 30, and 120 min; repeated if no resolution, with maximum 2 doses	Results for 3 mg dose 1st 15 min: 50% (alfimeprase) *vs.* 0% (t-PA), *P*= 0.0075; Overall CVC clearance 80%	

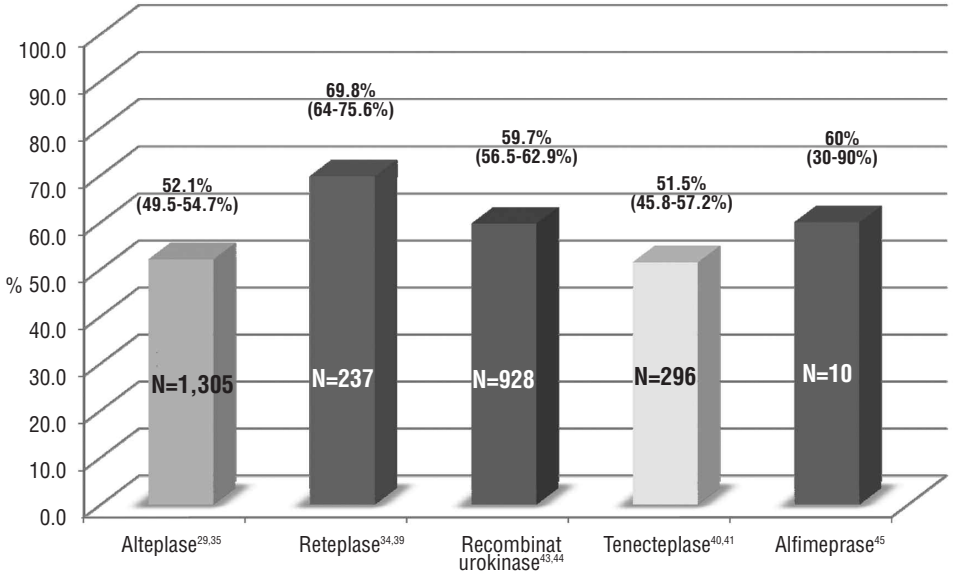

Figure 2. Average catheter clearance after 30 min with each of the thrombolytic medications evaluated in this study with 95% confidence intervals.

(*P*=0.0075). Additionally, overall catheter clearance in the 3 mg alfimeprase treatment group was 80% (*vs.* 62% in the alteplase group) (Table 2).[45]

Comparison of thrombolytic medications

Based on these studies, reteplase appears to be very effective in restoring patency to an occluded CVC. After only 30-40 min, catheter clearance rates for reteplase were 67-74% in comparison to the average rates for alteplase (52%), recombinant urokinase (60%) and tenecteplase (52%) (Figure 2).[29,30,35,36,38-44] Reteplase also appears to be more effective with longer dwell times and multiple doses. One dose of reteplase resulted in an average catheter clearance rate of 87% with dwell times of as little as 60 min compared to 76% average clearance with alteplase after twice as long (120 min).[28-30, 35,36,37-39] Furthermore, overall catheter clearance rates of 95.2% with reteplase suggest that it may be more effective than the other thrombolytics that demonstrate average overall clearance rates ranging from 72 to 86% (Figure 3), though randomized trials making a direct comparison between these agents are needed to confirm this supposition.[28-45]

When comparing tenecteplase to the other thrombolytics evaluated, it appears to be of equal or less efficacy after 30 min, with 51.5% clearance in the treatment group compared to the average clearance rates of 52-70% demonstrated with the other thrombolytic medications (Figure 2).[25,26,29,30,38-45] It demonstrated continued efficacy after

longer dwell times with catheter clearance rates similar to alteplase 120 min after one dose (70% with tenecteplase *vs.* 76% with alteplase) as well as overall clearance rates (83% tenecteplase *vs*. 87% alteplase) (Figure 3).[28-30,35,36,40,41]

When evaluating the efficacy of r-UK, it appears to be more effective than alteplase within the first 30 min, with an average clearance rate of 60% *versus* 52% for alteplase (Figure 2).[29,30,35,36,42-44] However, none of these trials left r-UK to dwell for more than 30 min. Therefore, the efficacy of r-UK in relation to alteplase at later time points following the first dose remains unclear. Randomized, double-blind trials are required to assess catheter clearance of all these medications at various time points to accurately determine which medication would be the most efficacious within the shortest time span. Use of a placebo control is not appropriate, since all thrombolytic agents are superior to placebo.

