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Reduction in Thrombolytic Usage in Hemodialysis Patients Following a Quality Assurance Review: A Research Letter

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Abstract

Background: Catheter malfunction in hemodialysis (HD) is increasingly managed with recombinant tissue plasminogen activator (rt-PA, alteplase), though evidence of improved catheter function is lacking.
Objective: To evaluate the effect of a standardized rt-PA administration protocol on rt-PA usage, catheter function, and adverse events.
Design: Observational quality improvement study.
Setting: Single, urban, community HD unit in Calgary, Alberta.
Patients: Patients treated with maintenance in-center HD through central venous catheter.
Outcomes: Incidence of rt-PA usage, catheter interventions, hospitalizations, and measures of dialysis efficacy.
Methods: The rt-PA protocol was designed following a consultative and iterative design period with dialysis shareholders, which included focusing on standard objective criteria before use and targeting use to the problematic lumen. Protocol implementation occurred over a 6-month period in 2021. Patient and dialysis data were collected through our regional dialysis electronic health record.
Results: Implementation of the rt-PA protocol resulted in decreased rt-PA use (standardized per 100 dialysis sessions) compared to the preprotocol period (incidence rate ratio [IRR] of 0.57, 95% confidence interval [CI]: [0.34, 0.94]). Line procedures were also less frequent (IRR = 0.42, 95% CI: [0.18, 0.89]). Hospitalization rates and measures of dialysis efficacy were similar in both periods.
Limitations: Small sample size with single dialysis center and short duration of follow-up.
Conclusions: Implementation of a multidisciplinary designed rt-PA administration protocol decreased incident rt-PA usage

Abrégé

Contexte: L'activateur tissulaire du plasminogène recombinant (rt-PA, alteplase) est de plus en plus utilisé pour la prise en charge du dysfonctionnement du cathéter en hémodialyse, bien qu'on manque de preuves sur l'amélioration de la fonction du cathéter.
Objectif: Évaluer l'effet d'un protocole normalisé d'administration de rt-PA sur l'utilization de rt-PA, la fonction du cathéter et les événements indésirables.
Type d'étude: Étude observationnelle d'amélioration de la qualité.
Cadre: L'unité d'hémodialyse communautaire d'un center urbain de Calgary (Alberta).
Sujets: Patients traités en center par hémodialyse d'entretien avec cathéter veineux central.
Résultats: Mesure de l'efficacité de la dialyze et incidence de l'utilization du rt-PA, des interventions par cathéter et des hospitalisations.
Méthodologie: Le protocole rt-PA a été élaboré après une période de consultation et d'itération auprès des intervenants en dialyze qui consistait à mettre l'accent sur les critères objectifs normalisés avant son utilization et à cibler son utilization dans la lumière problématique du cathéter. La mise en œuvre du protocole s'est déroulée sur une période de 6 mois en 2021. Les données sur les patients et les séances de dialyze ont été recueillies par le biais du dossier médical électronique régional pour la dialyze.
Résultats: La mise en œuvre du protocole rt-PA a entraîné une diminution de l'utilization de rt-PA (normalisée pour 100 séances de dialyze) par rapport à la période pré-protocole (rapport du taux d'incidence [RTI] de 0,57; intervalle de confiance

à 95% [IC 95 %] de 0.34 à 0.94). Les interventions au niveau des cathéters ont également été moins fréquentes (RTI: 0.42; IC 95 %: 0.18-0.89). Les taux d'hospitalization et les mesures de l'efficacité de la dialyze étaient semblables pour les deux périodes.
Limites: Étude menée dans un seul center de dialyze, sur un échantillon de petite taille, avec un suivi de courte durée.
Conclusion: La mise en œuvre d'un protocole d'administration de rt-PA conçu de façon multidisciplinaire a diminué l'incidence de l'utilization de rt-PA.

