Recombinant urokinase for restoration of patency in occluded central venous access devices

A double-blind, placebo-controlled trial

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Summary

The interval occlusion of central venous access devices (CVADs) remains a significant clinical problem, often requiring re-intervention for catheter exchange or replacement. The purpose of this Phase 3, multi-center, double-blinded study was to test the hypothesis that instillation of recombinant urokinase (r-UK) 5000 IU/ml is superior to placebo in restoring total catheter patency to an unselected cohort of occluded CVADs. After obtaining informed consent, adult and pediatric patients with occluded, non-hemodialysis CVADs of any duration or type were randomized (2 : 1) to receive either r-UK 5000 IU/ml or placebo instilled into all occluded lumens of their catheter. Catheter function was assessed at 5, 15 and 30 min after the first instillation. If the catheter remained occluded after 30 min, a second dose was instilled with repeat assessments at 5, 15 and 30 min. The primary efficacy variable was the restoration of catheter function to all treated lumens (i.e., total catheter patency) after one or two instillations. Catheters that were not successfully recanalized after two instillations were allowed to receive up to two instillations of open-label r-UK administered in the same manner. The primary safety variable was the occurrence of hemorrhagic and non-hemorrhagic events within 72 hr after instillation. A total of 180 patients were enrolled at 43 sites in the United States and Canada. Most patients were adults, although 20% were ≤18 years of age. CVAD types included totally implanted subcutaneous ports (45%), PICC lines (26%), non-tunneled percutaneous catheters (18%), and tunneled percutaneous catheters (10%). All CVADs were occluded by virtue of their inability to withdraw blood (withdrawal occlusion). Additionally, 32% of catheters were completely dysfunctional as blood could not be withdrawn and fluids could not be infused (total occlusion). Analysis of the results showed that r-UK was significantly better than placebo in restoring catheter function (54% versus 30%, p = 0.002). There were no major hemorrhagic events within 72 hr after up to four r-UK instillations, and the incidence of non-hemorrhagic events was similar among the r-UK and placebo groups. In conclusion, r-UK is superior to placebo in restoring total catheter patency to occluded CVADs. In patients with occluded CVADs, intra-catheter thrombolysis can restore patency and may obviate the need for catheter replacement.

Keywords

Urokinase, central venous catheter, thrombolysis

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Introduction

Establishing access to the central venous circulation is a critical component of medical and surgical management. Placement of a central venous access device (CVAD) is one of the most common interventional procedures, with over 5,000,000 new devices placed annually (1). Despite their usefulness and convenience, maintenance of patency continues to be problematic, with obstruction occurring in up to 30% of all devices at some point in their lifetime (2).

Prior to 1998, the treatment of choice for catheter occlusion was instillation of low-molecular-weight human-sourced urokinase (Abbokinase® Open-Cath®, Abbott Laboratories, Abbott Park, IL). In 1998, production of Open-Cath® was halted in order to upgrade manufacturing processes. Concurrently, development of a recombinant high-molecular-weight urokinase (r-UK) derived from a non-human mammalian cell line was undertaken. This new formulation has similar fibrinolytic activity as the human-sourced compound (3). The purpose of the present study was to test the hypothesis that r-UK is superior to placebo in re-establishing CVAD patency in a multi-center, randomized, double-blinded fashion. Unlike most studies of catheter patency, this trial included adult and pediatric patients with both withdrawal and/or total CVAD occlusions of any duration.

Materials and methods

Objective

This Phase 3, double-blinded, multi-center, placebo-controlled study was designed to test the hypothesis that intra-catheter instillation of recombinant urokinase (r-UK) is superior to placebo in restoring function to occluded CVADs. The primary efficacy variable was the restoration of catheter function to all treated lumens (i.e. total catheter patency) after one or two instillations. The primary safety variable was the occurrence of hemorrhagic and non-hemorrhagic adverse events within 72 hr after instillation. The protocol was approved by the Institutional Review Board/Independent Ethics Committee at each site and patients provided written informed consent prior to enrollment.

