

# CRYOPRESERVED RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR FOR THE RESTORATION OF OCCLUDED CENTRAL VENOUS ACCESS DEVICES IN PEDIATRIC ONCOLOGY PATIENTS

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**Background:** Thrombolytic therapy with urokinase 5000 units has been the standard therapy for the restoration of thrombosed central catheters. However, with the decreased availability of urokinase, alternatives needed to be sought. The aim of the study was to determine the efficacy, bioactivity, dwell time and cost of cryopreserved recombinant tissue plasminogen activator (rTPA) in the restoration of occluded central venous access devices.

**Materials and Methods:** For children < 10 kg, a dose of 0.5 mg, and for children >10 kg, a dose of 1mg was used. The dwell time was 1-2 hours.

**Results:** Of the 40 courses of rTPA, 39 fully restored central venous line patency (97%). Successful courses were instilled for an average of 1 hour.

**Conclusion:** Cryopreserved rTPA appears to be safe and effective in the dose used to restore the patency of occluded central venous access devices in pediatric oncology patients.

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**Key words;** Urokinase; cryopreserved recombinant tissue plasminogen activator.

Central venous catheters in pediatric oncology provide a reliable means of venous access for the administration of medications, blood products, nutritional support and a source of obtaining blood samples. They are, however, prone to a number of complications. Obstruction, secondary to drug precipitation, and/or thrombotic occlusion, with resultant loss of ability to infuse or withdraw material occurs in 25% of catheters.<sup>1</sup> Until 1999, Abbokinase Open Cath (Urokinase, Abbott, Abbott Park, IL) a thrombolytic agent was the standard therapy for clearing thrombosed catheters. However, changes in the manufacturing process mandated by FDA has resulted in a lack of availability of urokinase.<sup>2</sup> Our institution modified its declotting policy to incorporate recombinant tissue plasminogen activator (rTPA) as an alternative. This study provides initial results in the restoration of occluded catheters in pediatric oncology patients.

## Materials and Methods

Inclusion criteria included infants and children up to 12 years of age with acquired central venous catheter

dysfunction characterized as: 1) inability to withdraw blood from the catheter after at-least one successful attempt; and or 2) inability to infuse through the catheter or the need of high pressure for successful infusion.

Our institution's modified policy incorporating rTPA to restore the patency of occluded central venous catheters was approved by the Hospital Pharmacy and Therapeutic Committee in December 2000 and was applied as follows:

1. A 50 mg vial was diluted in 50 mL sterile water to produce a concentration of 1 mg/mL, in a laminar airflow hood
2. 1 mL (1 mg) was transferred to 1 mL sterile syringe and stored at -30°C for three months
3. Preparation and expiration dates were written on all aliquots
4. Initial freezing was performed in January 2001. Samples from initial day of compounding and at one, two, and three months of freezing were sent for evaluation of bacterial contamination
5. After thawing at room temperature, the samples were sent to the requested ward
6. 1 mg/mL rTPA was instilled in the occluded catheter for patients who weighed >10 kg and 0.5 mg/0.5 mL for patients <10 kg, with rest of the lumen filled with 0.9% normal saline. Dwell time of 1-2 hours was maintained. The catheter was then aspirated and finally flushed with 0.9% normal saline.

As a part of our protocol and before the administration of rTPA, alternative methods such as positioning of patient, accessing for kinks and gentle push/pull technique were

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tried. If these maneuvers failed to restore patency, it was assumed that catheter thrombosis had occurred. No radiographic evaluation was performed.

## Results

Over a period of 10 months (January 2001 to October 2001), 40 pediatric patients with thrombosed central venous catheters were treated in our ward. Of the 40 courses of rTPA, 39 central venous line (CVL) patency (97%) were fully restored. Successful courses were instilled for an average of 1 hour, and the only unsuccessful course was instilled for 30-45 minutes. This patient needed two treatments for the same incident of the loss of patency. The first course was administered for 30-45 minutes and failed. A day later, a second course was administered for 1 hour and was successful. All bacterial contamination results for one, two and three months were negative.