Alfimeprase acts rapidly and clears 40% of catheters within 5 min and 50% within 15 min, although the effect of this medication seems to plateau after 30 min and has an overall rate of clearance that is no higher than that of other thrombolytics (Figure 3).[28-30,35-45] In this study, the clearance rates for alteplase were significantly lower than those found in several other studies, a finding that makes interpretation of the study difficult (13 patients received alteplase in the Moll *et al.* trial *vs*. 122 to 955 patients in other studies with alteplase).[28-30,35,36,45] Alfimeprase has a rapid onset of action, but a second dose may be required after a short period of time for maximum efficacy. A strategy of early re-dosing (after 15 or 30 min) has not yet been studied.

One limitation of this study was the relatively small sample size. Therefore, additional studies with larger study populations are required to further evaluate the effect of alfimeprase in restoration of patency to an occluded CVC, as well as directly compare its efficacy and time to clearance to the other thrombolytics using a randomized study design.

Although ports develop occlusions less frequently, some studies indicate that when an occlusion does occur, it resolves less readily with thrombolytic therapy than occlusions that occur in external catheters. Alteplase, tenecteplase, and recombinant urokinase all demonstrated improved efficacy when treating external CVCs or PICC lines *versus* ports.[29,30,34,41-43] However, two studies utilizing alteplase only supported these results in triple lumen external CVCs, while the double and single lumen catheters had an equivalent response to ports.[35,36] The only reteplase study that reported clearance rates based on CVC type was performed mostly in ports, so it remains unclear whether CVC type would affect response to this medication. The alfimeprase trial had too few subjects to address this issue.

Prophylaxis

As a result of the morbidity that can result from an occluded CVC, various methods for prophylaxis have been investigated. Although most facilities have standard guidelines for catheter care, specifically regarding the frequency and type of solution utilized to maintain catheter patency, there are very few data to support these practices. Some studies investigating peripheral intravenous catheters have shown no difference in catheter maintenance with the use of heparin *versus* saline, although there are no studies to confirm these findings in children.[46-48] Controversy continues regarding optimal practices for CVC care. Some benefits associated with heparin prophylaxis include presumed improved CVC patency and decreased need for replacement catheters, although various risks have been demonstrated as well, such as heparin-induced thrombocytopenia, anaphylaxis, and bleeding as a result of errors in medication administration.[49]

The few trials evaluating the use of heparin for CVCs in adults suggest there is no difference between a saline or heparin lock.[50,51] The evidence reported in Mitchell *et al.*'s systematic review was not adequate to enable definitive conclusions to be made. The trials analyzed provided only weak evidence to support the use of heparin flushes to decrease the frequency of CVC occlusions with no impact on the rate of catheter-related bloodstream infections.