Patient population

Patients were included in the trial if they met the following inclusion criteria: any type of semi-permanent or temporary central venous access device (CVAD), excluding hemodialysis access devices, with either a withdrawal occlusion (inability to withdraw blood but able to infuse fluids) or a total occlusion (inability to either withdraw or infuse). The CVAD must have been properly placed and successfully used at least once. There was no restriction on the duration of CVAD occlusion, on the age of patients or catheters enrolled. Patients were excluded from the study based on the following criteria: if the occlusion was due to incorrect placement or suspected drug precipitation, if they were pregnant or nursing, had sustained systolic hypertension, had undergone puncture of a non-compressible vessel within the previous 48 hr, had sustained a known or suspected hemorrhagic event within the previous 7 days, had undergone major surgery, organ biopsy, major trauma, obstetrical delivery, bloody subarachnoid puncture, cardiopulmonary resuscitation, or intraocular surgery within the previous 7 days, had sustained a cerebrovascular accident within the previous six months, or were at significant risk for bleeding, including active internal bleeding.

Procedures

Prior to administration of blinded study drug, the device was assessed by the investigator to confirm either total or withdrawal occlusion. Mechanical catheter obstruction was ruled out by attempting infusion in various patient positions and after Valsalva, if possible. If the device remained occluded, subjects received either 5000 IU/ml of r-UK or placebo in a double-blind fashion in a 2 : 1 ratio. The placebo was identical to the active formulation, excluding r-UK.

All occluded CVAD lumens were treated. Instillation for withdrawal occlusions consisted of slightly overfilling (0.2 ml) the occluded catheter lumen with study medication. For total occlusions, an attempt was made to aspirate fluid from the catheter lumen, and then as much medication as possible was instilled up to but not exceeding the maximum lumen volume plus 0.2 ml. The maximum volume of r-UK or placebo instilled was determined according to the internal lumen volume specified by the CVAD's manufacturer. If unspecified, the following volumes were utilized: 1.5 ml for all peripherally inserted central catheters (PICC lines), 7-9 Fr catheters, and low-profile port catheters; 2.0 ml for 10-13 Fr catheters; and 2.5 ml for implanted subcutaneous ports. The use of a 3-way stopcock for instillation was permitted with total occlusions in order to maximize the amount of instilled study drug.

Assessments of CVAD function were made at 5, 15, and 30 min after instillation in all treated lumens by attempting to aspirate blood and infuse fluids. If lumen function was not restored after 30 min, the lumen was flushed with normal saline (for withdrawal occlusions) and a second instillation was performed with repeat assessments after another 5, 15, and 30 min. CVADs were considered functional if both withdrawal (1, 3, or 5 ml of blood, depending upon patient age) and infusion (1, 3, or 10 ml of normal saline, depending on patient age) were possible through all treated lumens. If function was not restored in all treated lumens of multi-lumen catheters after one hr, the treatment was considered unsuccessful (that is, total catheter patency was required for success). This algorithm is depicted schematically in Figure 1. In unsuccessful cases, further treatments for restoration of catheter patency were left to the discretion of the treating physician. If additional thrombolytic therapy was chosen, then up to two instillations of open-label r-UK were allowed.

