The Use of Tissue Plasminogen Activator Over Urokinase for Reopening Occluded Venous Catheters In A Veteran's Administration Health Center: Therapeutic and Economic Reasons

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Introduction:

Problem:

Reliable venous catheter access is an essential part of renal replacement therapy for hemodialysis patients. Unfortunately, a large number of these catheters fail, usually due to occlusion by blood clots. As a result, great complications occur in the patient's therapy often translating into higher costs for providers and decreased quality of life for the patient. Since catheter access essentially requires introducing an injury to the patient, it is understandable that normal body hemodynamics will initiate efforts to seal the hole left by the catheter. The challenge resides in the fact that pharmacological means must be found to circumvent the normal clotting cascade and thus keep hemodialysis catheters patent. This challenge has recently become more difficult, however, with revelations of the source of commercially available Urokinase. Revelations of the source of Urokinase and the uncertainty of its infectious nature has left many providers without means to effectively and safely clear occluded venous catheters. One drug that may offer a solution to this dilemma is recombinant tissue plasminogen activator manufactured by Genentech under the trade name Activase. In several studies, 2mg aliquots of tissue plasminogen activator has been shown to be effective in successfully clearing occluded venous catheters. A dilemma exists, however, since Activase is only manufactured in 50mg and 100mg vials. Furthermore, questions remain about the actual expiration date that should be assigned to the Activase once it has been reconstituted. It is not logical or economically sound to use 2mg of tissue plasminogen activator and throw the other 48mg away after the manufacturer recommended 8 hour expiration date has elapsed. For tissue plasminogen activator to be effectively utilized to break up the thrombi occluding hemodialysis catheters, its effectiveness and long-term stability must be proven.

Objective:

This paper will show that tissue plasminogen activator is an effective alternative to current thrombolytics currently used to clear occluded hemodialysis catheters. In addition, this paper will show that tissue plasminogen has been proven to be therapeutically effective for as long as 12 months post-reconstitution. Finally, by data presented in this paper, it will be apparent that the cost per dose of tissue plasminogen activator necessary for clearing occluded catheters is actually less than the comparable dose of Urokinase for injection. These three points will help to prove that tissue plasminogen activator is a safe, effective, and economical means of clearing hemodialysis catheters.

Background:

Venous Catheter Access History:

Venous access catheterization technology has become a cornerstone within the practice of medicine for delivering hemodialysis to patients experiencing renal insufficiency or partial to complete renal failure. Venous catheters were utilized as early as 1832 to introduce silver cannulas into basic veins to facilitate hydration in severely dehydrated patients suffering from cholera(1). The next advance in venous catheter technology, however, did not occur until 1945 when rubberized materials were replaced with malleable plastic components(2). As late as 1943, temporary access for hemodialysis was accomplished by accessing distal arteries and veins by means of glass or metal cannulae (3) By changing the basic components of the

venous catheter to a more flexible polytetrafluoroethylene polymer, the venous catheter became a viable piece of equipment to clinicians.

Venous catheterization, as we know it today, appeared in 1975 and quickly proved its worth by reducing the phlebitis synonymous with steel canulae access(1). However, the most common problem for venous catheterization in clinical settings presently is maintaining patency particularly in those patients currently undergoing chronic renal hemodialysis and total parenteral nutrition administration.

Hemodialysis:

Renal failure may occur as a result of several different etiologies. When renal failure progresses to end-stage renal disease, renal replacement therapy may become necessary (4). Intermittent dialysis therapy may be used during chronic uremia to re-establish body water solute concentrations that cannot be achieved by the natural biological function of the kidneys (3).

Simple in design, hemodialysis allows for blood and dialysis fluid to be circulated separately on opposite sides of a semi-permeable membrane. This semi-permeable membrane permits passage of metabolites related to renal failure, while restricting the transfer of blood proteins (3). A favorable outcome is achieved when the hypercatabolic state of the dialysis patient is returned to a normal body hemostasis (5).

The venous access necessary to achieve hemodialysis of hypercatabolic patients may be accomplished by several accepted techniques. Grafts or fistulas for venous access are universally accepted techniques utilized today to accomplish hemodialysis. However, most patients new to hemodialysis may be required to start their therapy using such devices as the Perma-Cath hemodialysis catheter. Likewise, many patients are not considered candidates for fistula or graft venous access due to physical or allergy reasons. The Perma-Cath hemodialysis catheter is usually inserted n the right internal jugular vein, the right subclavian vein, or the superior vena cava.