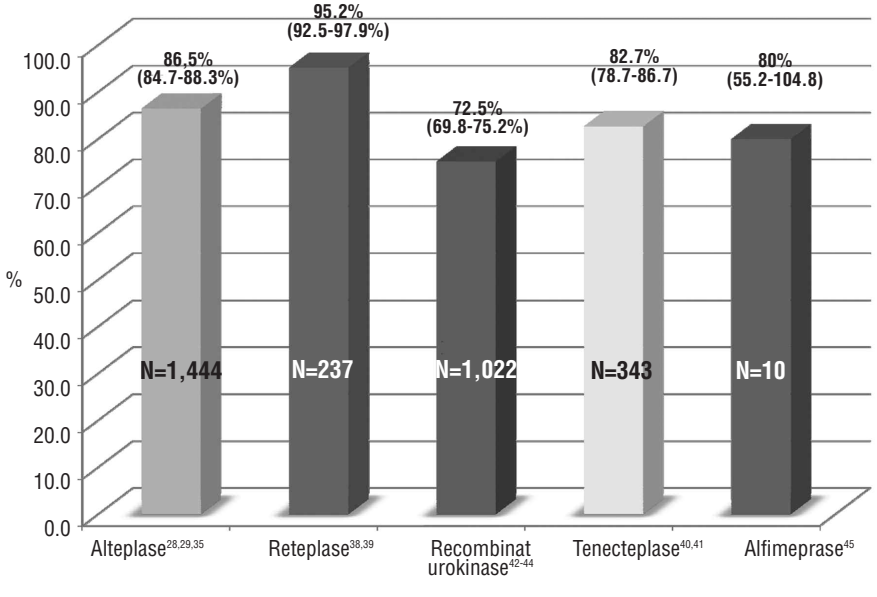

Figure 3. Cumulative incidence of successful catheter clearance for each of the thrombolytic medications evaluated after a maximum of 2 treatment doses, calculated as a weighted average with 95% confidence intervals. With each dose, maximum dwell times of 30 and 60 min were utilized for recombinant urokinase and reteplase, respectively. Alteplase, alfimeprase, and tenecteplase used dwell times of a maximum of 120 min.

Table 3. Urokinase prophylaxis.[1,56-60]

Citation	Study design	Patients	Methods	Outcomes	Comments
Dillon[1]	Prospective, randomized, multi-center trial	Children N=577	Treatment - urokinase 5000 IU/mL Control - heparin 100 U/mL Volume of the lumen, dwell time = 1 h, every 2 weeks	Occlusion: 23% (treatment) *vs.* 31% (control) Infection: 1.4 decrease in urokinase (only in external CVCs)	Port & external CVC
Kalmanti[56]	Historical control	Children N=30	Treatment - 10,000 IU/mL urokinase weekly, dwell 4 h + heparin every 3 days Control - heparin every 3 days	Occlusion: 19% (treatment) *vs.* 68% (control) P=0.05 Bacteremia: 12.5% (treatment) *vs.* 42% (control) P=0.05	
Ray[57]	Prospective, randomized trial	Adults N=105	Treatment - urokinase 5000 IU/mL weekly, dwell 12 h + heparin flush twice daily Control - heparin flush twice daily	Occlusion: 4% (treatment) *vs.* 16% (control) P<0.05 Infection: 2% (treatment) *vs.* 6% (control) (P>0.05)	External CVCs
Solomon[58]	Prospective open-label randomized trial	Adults N=100	Treatment - urokinase 5000 IU/mL twice weekly control - heparin 50 IU/5 mL dwell - at least 1 h	Occlusions: 63% (treatment) *vs.* 74% (control) (P=0.681) Bacteremia: 20% (treatment) *vs.* 25% (control) (P=0.5)	Hickman catheters; high rate of occlusions & infections
Aquino[60]	Prospective, double-blind, randomized trial	Children N=74	Treatment - urokinase 5000 IU/mL weekly + heparin Control - heparin flush with 300 IU/mL	Bacteremia: 12.5% (treatment) *vs.* 21% (control) (P=0.27)	Ports only
van Rooden[59]	Prospective, double-blind randomized trial	Adults N=160	Treatment - urokinase 25,000 IU/mL Control - placebo Both groups - standard heparin flush infused over 15 min, then locked for at least 30 min	CVC-related bloodstream infection: 7% (treatment) *vs.* 18% (control) with RR=0.41 (95% CI 0.17-0.97)	

Additionally, there was moderate evidence to support the use of continuous heparin infusions to prevent venous thrombosis with weak evidence indicating that this practice would decrease catheter-related bloodstream infections as well.[49] However, one must consider the feasibility of this method in clinical practice.