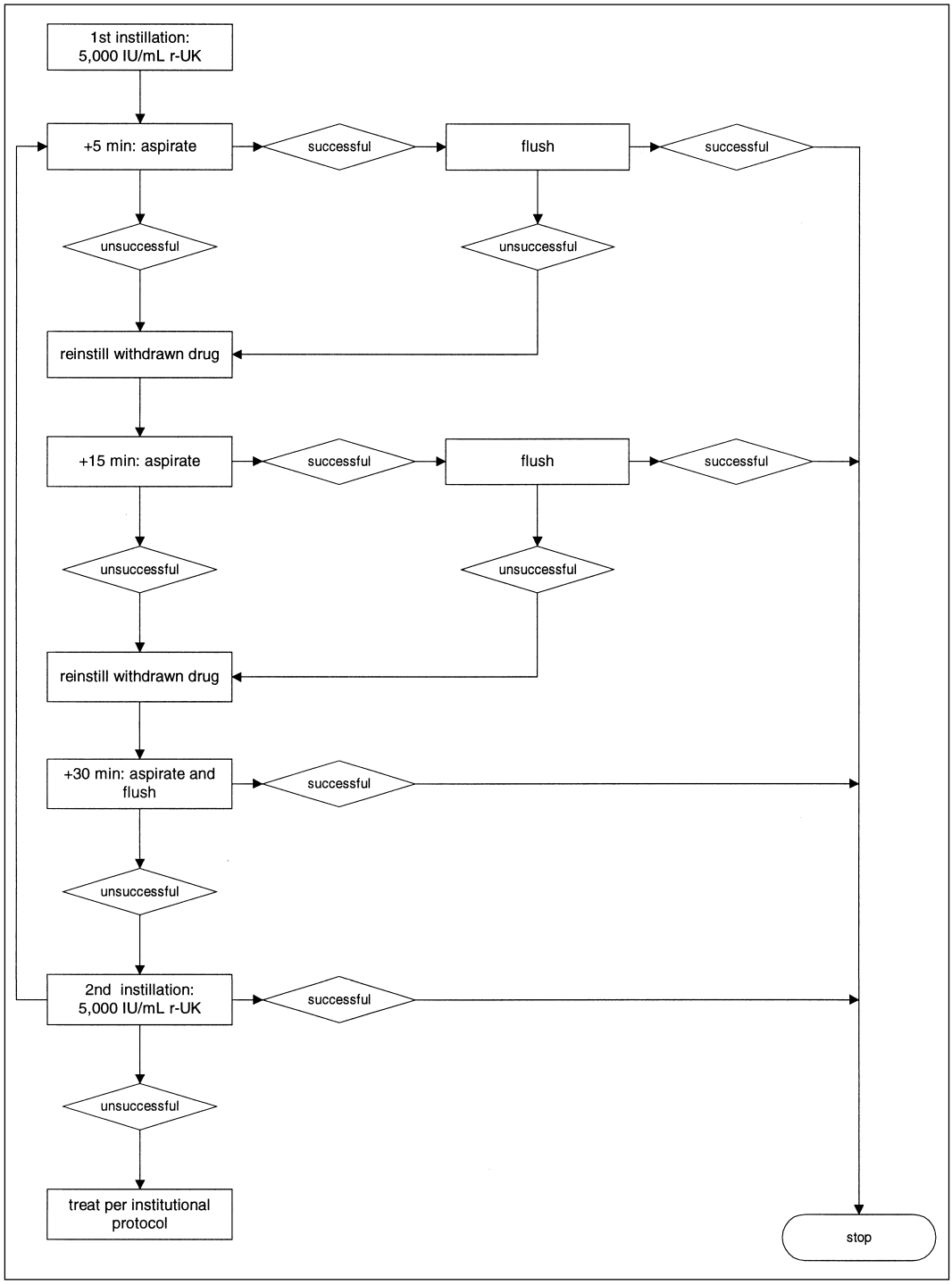

Figure 1: Treatment algorithm.

Patients were monitored for hemorrhagic and non-hemorrhagic adverse events during the procedure and the subsequent 30 days. Hemorrhage was classified according to a standard classification scheme as major events (intracranial hemorrhage, retroperitoneal hemorrhage, any hemorrhage resulting in death, or overt bleeding associated with transfusion of two or more units of blood or a hemoglobin decrease of at least 2.0 g/dL) or minor events (all other hemorrhagic events) (4).

Statistical analysis

Data were analyzed using the Statistical Analysis System (SAS Institute, Cary, NC). All statistical tests were two-sided and conducted at the 0.05 level of significance. Baseline and efficacy analyses were performed for all randomized subjects (intent-to-treat population; primary data set); one patient who had two catheters simultaneously treated was not included. Baseline parameters were compared between treatment groups using

Fisher's exact test (categorical variables) and one-way ANOVA (continuous variables). Patients who were randomized but not treated and patients who were treated but had no catheter assessments were included in the intent-to-treat analysis of catheter patency as failures. Comparisons of catheter patency between treatment groups were made using a Cochran-Mantel-Haenszel test, with investigative site as the stratification factor. Fisher's exact test was used to test for differences between treatment groups in catheter patency within subgroups based on CVAD type, number of occluded lumens, occlusion type and age; the Breslow-Day test of homogeneity of odds ratios was used to test for a difference in treatment effect across the subgroups.

