Applying a Successful New Protocol for Storing a Tissue Plasminogen Activator for Locking Dysfunctional Permcath: A Single-Center Study

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Dear Editor in Chief

The use of permanent catheters (permcath) is the least favored dialysis access method because of the associated thrombotic and infectious complications with increased morbidity and mortality [1]. Permcath have a high rate of failure mainly due to thrombosis. The use of the recombinant tissue plasminogen activator (rt-PA) as a catheter lock reduces the risk of permcath malfunction and requirements for rt-PA as a treatment method [2]. Blood flow rate (BFR) during dialysis is a marker of catheter malfunction and is directly related to the ability to maintain adequate dialysis [3].

Our unit protocol was developed to maintain good blood flow in dialysis catheters. We generally use different catheter lock solutions between dialysis sessions to keep the catheter open including Tauridine citrate with heparin – heparin 5,000 unit/mL solution and Tauridine with Urokinase. We use rt-PA catheter lock as prevention (in between 2 HD sessions) when BFR <250 mL/min during session) and as treatment (for 30–60 min instillation during HD session; for acute catheter malfunction BFR <200 mL/min) [4]. Our protocol for rt-PA lock specifies indications as mentioned above. For cutting down costs leading to financial saving, rt-PA vial (50 mg) is being reconstituted and stored in syringes (5 mg in 5 mL), as the dose needed for a lock is much smaller than the vial size.

The reconstitution is done in our clean rooms in the hospital pharmacy under aseptic condition by pharmacy technicians supervised by pharmacists. We apply the U.S. Pharmacopeial Convention 797 safety rule for Pharmaceutical Compounding – Sterile Preparations to ensure best quality practices. The bag (50 mg/50 mL) after reconstitution is split into 10 syringes and labeled. The label includes the name of the product with the concentration as 5 mg/5 mL and information related to the preparation and expiration dates.

Traditionally, we have used rt-PA up to 14 days after reconstitution stored in temperature 2–8 degrees' centigrade temperature (2W-rt-PA) for many years based on Davis et al. [5] report. But the manufacture package insert recommends using rt-PA within 8 h in room temperature and up to 24 h after reconstitution stored in 2 degrees centigrade temperature (24H-rt-PA). There have been many reports describing the successful prolonged use of rt-PA after reconstitution stored in temperature of –20 to –30 degree centigrade for up to 1 year [6].

We did a prospective cohort study to compare our previous protocol using 2W-rt-PA with our current protocol (manufacturer recommendation) using 24H-rt-PA. Inclusion criteria included adult patients on maintenance HD using permanent catheter for at least 6 months and receiving

rt-PA lock (at least one session per week) for at least 3 months. Our protocol for rt-PA lock was to instill it in the catheter according to exact catheter lumen volume after HD session and lock in and remove it during the next dialysis session. We did the study over 2 phases. Phase 1 included observation for 4 weeks on our previous protocol using 2W-rt-PA and phase 2 included observation during the new rt-PA protocol using 24H-rt-PA. BFR, Kt/V, and the need for rt-PA as a treatment for acute malfunctioning catheters (BFR <200 mL/min) were recorded for 4 weeks in phase 1 with 2W-rt-PA and then in phase 2 with 24H-rt-PA. Mean BFR was calculated based on the mean of 8 readings of BFR during each session of the 4-week period (12 sessions total per patients). Rt-PA was reconstituted and provided to the patients within 24 h (24H-rt-PA) and stored under 2 degrees centigrade and given to patients at same frequencies for 4 weeks. We also analyzed incremental cost effectiveness.

We had a total of 360 HD patients. There were 103 HD patients dialyzed with permanent catheters. Twenty-two patients were using rt-PA lock and were included. We had 14 males and 8 females. Fourteen patients were receiving rt-PA once weekly, 4 patients twice weekly, and 4 patients 3 times weekly (frequency of rt-PA lock depended on the presence of heparin-induced thrombocytopenia and catheter malfunc-

tion pattern. Reasons for using rt-PA were poor BFR (<250 mL/min; 19 patients) and the presence of heparin-induced thrombocytopenia (3 patients but also have borderline BFR [mean of 265 mL/min]) and were using rt-PA 3 times weekly.

1. Phase 1 observation period: BFR for all sessions was 247 ± 36.6 mL/min, while BFR after 2W-rt-PA session was 252 ± 36.4 mL/min, Kt/V was 1.37 ± 0.23 , and 2 patients required rt-PA treatment.

2. Phase 2 24H-rt-PA: BFR for all HD sessions was 252 ± 30 mL/min, while BFR after 24H-rt-PA sessions was 253 ± 32 mL/min, Kt/V was 1.4 ± 0.3 , and rt-PA treatment was needed in 2 patients. Figure 1 shows BFR in phase 1 2W-rt-PA and phase 2 24H-rt-PA in our cohort. There was no statistical difference in BFR for all HD sessions – HD sessions after rt-PA lock or Kt/V between phase 1 2W-rt-PA and phase 2 24H-rt-PA. Patients achieving BFR >300 did not encounter significant differences between the 2 phases (2 vs. 3 patients). There were no bleeding episodes in patients of both groups. One patient had self-reported fever with negative culture during phase 2 24H-rt-PA with no consequences. No visual precipitation of rt-PA was noted during the study period.

We present the first clinical data to compare 24H-rt-PA to an extended use clinical protocol (2W-rt-PA). The 2 protocols were comparable in terms of their clinical parameters (BFR in both all HD sessions and post rt-PA sessions or Kt/V).

Multiple advantages achieved with extended protocol 2W-rt-PA including flexibility to have 2 weeks' window to give rt-PA after reconstitution including arranging transportation to remote HD units, pharmacy, and nursing staff time.

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Fig. 1. Blood flow rate in phase 1 2W-rt-PA and phase 2 24H-rt-PA.

Direct cost saving was a major factor. The estimated cost for 50 mg vial versus 120 dollars per dose of Cathflo Activase (2 mg) was 447 dollars. The estimated total direct cost saving for our cohort over a follow-up period of 1 month was 26,000 dollars.

Due to financial burden and rare use of rt-PA lock, reconstituted rt-PA required innovative resolutions for it to be stored for long durations of time. Our current storing protocol is the first one to provide such flexibility without affecting the safety or efficacy over a prolonged period of time.

Ethics Statement

This study was approved by the Hamad General Hospital Institutional Board Review committee (research proposal #15359/15). No animals were involved in this study.

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