Occlusion of Hemodialysis Catheters:

Many complications may occur over the life of the Perma-Cath or similar type catheter as it resides inside the human body. Arguably, the most damaging, therapeutically and economically, occurs upon the occlusion of these catheters by blood thrombi or other blood derivatives. In fact, the major documented reason for the failure of Perma-Cath catheters is due to occlusion by blood thrombi. The Perma-Cath catheter has survivability similar to that of fistulas and to a lesser degree grafts. The survival rates of Perma-Cath catheters range between 74% for one year and 43% for two years. Similarly, for fistulas, the survival rates are 65% and 58% (6).

Until recently, the occlusion of hemodialysis catheters required them to be replaced by surgery. Surgical replacement of long-term hemodialysis patients can be extremely high. The national average total cost for placement is currently $1849 (7). A breakdown of the associated costs can be viewed in Table 1. It is important to note that this price does not include the surgeon's fees for performing the procedure.

The utilization of thrombolytic drugs has enabled the reopening of occluded venous catheters. The FDA approved the use of Urokinase for the lysing of hemodialysis catheter clots in 1994. However, recent revelations regarding the source of commercially available Urokinase has required the medical community to look for new sources of thrombolytic therapies. One such therapy that shall be explored in this paper is the use of tissue plasminogen activator.

Overview of Tissue Plasminogen Activator (t-PA):

Tissue plasminogen activator is available commercially as Activase and is manufactured by Genentech, Inc. USA. Activase is classified as a thrombolytic agent and is currently prepared from cultures of genetically modified mammalian cells by the process of recombinant DNA technology. The drug is synthesized from complement DNA obtained from the Bowes human melanoma cell line. As a result of this, it may be postulated that tissue plasminogen activator has little allergenicity related to administration

(8). Tissue plasminogen activator, much like Urokinase and streptokinase, promotes thombolysis by hydrolizing the arginine-valine peptide bonds in plasminogen to form the proteolytic enzyme plasmin. Plasmin, a serine protease, degrades fibrin, fibrinogen, and many other procoagulant factors such as factor V, VIII, and XII (8). Currently, Activase is approved for use as a treatment in coronary artery thrombosis and myocardial infarction, pulmonary embolism, acute ischemic stroke, and arterial thrombosis and embolism. Unlike Urokinase, however, tissue plasminogen activator is not currently indicated for the lysing of thrombi occluding hemodialysis catheters. The reason for the exclusion of the catheter clearance application is due to topics regarding questions of efficacy and stability that shall be examined later in this paper.

Urokinase indiscriminately activates both fibrin-bound and circulating plasminogen. Tissue plasminogen activator, on the other hand, is a highly selective plasminogen activator and will only effect the fibrin-bound plasmin closely associated with thrombi. As a result, tissue plasminogen activator will have selective and potent effectiveness against thrombi occluding hemodialysis catheters while having little to no effect on the systemic circulation itself (8). This characteristic is also apparent when dissolving clots associated with occluded central venous catheters. Activase has an advantage over Urokinase in this regard since it will show little effect on the general circulation.

The Use of Activase In Lysing Clots Occluding Hemodialysis Catheter Thrombi:

Effectiveness of Tissue Plasminogen Activator:

On several occasions, tissue plasminogen activator has been proven to be effective as a systemic antithrombolytic for such conditions as myocardial infarction and peripheral arterial occlusion. Its usefulness as a thrombolytic for clearing hemodialysis catheters has not been fully accepted, however. Much work is currently being undertaken to prove that 2mg doses of tissue plasminogen activator is adequate to reopen occluded hemodialysis catheters. In several studies, it has been found that 2mg of tissue plasminogen activator is actually better than other clinically accepted means (such as 10,000 units of Urokinase) for clearing hemodialysis catheters.

According to Haire et al., tissue plasminogen activator has a much higher affinity for fibrin than Urokinase or other similar thrombolytics. This higher affinity would theoretically allow tissue plasminogen activator to bind occlusive thrombi and break up clots in occluded hemodialysis catheters. In this same study, 50 thrombosed central venous catheters were separated into two test groups and treated with tissue plasminogen activator and Urokinase. Twenty-eight catheters were treated with 2mg of tissue plasminogen activator while twenty-two catheters were treated with 10,000units of Urokinase for injection and allowed to incubate for two hours. Twenty-five of the twenty-eight (89.3%) catheters treated with tissue plasminogen activator were restored to function. This is compared to thirteen of the twenty-two (59.1%) catheters treated with 10,000 units of Urokinase that showed restored function. From these findings, Haire derived four basic points:

1. A dose of 2mg tissue plasminogen activator restores catheter function more often than twice the approved dose of Urokinase (10,000 units).
2. Tissue plasminogen activator at a 2mg dose restores catheter function two times faster than twice the accepted dose of Urokinase.
3. Neither tissue plasminogen activator or Urokinase shows detectable effect on the systemic circulation.
4. With increasing doses of Urokinase, a greater percentage of clots were dissolved.