Safety data are presented for treated subjects only, defined as patients receiving any blinded study drug (r-UK or placebo). Since the majority of patients who received placebo went on to receive open-label r-UK, safety data are presented for treated patients who received any r-UK (randomized or open-label) and for patients who received no r-UK. No formal statistical comparisons were made between these two groups, as the cohorts were not randomized.

Results

Patient demographics and CVAD profiles

A total of 180 patients were enrolled at 43 sites in the United States and Canada from December 2001 to July 2002. One hundred and nineteen patients were randomized to receive r-UK,

Table 1: Patient demographics: randomized population (n = 180).

	Placebo n (%)	r-UK n (%)	p-value
Sex			0.27
Female	39 (64%)	65 (55%)	
Male	22 (36%)	54 (45%)	
Race			0.61
Caucasian	46 (75%)	89 (75%)	
Black	14 (23%)	24 (20%)	
Other	1 (2%)	6 (5%)	
Age (years)			0.97
≤2	6 (10%)	13 (11%)	
2–11	3 (5%)	5 (4%)	
12-18	2 (3%)	7 (6%)	
19-64	32 (52%)	62 (52%)	
≥65	18 (30%)	32 (27%)	
Mean ± SD	48 ± 25	45 ± 25	0.56
Range	52 days – 83 years	33 days – 80 years	

Table 2: Catheter profiles: intent-to-treat population (n = 179)*.

	Placebo (n=61)	r-UK (n=118)	p-value
Indication for CVAD			0.83
Chemotherapy	31 (51%)	50 (42%)	
Chronic antibiotic therapy	10 (16%)	27 (23%)	
Total parenteral nutrition	4 (7%)	9 (8%)	
Blood sampling	3 (5%)	6 (5%)	
Other/multiple	13 (21%)	26 (22%)	
Catheter Type			0.36
Implanted port	32 (52%)	48 (41%)	
PICC line	15 (25%)	32 (27%)	
Non-tunneled percutaneous	11 (18%)	22 (19%)	
Tunneled percutaneous	3 (5%)	15 (13%)	
Unspecified	0 (0%)	1 (1%)	
Number of Lumens			0.64
One	31 (51%)	56 (47%)	
Two	24 (39%)	44 (37%)	
Three	6 (10%)	18 (15%)	
Occlusion Type			0.74
Withdrawal**	40 (66%)	81 (69%)	
Total***	21 (34%)	37 (31%)	

*Does not include one subject with two treated catheters.
**At least one lumen with a withdrawal occlusion, but no lumen with a total occlusion.
***At least one lumen with a total occlusion.

and 61 randomized to receive placebo. Demographic information is shown in Table 1. There were no significant differences in gender, race, or age between the r-UK and placebo groups. Most patients enrolled were adults, although 20% were ≤18 years of age, with the youngest patient being 33 days old. Serious underlying medical conditions were prevalent including malignancy (51%), anemia (53%), and thrombocytopenia (14%).

One patient in the r-UK group was treated for two separate occluded catheters. This was considered a protocol deviation and the results were excluded from efficacy analysis. The profile of the remaining 179 CVADs is given in Table 2. A variety of CVAD types were enrolled, but implanted ports predominated. About half of the catheters had multiple lumens. Approximately one-third of the catheters were totally occluded (inability to withdraw or infuse). There were no significant differences in catheter indication, type, number of lumens, or occlusion category (total or withdrawal) between the r-UK and placebo groups.

Six patients (4 r-UK; 2 placebo) did not receive study drug after enrollment because the catheter was found to be patent on re-examination (n = 3), no volume of drug could be instilled (n = 2), or a medical event precluded participation in the study (n = 1). Therefore, a total of 174 patients received randomized treatment. The statistical analysis for efficacy was performed by intention-to-treat, however, so these six patients were included as failures in their respective randomized treatment groups even though they received no treatment.

Efficacy and safety

The concentration of 5000 IU/ml of r-UK resulted in administration of a mean total intracatheter dose of 15,554 IU (range 1,000-75,000 IU) in the blinded portion of the trial. Determination of efficacy was based upon this dose. The total dose for the determination of safety included r-UK given in both blinded and non-blinded fashions (mean total dose of 21,084 IU, range 1,000-100,000). The total amount of r-UK that reached the systemic circulation could not be determined, since intraluminal fill volumes were not always known.