Keywords
vascular access, catheter-related thrombus, hemodialysis catheter, quality improvement, Alberta

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Introduction

Management of central venous catheter (CVC) complications remains a considerable problem in hemodialysis (HD) care.[1] In patients who utilize CVCs as their vascular access, dysfunction can result in poorer quality dialysis and deleterious clinical outcomes, such as infections, additional interventions, and hospitalizations.[2]

While approaches to catheter dysfunction differ between centers and regions, the mainstay of conventional medical therapy involves use of thrombolytic agents, such as the recombinant tissue plasminogen activator (rt-PA, also known as alteplase). In the Alberta Kidney Care (AKC) program, after identifying a problematic CVC and attempting conservative corrective measures (ie, flushing, patient repositioning), nurses must inform the on-duty nephrologist to receive an order to administer rt-PA. Following this, administration of 1 to 2 mg (per lumen, as a dwell/lock, or infusion) is used incrementally at the discretion of the nephrologist. In comparison, Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations suggest 2 mg of rt-PA per lumen, admittedly based on small studies with large variability in outcome measurements.[3,4] Furthermore, rt-PA administration is typically initiated based on *ad hoc* bedside nursing clinical assessment, leaving significant opportunity for variation in practice.

Numerous studies have supported a role for rt-PA, as inclusion into routine dialysis care is associated with lower rates of CVC procedures (which are invasive, costly, and do not always result in durable solutions), albeit, at possible increased overall cost ($68 Canadian dollars per 2-mg dose).[5,6] Within our dialysis program, expenditures for rt-PA have risen 10% to 15% annually over the last decade, nearing $500 000 yearly (internal unpublished data). With limited standardized and quantitative measures to assess the effect rt-PA administration, it remains unclear if this increased usage has meaningfully impacted the provision of dialysis care. With these challenges in mind, we assessed the effect of implementing a standardized rt-PA administration protocol in an urban community dialysis unit on catheter dysfunction, dialysis efficiency, resource use, and other clinical outcomes.

Methods

Study Design, Setting, and Data Sources

We performed a prospective pre-post study at a single, community dialysis unit in Calgary, Alberta from July 1, 2021 to December 31, 2021. This 20-station unit provides maintenance in-center conventional HD for approximately 110 patients with 300 dialysis sessions per week. The rt-PA protocol (Supplemental Figure S1) was designed after a series of multidisciplinary meetings identifying systemic issues with rt-PA usage. Key shareholders included dialysis nurses, vascular access coordinators, unit managers, and nephrologists. This protocol standardized use of rt-PA after specific objective criteria were met, and aimed at focusing the use on the problematic lumen (ie 2 mg in the problematic lumen vs 1 mg in each lumen). An iterative protocol development process occurred over a 6-month period prior to study initiation. Inclusion criteria included all patients receiving maintenance HD through a CVC having completed at least 2 consecutive HD sessions to compare the effect of rt-PA administration. Most of the patients (>95%) in our regional program use tunneled Hemostar CVCs inserted in the right or left internal jugular vein. As the half-life of rt-PA is generally less than 60 to 120 minutes, any positive effect on dialysis metrics would be hypothesized to be observed in the dialysis session immediately following rt-PA administration. Patients were excluded if they used an arteriovenous fistula or graft for HD. Baseline characteristics, dialysis metrics, and rt-PA administration were assessed from our local dialysis electronic health record. The protocol was implemented from July 1, 2021 to December 31, 2021, with a preprotocol

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comparison period from July 1, 2020 to December 31, 2020. This preprotocol period was intentionally selected prior to study conception and planning phases as to avoid inadvertent influence on study outcomes. As this was a quality improvement study, whereby the primary purpose was to evaluate implementation of an rt-PA usage protocol, waiver of individual patient consent was not required.

Protocol Outline

The preintervention and postintervention protocols for rt-PA administration are outlined in (Supplemental Figure S1). In brief, after identification of a malfunctioning CVC, HD nurses completed several conservative measures, including saline flushes and patient repositioning. Nurses were asked to identify if a problematic lumen could be identified based on this assessment. The ports were then reversed (ie, arterial-venous lumen) as an initial intervention. Following this initial intervention, if 2 of 3 criteria were met (unable to main blood flow $>$ 250 ml/min, recirculation rate $>$ 30%, or high alarm rate of $\geq$ 5 alarms during run), then 2 mg of rt-PA was administered into the problematic lumen as identified on earlier assessment. The mechanism of delivery (ie, lock, dwell, infusion) was left at the discretion of the nephrologist. If catheter dysfunction continued to occur in 4 runs, then the nephrologist on duty was notified to see whether additional interventions were required.