## Discussion

Due to the non-availability of urokinase on the market, a search for an effective, and safe thrombolytic agent for the restoration of occluded central venous access devices (CVADs) was mandatory. Not many options were available. Streptokinase (SK) was a possibility, however, because of its inherent property of being an allergenic thrombolytic agent with an issue of anaphylactic reaction and producing a neutralizing antibodies after first exposure that would minimize subsequent response, it was not a preferable option.<sup>3</sup> Recombinant tissue plasminogen activator (rTPA) seemed the only alternative.

Many studies have been conducted in adults, establishing the effectiveness of rTPA as an effective thrombolytic agent in obstructed CVADs.<sup>4,7</sup> However, there is limited data on the use of rTPA for the restoration of occluded catheters in pediatric patient.<sup>4,5</sup> The effectiveness of rTPA in the restoration of occluded CVADs rests on its higher affinity for fibrin, as compared to urokinase which was first established in a double-blinded randomized trial conducted by Haire et al.<sup>8</sup> In their series, a novel dose of 2 mg of rTPA instilled for 2 hours restored catheter function more readily and dissolved thrombus faster than twice the standard dose of urokinase in patients over 19 years of age. Kleta et al. reported that a single dose of 0.5 mg/0.5mL of rTPA when injected and allowed to remain for 20-30 minutes was sufficient to open more than 97% of all the occluded catheters in patients aged between 3 months and 25 years.<sup>4</sup> Choi et al. demonstrated 82% line restoration in a group of pediatric patients (7 weeks to 16 years) when a dose of 2 mg/2mL was employed with a dwelling of 2 hours.<sup>5</sup> In another case series that included five children, rTPA was successful in 5 of 6 patients in re-establishing patency after urokinase failure in all patients.<sup>9</sup> In our series,

a dose of 1 mg/mL of rTPA was allocated for all pediatric patients (>10 kg) and 0.5 mg/0.5mL for patients (<10 kg). We speculated that 1 mg/mL of rTPA would suffice in pediatric patients with central venous catheters as the lumens of CVADs are small, as compared to those in adults. In our study, the function of all (97%) but one occluded catheters was restored, showing that a single dose of 1 mg/mL of rTPA was as effective in restoring the patency of occluded catheters as a dose of 2 mg/2mL of rTPA in other series.<sup>3</sup> Repeat dosing was required in one, and was successful.

The dwell time in our declotting process was 1-2 hours, which seemed sufficient to restore patency in our series. In most series, successful courses of rTPA were instilled in CVADs for varying lengths of time, from 1-4 hours or overnight.<sup>5</sup> Choi et al. reported that the average unsuccessful course was instilled 30 minutes less than the recommended amount of time, and that a longer instillation time did not appear to affect safety.<sup>3</sup>

The type of CVAD does not appear to affect the efficacy or safety of the treatment in different series.<sup>3</sup> In our series, 37 courses involved subcutaneous ports and three involved Hickman catheters. Of the subcutaneous ports involved, all courses were able to restore patency after a single instillation of rTPA, while out of the three Hickman catheters involved, one needed a second dose. The number of patients with Hickman catheters in our series was too small to make a meaningful comparison.

Cost is increasingly becoming an issue in pharmacotherapy. This holds true when rTPA is used instead of urokinase in restoring the patency of occluded catheters. This is not because of its inadequacy as a fibrinolytic agent, rather it is because of the uncertainty of cost. rTPA is not commercially available in a 1 mg dose. The smallest commercially available dose of rTPA is 50 mg which costs the National Guard Health Affairs 4170 Saudi riyals (over \$1100) at wholesale price. Compared to the wholesale cost of SR10 (\$2.6) for a 5000U "Open Cath" dose of urokinase, the cost of rTPA at first glance would appear prohibitive. However, when dealing with large populations with CVADs, institutions have found it cost effective, where rapid restoration of occluded catheters is required.<sup>10</sup>

This study describes our initial experience with the use of rTPA for the occlusion of CVADs. Our results seem encouraging for the following reasons: 1) the administration of rTPA is easy and practical when an aliquot of 1 mg/mL is frozen and stored for ready use; 2) in the dose used, we did not experience any side effects; 3) treatment with rTPA is relatively inexpensive when used as described; 4) reconstituted rTPA shows efficacy of up to 28 days after initial compounding, though strict aseptic technique is critical. Needless to remember that our study needs further evaluation since none of the catheter treated had radiological confirmation of thrombosis.

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