Results for re-establishment of total CVAD function (patency of all treated lumens), including patency rates of various subgroups, are presented in Table 3. Overall, r-UK was significantly better than placebo in restoring catheter function (54% versus 30%, p = 0.002). r-UK was also successful in restoring patency to 60% of occluded catheters in the randomized placebo group that received open-label r-UK as salvage treatment (24/40), as well as in 26% of catheters in the randomized r-UK group that did not respond to the initial instillations, but then received up to two additional instillations of open-label r-UK (11/43). In infants (n = 19), r-UK was also superior to placebo (69% vs. 0% restoration of patency; p = 0.01).

Adverse event rates are presented in Table 4 for the total number of patients receiving any intracatheter r-UK during the study (n = 155) and the 19 patients receiving placebo only. There were no major hemorrhagic events within the first 72 hr in either group. Minor hemorrhagic events occurred within the first 72 hours in 5% of patients receiving any r-UK. As in pre-

Table 3: Efficacy of r-UK 5000 IU/ml for recanalization of occluded CVADs: intent-to-treat population (n = 179)*.

	Patency after Placebo Instillation	Patency after r-UK Instillation	p-value
All CVADS	18/61 (30%)	64/118 (54%)	0.002
CVAD Type			
External percutaneous	9/29 (31%)	45/70 (64%)	0.004
Implanted port	9/32 (28%)	19/48 (40%)	0.34
Number of Occluded Lumens			
One	15/48 (31%)	61/96 (64%)	<0.001
Two	3/11 (27%)	2/18 (11%)	0.34
Three	0/1 (0%)	1/2 (50%)	0.99
Occlusion Type			
Withdrawal only**	10/40 (25%)	45/91 (56%)	0.002
Total***	8/21 (38%)	19/37 (51%)	0.42
Age Category			
28 days - 23 month	0/6	9/13 (69%)	0.01
2 – 11 years	1/3 (33%)	3/4 (75%)	0.49
12 – 18 years	0/2	5/7 (71%)	0.17
19 – 64 years	10/32 (31%)	32/62 (55%)	0.05
>64 years	7/18 (39%)	13/32 (41%)	>0.99

CVAD=central venous access device
*does not include one subject with two treated catheters
**no lumen with a total occlusion
***at least one lumen with a total occlusion
p-values for Breslow-Day Test for Interaction: CVAD Type, p-value=0.200; Number of Occluded Lumens (1 lumen v. > 1 lumen), p-value=0.034; Occlusion Type, p-value=0.264; Age Category, (<2, 2-18, 19-64, >64 years), p-value=0.061.

Table 4: Number of patients sustaining adverse events.

	No r-UK (n=19)		Any r-UK (n=155)*	
	72-hr	30-day**	72-hr	30-day**
Hemorrhagic***				
Minor	0 (0%)	1 (5%)	7 (5%)	20 (13%)
Major	0 (0%)	1 (5%)	0 (0%)	3 (2%)
Non-hemorrhagic***				
Mild	1 (5%)	1 (5%)	20 (13%)	30 (19%)
Moderate	1 (5%)	5 (26%)	9 (6%)	27 (17%)
Severe	2 (11%)	5 (26%)	1 (0.6%)	19 (12%)

*All patients receiving either blinded or open-label intracatheter r-UK, regardless of randomized treatment assignment.
**Counts are cumulative (i.e., includes events within 72 hr).
***For each time period, each patient is counted in only one severity category according to the most severe event experienced.

Table 5: Number of patients sustaining pulmonary embolism, sepsis, and mortality.

	No r-UK (n=19)		Any r-UK (n=155)*	
	72-hr	30-day **	72-hr	30-day**
Pulmonary embolism***				
Mild	0	0	0	0
Moderate	0	0	1	2
Severe	0	0	0	0
Sepsis***				
Mild	0	0	2	3
Moderate	0	0	0	0
Severe	0	1	0	1
Mortality	1	1	0	9

*All patients receiving either blinded or open-label intracatheter r-UK, regardless of randomized treatment assignment.
**Counts are cumulative (i.e., includes events within 72 hr).
***For each time period, each patient is counted in only one severity category according to the most severe event experienced.

vious studies using this rigorous reporting protocol (5), the incidence of non-hemorrhagic events across the population receiving any r-UK was high, 49% (76/155 patients receiving any r-UK) within 30 days.