One trial in 14 children with cancer compared weekly saline flushes to twice-daily heparin flushes and found no difference in the frequency of catheter occlusion.[52] However, a prospective study that evaluated twice weekly heparin flushes *versus* weekly saline flushes in 203 children with Broviac-Hickman CVCs demonstrated an increased rate of catheter occlusions (83% *vs.* 41%, P=0.0002) and catheter infections (65% *vs.* 44%, P=0.01) with saline flushes.[53] Although most guidelines for subcutaneous ports recommend monthly flushes when not in use, two studies have demonstrated that increased periods of time between flushes, from six weeks to three months, may not increase the frequency of complications.[54,55] Additional prospective trials are required to accurately determine the frequency and type of solution required to optimize CVC function and minimize complications.

Investigators have also studied the use of thrombolytics, such as urokinase, to prevent CVC occlusions (Table 3). In two pediatric trials, a statistically lower incidence of occlusive events was demonstrated in the urokinase group, 19-23% *versus* 31-68% in the control group.[1,56] Furthermore, a prospective trial in adults reported that twice-daily heparin plus weekly urokinase was associated with a lower rate of CVC occlusions compared to heparin alone.[57] Additional studies were unable to corroborate these results (Table 3).[58] Therefore, although some studies indicate urokinase prophylaxis may reduce CVC occlusions, additional studies are required to determine the optimal regimen and true efficacy. Furthermore, considering that catheter clearance rates are 80-90% after only one or 2 doses of thrombolytic, the cost-effectiveness of prophylaxis requires evaluation before widespread implementation. Cost analysis should consider the cost of additional hospital or clinic time needed to treat an occluded catheter and account for any delay in treatment due to CVC dysfunction.

As a result of the association between CVC related obstruction and infection, many investigators have also analyzed the effect of thrombolytic prophylaxis on the incidence of CVC infections (Table 3). The two pediatric trials also demonstrated a reduced incidence of CVC infection in the treatment group.[1,56] A randomized trial comparing urokinase to placebo found a significantly lower incidence of major CVC-associated coagulase negative *staphylococcus* infections in the urokinase treatment group with a relative risk of 0.09 (95% CI, 0.01 to 0.5).[59] Two additional studies that were evaluated were unable to support these findings, although in these trials the urokinase was administered as a flush, not allowing the solution to dwell in the catheter lumen for any significant amount of time, which may have affected its efficacy (Table 3).[58,60]

Although there are some conflicting data, it appears that urokinase prophylaxis decreases the rate of catheter-related infections and catheter-related thrombosis.[1,56] Therefore, the effect of prophylaxis on the complications associated with catheter occlusions, such as catheter infections, catheter-related thrombosis, and catheter removal, must also be analyzed in depth. While this practice may not have a substantial impact on thrombotic obstructions in CVCs, it may have a clinically important effect on the complications associated with these obstructions and should be studied further.

Conclusions

Catheter obstruction remains a common problem associated with CVC use. Alteplase clears obstructed catheters safely and effectively, but may require a dwell time of up to 4 h to achieve catheter clearance. Newer forms of thrombolytic therapy, such as reteplase, tenecteplase, and recombinant urokinase, safely and effectively treat CVC obstruction and require shorter dwell times than alteplase. Alfimeprase, a new thrombolytic with a site of action separate from the plasminogen activation system, also rapidly clears thrombotic catheter occlusions, but it is unclear whether a treatment regimen with this medication would be superior to alteplase. Further studies are required to directly compare alteplase with newer agents, with special attention to clearance rates at early time points (5, 15 and 30 min), in addition to overall clearance rates. Anticoagulation prophylaxis may reduce the incidence of catheter occlusions and infections in children, and possibly catheter-related thrombosis, but the cost-effectiveness and clinical impact of this practice has yet to be determined.

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