In a similar study conducted by Atkinson et al., it was found that catheter opening was accomplished in 5 out of 6 (83%) tested catheters treated with tissue plasminogen activator. As a result of his study, Atkinson concluded that tissue plasminogen activator was successful in clearing 90% of catheters resistant to an initial bolus dose of Urokinase. Like Haire, Atkinson also found that there were no systemic effects or subsequent internal bleeding associated with tissue plasminogen activator at the 2mg dose.

At the Durham VAMC in Durham, North Carolina, efforts are currently under way to find a viable alternative to Urokinase for the treatment of occluded hemodialysis catheters. A solution to the problem presented itself when it was realized that intraocular tissue plasminogen activator was already being compounded in the inpatient pharmacy for intraocular procedures in the hospital's eye clinic. The preparation was being compounded into a concentration of 0.625µg/0.1mL using the flowchart in figure 1. Essentially 1mg of the 50mg Activase vial was being used to compound the intraocular tissue plasminogen activator preparation and the other 49mgs were being discarded. 50mg Activase vials can be purchased by the Durham VAMC for a price of $823.56 under the guidelines of government contract. If 1mg ($16.47 per 1 mL) of Activase is utilized while the other 49mg are discarded, the hospital has incurred a loss of $807.09. The logical alternative would be to use the remaining Activase to prepare 2mg/2ml aliquots for use in clearing occluded hemodialysis catheters. As of July 1999, 14 out of 14 occluded Perma-Cath catheters have been reactivated after treatment with tissue plasminogen activator in the Durham VAMC dialysis clinic.

Stability of Tissue Plasminogen Activator:

The comparability of activity of tissue plasminogen activator and other similar thrombolytics has long been established. However, one of the chief complaints concerning the use of Activase for clearing hemodialysis catheters is its apparent short expiration date after initial reconstitution. According to Genentech guidelines, Activase must be discarded after only 8 hours post-reconstitution. However, in several studies it has been shown that the actual viability of reconstituted Activase is much longer. In a study performed by Grewing et al., tissue plasminogen activator reconstituted to a concentration of 5µg/0.1ml and stored at -20°C showed no loss of activity for a period of up to six months. In addition, a similar study performed by Jaffe et al showed that tissue plasminogen activator reconstituted to a strength of 25µg/100µL and drawn up into 0.3ml aliquots showed prolonged stability after freezing. These 0.3mL aliquots were frozen in ultra-low freezers at a temperature of -70°C for a period of 13 months. Chemical assays were then performed on three of the 0.3mL aliquots at both one week and 13 months with the start date beginning after the initial reconstitution. The results of the chemical assays showed that none of the samples had lost any significant amount of activity at either one week or 13 months. Similarly, upon microbiological testing, none of the 0.3mL syringes showed any bacterial or fungal contamination on either of the two testing dates.

In unpublished studies, tissue plasminogen activator reconstituted to a 1mg/1mL strength and stored at -20°C in varying aliquots has been shown to be effective in human studies for periods of up to 24 months. Furthermore, this same stock solution from which all aliquots were drawn was found to be efficacious in animal applications for a period of up to 7 years. If such prolonged activity is possible for tissue plasminogen activator stored at -20°C, then its usefulness as an antithrombolytic in catheter clearance would be assured and its widespread use accepted.

Economic Advantages of Using Tissue Plasminogen Activator:

Until recently, Urokinase was the drug of choice for reopening occluded hemodialysis catheters. This resided in the fact that it was a trusted drug and was proven to be effective. Furthermore, at a cost of $64.00 per 5,000 unit dose and $128.00 per 10,000 unit dose, the price of Urokinase paid by government institutions was much lower than other comparable therapies. This changed, however, when Urokinase was found to be derived from questionable sources.

As established earlier, tissue plasminogen activator is equally if not more effective than Urokinase. Furthermore, it has been discovered that the stability of tissue plasminogen activator is considerably longer than that currently allowed by the Food and Drug Administration or recommended by Genetech, Inc. Lastly, when utilized properly, the price of a comparable dose of tissue plasminogen activator is actually less than that of Urokinase.