Primary and Secondary Outcomes

The primary outcome of the study was the rate of rt-PA administration (numerator) over the number of HD sessions at risk (denominator). Secondary outcomes included incidence of catheter-related procedures, hospitalizations (categorized by dialysis-related and non-dialysis-related diagnoses) and change in dialysis metrics. CVC interventions were defined as either CVC exchange, fibrin sheath stripping, or angioplasty. Hospitalizations were categorized as dialysis- (ie, hyperkalemia, volume overload, CVC complications, line infections) and non-dialysis-related (ie, orthopedic, nondialysis infections, acute coronary syndrome). Dialysis metrics of interest were the difference in Kt/V, average blood flow, and blood volume processed between the "incident" run (session requiring rt-PA), and "effect" run (session immediately following rt-PA administration). Given the outcomes were to assess the effect of rt-PA usage, patients could receive multiple rt-PA doses, line exchanges or hospitalizations during the study period.

Statistical Analysis

Descriptive statistics were used for baseline demographic information. Continuous variables were compared with the Mann-Whitney *U*-test or, 2-proportion *Z*-test where appropriate. Comparisons prior to and following protocol implementation were completed using Poisson regression accounting for the number of HD sessions as an offset. Models were adjusted for covariates of interest (age, biological sex, duration of dialysis time, warfarin or antiplatelet use, and diabetes). As we detected over-dispersion during modeling, we used multivariable negative binomial models to correct for this. Our analyses were completed using RStudio (2022.07.1 build 554) packages epiR (v2.0.52) and MASS (v7.3.57). Original source code is available upon request.

Results

Baseline Characteristics

Patient characteristics and demographics are presented in Supplemental Table S1. The study cohort consisted of 138 patients in the preprotocol period and 126 in the postprotocol period. Diabetes was the most frequent cause of kidney failure in both groups and male patients were more represented in both cohorts. Patients on warfarin comprised 12% and 11% of the preprotocol and postprotocol groups, respectively. Approximately, 50% of patients in both groups were on an antiplatelet agent. In the postprotocol cohort, rt-PA usage was compliant with the protocol in 81% of administrations.

Effect on rt-PA Usage

The incidence of rt-PA use was 5.7 deliveries per 100 HD sessions in the preperiod versus 3.8 deliveries per 100 HD sessions in the post period (Table 1). The unadjusted incidence rate ratio (IRR) of HD sessions requiring rt-PA administration decreased after implementation of the standardized protocol (IRR = 0.57, 95% CI: [0.35, 0.96]). This rt-PA IRR did not change despite adjusting for prespecified confounders. Cost analysis between the control and intervention period also reflected a total cost reduction of an estimated $10 132 (Supplemental Table S2).

Effect on Catheter-Related Interventions and Hospitalizations

Patients requiring invasive line interventions following protocol implementation was significantly decreased (IRR = 0.42, 95% CI: [0.18, 0.89]). Overall, hospitalizations were unaffected (adjusted IRR = 0.8, 95% CI: [0.57, 1.11]); and no statistically significant difference was noted when separating dialysis-related and non-dialysis-related hospitalizations.

Effect on Dialysis Metrics

To assess whether implementation of our protocol affected measures of dialysis adequacy, we compared the changes

Table 1. Primary and Secondary Outcomes Following Protocol Implementation.

Variable	Preprotocol	Postprotocol
Primary outcome		
Total number of hemodialysis sessions requiring rt-PA	272	153
Total number of hemodialysis sessions	5203	4706
Rate of rt-PA use per 100 hemodialysis sessions	5.2	3.3
Unadjusted incidence rate ratio for post versus preprotocol (95% confidence interval)	0.57 [0.35, 0.96]	
Adjusted incidence rate ratio for post- versus preprotocol (95% confidence interval)[a]	0.57 [0.34, 0.94]	
Secondary outcomes		
CVC-related procedures	0.42 (0.18-0.89)	
Total hospitalizations	0.8 (0.57-1.11)	
Dialysis-related	1.18 (0.67-2.09)	
Non-dialysis-related	0.69 (0.46-1.04)	

Note. CVC = central venous catheter.
[a]Adjusted for age, biological sex, duration of dialysis time, warfarin or antiplatelet use, and diabetes.