The incidences of pulmonary embolism, sepsis, and mortality are presented in Table 5. Rigorous assessment for occult pulmonary embolism via routine ventilation-perfusion or computed tomography scanning was not performed. One patient was admitted to the hospital the day after treatment with pleuritic chest pain. A computed tomography scan was suggestive of pulmonary embolism, however, pulmonary angiography was negative and a ventilation-perfusion scan was interpreted as "low probability." The severity was categorized as "moderate"; both the investigator and the Data Safety Monitoring Board felt it was not related to study drug. Two patients each sustained episodes of mild sepsis within 72 hr of study drug administration. Both occurred in patients with hematologic malignancies in whom the catheters were removed following reports of positive blood cultures. The only death within 72 hr was in a 26 year-old patient with end-stage cystic fibrosis and respiratory failure who was treated with placebo only.

Discussion

Central venous access device (CVAD) failure continues to be a persistent problem even after 30 years of widespread clinical use. The most common cause of failure is thrombotic catheter occlusion, which occurs in up to 30% of CVADs (2), and interrupts the planned therapeutic program of chemotherapy, transfusion, antibiotic administration, nutrition, and/or infusions critical for hemodynamic support. A variety of treatment options are available to restore central venous access, including catheter replacement, thrombolytic therapy, and/or endovascular fibrin sheath stripping. Due to the risk and expense of CVAD replacement, the initial treatment of choice for catheter thrombosis is intracatheter thrombolysis. It is highly effective in restoring patency to occluded CVADs, with reported success rates in uncontrolled studies varying from 74-100% (6-18).

This report details the results of a double-blind, placebo-controlled Phase 3 trial testing a new agent, recombinant urokinase (r-UK), for the treatment of occluded CVADs. r-UK is a high-molecular-weight, recombinant form of urokinase derived from a transfected, non-human mammalian cell line (3). Using

DNA technology, r-UK can be produced with greater efficiency and purity than its natural predecessor. The results of this double-blinded study show that r-UK was highly effective and significantly better than placebo in restoring catheter function after one hour (total catheter patency 54% versus 30%, p = 0.002).

In this study, r-UK demonstrated a 24% absolute improvement in the rate of restoration of catheter function that can be attributed solely to drug effect. This was less than half of that observed in other randomized controlled trials (19), likely due to the relatively high rate of success of placebo in the catheters with total occlusion (38%), and the relatively low rate of success of r-UK in implanted ports (40%). As expected with an endpoint of restoration of total CVAD function (i.e., patency of all treated lumens), a larger treatment effect was seen in CVADs with single occlusions as compared to those with multiple occlusions (Breslow-Day p-value = 0.034). Although there were no statistically significant differences in treatment effect across subgroups, the effect of r-UK relative to placebo tended to be lower for implanted ports than external percutaneous CVADs, and lower for CVADs with total occlusions than those with only withdrawal occlusions.

The mechanism of CVAD occlusion is multifactoral, involving not only thrombosis but also mechanical disruption, intracatheter drug precipitation, and fibrin encasement (20). In addition, all occluded lumens were treated in this trial and success was defined as restoration of function to all treated lumens. The thrombolytic drug effect observed in this study is probably more representative of the real effect observed in clinical practice, and is indicative of the percentage of catheter malfunctions that are due to thrombotic occlusion alone.

While safety was not the primary objective of this study, the results demonstrated that there were no major safety concerns following the administration of up to a mean total intracatheter dose of 21,084 IU r-UK (range 1,000-100,000), at a concentration of 5000 IU/ml. There were no major hemorrhages within the first 72 hr. There was only one death within 72 hr of study drug administration, and it occurred in a patient randomized to placebo who subsequently did not receive any open-label r-UK.

In summary, the results of this double-blinded, placebo-controlled, multi-center study demonstrate that r-UK 5000 IU/ml is effective and safe for restoring total function (all lumens functional) to occluded CVADs. As the risk and cost of catheter replacement is considerable, intracatheter thrombolysis remains the treatment-of-choice for CVAD occlusion.

Appendix

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