For these reasons, the logical alternative to Urokinase is Activase for the clearing of occluded hemodialysis catheters. A 2mg dose of Activase is $32.94 while the comparable dose of 10,000 units of Urokinase is $128.00. See comparison of prices in Table 2. By using Activase, hospitals such as the Durham VAMC will be able to enjoy considerable economic savings. Since tissue plasminogen activator is already being compounded by the pharmacy for use in intraocular procedures, a savings of $807.09 per procedure may be accomplished simply by not discarding what remains in the stock bottle. Further, if surgical replacement of occluded hemodialysis catheters can be avoided by utilizing tissue plasminogen activator, an automatic savings of $4,021.75 may be realized. Please see table 3 for a summary of cost savings.

Conclusion

Using thrombolytics like tissue plasminogen activator for systemic activity has long been an accepted technique for improving the prognosis of patients suffering from myocardial infarction or peripheral arterial occlusion. However, the acceptance of tissue plasminogen activator as a viable means of clearing hemodialysis catheters has not been widely existed to date. As eluded to earlier, this non-acceptance of tissue plasminogen activator has been determined by three factors. First, until recently, the medical community has not had the proof that tissue plasminogen activator is as effective as other thrombolytics like urokinase. In fact, tissue plasminogen activator has been proven more effective than urokinase in breaking up hemodialysis catheter clots. Secondly, tissue plasminogen activator has never been utilized for catheter reopening because of its short eight hour expiration date. In actuality, by facts presented in this article, it may be derived that reconstituted tissue plasminogen activator has an actual expiration date between a minimum of six months to a theoretical maximum of two years. Lastly, until now tissue plasminogen activator has been viewed as too expensive to use on procedures such as clearing hemodialysis catheters. This belief resided in the belief that the remaining tissue plasminogen activator would have to be thrown away after its short expiration date expired, thus resulting in a huge loss of money and pharmacy resources. In actuality, however, if utilized properly a 2mg dose of tissue plasminogen activator ($32.94) is less expensive than 5,000 units of urokinase ($68.00).

As a result of these facts, we feel that it is apparent that tissue plasminogen activator can and should be used as a viable replacement to urokinase. In lieu of the short supply of urokinase and the necessity to have reliable thrombolytics on hand within the pharmacy, we feel that tissue plasminogen activator adequately and effectively fills the void left by urokinase. Proper utilization of tissue plasminogen activator will translate into greater clinical outcomes for the hospital, improved quality of life for the patient, and improved economic savings.

Tables

Table 1	Summary of Surgical Costs			
Category	**Total Cost**	**Variable Direct Cost**	**Fixed Direct Cost**	**Fixed Indirect Cost**
Operating Room Time and Nursing	$1,089.00	$573.00	$121.00	$395.00
Recovery Room Time and Nursing	$244.00	$125.00	$20.00	$99.00
Anesthesia	$385.00	$96.00	$179.00	$110.00
Portable Chest Radiography	$131.00	$45.00	$38.00	$48.00
	$1,849.00	**$839.00**	**$358.00**	**$862.00**
Surgeon's Fees	**$2,000.00**			
Total Cost:	**$3,849.00**			

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- **Variable direct costs** reflect such resources as short-term labor required to operate an interventional radiology suite, an operating room, or a recovery room and the supplies included in the procedures such as catheters ($172.75), contrast agents, and surgical instruments.
- **Fixed direct costs** reflect department overhead costs such as managerial labor, equipment leasing, and administration costs.
- **Fixed indirect costs** reflect hospital overhead costs such as climate control, office space, and hospital computer services.

Table 2	**Comparison of Pricing For Activase and Urokinase**		
Activase			
	Vial Price:	$823.56	
Regular dose for clearing catheters:		**2 mg / 2 mL**	
	Price Per Dose:	**$32.94**	
Urokinase			
	Vial Price:	$64.00	$128.00
Regular dose for clearing catheters:		**5,000 units**	**10,000 units**
	Price Per Dose:	**$64.00**	**$128.00**

Table 3 **Cost Savings Associated With Hemodialysis Catheters Saved By Tissue Plasminogen Activator Utilization**