(Δ) in Kt/V, average dialysis blood flow and blood volume processed for the "incident" and "effect" dialysis runs, between the preprotocol and postprotocol periods. Following protocol implementation, the absolute change in Kt/V, average blood flow and total blood volume processed were not statistically discernable in our sample (Supplemental Table S3).

Discussion

Within our dialysis program, modest increases in rt-PA usage have not clearly been associated with improvement in patient or dialysis outcomes. This study was conceptualized as part of an effort to more efficiently deploy rt-PA without negative clinical impact on patient care. As part of our protocol development, we identified that request for thrombolytic agents was driven by nonstandardized bedside clinical assessment in conjunction with dialysis machine outputs, such as alarms or measured flow rates, leading to considerable variability in practice. Here, we demonstrate that implementation of a standardized rt-PA administration algorithm may reduce rt-PA usage without negatively impacting hospitalization rates or dialysis metrics. Interestingly, protocol implementation appeared to reduce the number of CVC-associated procedures during the trial period. We hypothesize that these effects resulted from our iterative quality improvement process—culminating in nursing education, standardized objective criteria, and targeted use of rt-PA.

We did not find any differences in dialysis metrics following implementation of the protocol. Given the short half-life of rt-PA, any effect of thrombolytic activity on dialysis metrics (ie, increased clearance or mean blood flow) would be most evident the following HD session. Regardless of protocol exposure, following administration of rt-PA, the percentage of subsequent sessions with net positive deviations in the measured dialysis metrics ranged from 54% to 65% (Supplemental Table S3). These changes are in keeping with previously reported effects in literature.[7] Prior studies have examined various protocols for thrombolytic administration to varying degrees. Weekly rt-PA administration decreased the incidence of catheter malfunction, without affecting rates of bacteremia or catheter-related interventions.[6] However, this was associated with an overall increased system cost (due to increased rt-PA usage). Differences in delivery (ie, push vs dwell) have also not identified a superior strategy. A larger, Canadian, multicenter randomized controlled trial (RCT) was terminated prematurely due to inability to accrue enough patients (NCT00303420).[8] We believe that future studies on the impact of thrombolytic agents on vascular access should include quantitative metrics on dialysis efficacy to ensure rt-PA administration has the intended effects.

Despite this, our findings could have substantial implications. Based on current cost estimates for rt-PA ($34/mg), our intervention in this trial resulted in a savings of $170 per 100 CVC sessions. Approximating 50 000 CVC dialysis sessions per annum within our regional (Southern Alberta) program, the overall decrease in rt-PA could result in a modest cost savings of around $85 000 annually. Our study underscores the importance of ongoing quality improvement studies to ensure optimal administration of thrombolytics in dialysis patients. Strengths of our study include the development of the protocol with multidisciplinary input. We also noted a high compliance rate (81%) reflective of strong uptake by healthcare team members. Limitations to this study include the nonrandomized study design, limited populations' size, and short duration of follow-up. And while the incidence of CVC-related procedures may be influenced by the degree of rt-PA usage, we cannot rule out alternative explanations and confounding factors, such as patient hesitancy due to COVID-19 exposure risk. Our study was not prospectively powered to detect differences

in this outcome and larger studies will be required to examine the durability of this finding. Despite these shortcomings, our study highlights how a standardized protocol developed with multidisciplinary input may more efficiently use rt-PA without deleterious impacts on hospitalizations or dialysis efficacy.

Ethics Approval and Consent to Participate

After review by the Calgary Research Ethics Board at the Univeristy of Calgary, ethics approval was not required given the project was a quality improvement initiative. A waiver of individual patient consent was not required.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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