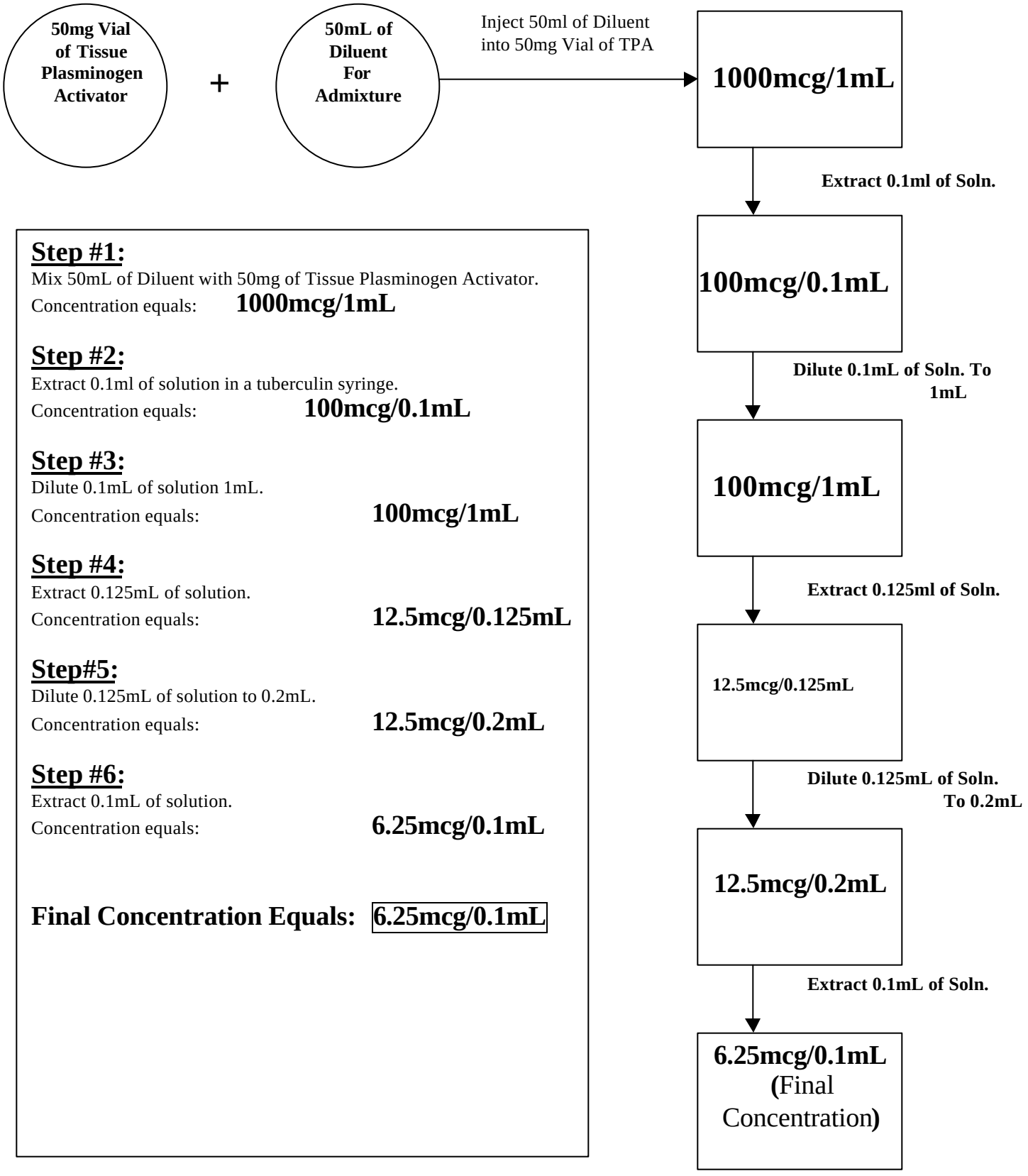
	Cost to VAMC			
2mg/2mL Activase Bolus	$32.94			
		Costs Avoided By VAMC		
		Utilization of 49mL of Activase	$807.09	note: this is a one-time savings
		Avoidance of Surgery	$3,849.00	
			Total Savings To VAMC	
			14 Catheters Saved	**$54,231.93**

Summary

Costs:	
Cost of 2mg of Activase for 14 Catheter Clearances:	-$461.16
Savings:	
One-Time Savings Associated With Proper Utilization of 50mg Stock Activase:	$807.09
Savings Associated With Avoiding 14 Catheter Replacements:	$53,886.00
Total Savings To VAMC:	**$54,231.93**

Figures

Figure 1: Procedure for Preparation of Intraocular Tissue Plasminogen Activator



Step #1:
Mix 50mL of Diluent with 50mg of Tissue Plasminogen Activator.
Concentration equals: **1000mcg/1mL**

Step #2:
Extract 0.1ml of solution in a tuberculin syringe.
Concentration equals: **100mcg/0.1mL**

Step #3:
Dilute 0.1mL of solution 1mL.
Concentration equals: **100mcg/1mL**

Step #4:
Extract 0.125mL of solution.
Concentration equals: **12.5mcg/0.125mL**

Step#5:
Dilute 0.125mL of solution to 0.2mL.
Concentration equals: **12.5mcg/0.2mL**

Step #6:
Extract 0.1mL of solution.
Concentration equals: **6.25mcg/0.1mL**

Final Concentration Equals: 6.25mcg/0.1mL