Efficacy of Reducing Alteplase Dose to Restore Patency in Nonhemodialysis Central Vascular Access Devices

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ABSTRACT

Central line-associated bloodstream infections (CLABSIs) are preventable through vigilant and thorough care.[1] When CLABSIs occurred at a facility in Southwest Arizona, the root cause analysis discovered that declotting agents, such as alteplase, were not given routinely when nonhemodialysis (non-HD) central vascular access devices (CVADs) lacked blood return. A PICO question was developed that guided the review of literature and central line care standards of practice: In the adult patients with non-HD central lines, what medications are currently recommended to restore patency? As a result of this project, our facility instituted a new protocol using a reduced dose of alteplase to restore patency to non-HD CVADs.

Key words: alteplase, declotting central lines, evidence-based practice, reduced-dose alteplase

Central line–associated blood stream infections (CLABSIs) are preventable through vigilant and thorough care.[1] The use of central line bundles can help standardize processes to prevent CLABSIs.[2] When CLABSIs occur at a facility in Southwest Arizona, an investigation is conducted to determine possible causes. While investigating CLABSIs, it was discovered that declotting agents, such as alteplase, were not given routinely when nonhemodialysis (non-HD) central vascular access devices (CVADs) lacked blood return and were considered not patent. Staff identified a delay of care in notifying physicians to obtain an order to administer alteplase because alteplase was not included in the bundled CVAD care set. A process improvement to add alteplase to a care set evolved into an evidence-based practice project after a review of the literature. The purpose of this article is to discuss and share the experience and results of 1 facility's experience with using a reduced dose of alteplase in restoring patency to non-HD CVADs.

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BACKGROUND

A standard of practice for CVADs requires all catheters are flushed and aspirated for a blood return before each infusion to assess catheter function and prevent complications.[3(S77,S104)] CVADs are assessed for function by flushing and aspirating for blood return prior to each intermittent vascular access device use daily. Within the facility, the policy is to assess for function at least once a shift.[3(S81)] For CVADs with no blood return, an order is received from the physician/independent practitioner to administer the manufacturer-recommended dose of 2 mg of alteplase intravenously (IV). The dose may be repeated 1 time to restore patency, as needed for a maximum of 4 mg of alteplase. To administer the 2 mg of alteplase, the medication requires reconstitution with 2.2 mL sterile water, according to manufacturer recommendations. In our facility, the nurse reconstitutes the medication immediately before use.

The facility policy for declotting a CVAD recommends the nurse instill alteplase 2 mg/2 mL alteplase and allows a 2-hour dwell time. If no blood returns in 2 hours, the nurse repeats alteplase 2 mg/2 mL for another 2-hour dwell time. If patency is not restored as evidenced by a positive blood flow return, the CVAD must be evaluated further for position and possibility of replacement or removal.

While investigating cases of CLABSIs, it was discovered that alteplase was not given routinely when non-HD CVADs were not patent; thrombi in and around the CVAD facilitate adhesion of bacteria, leading to colonization and potentially infection.[3(S105),4] The facility policy recommends that every nurse

check every CVAD for patency every shift. Initial evaluation of the process determined a need for process improvement measures to overcome barriers, such as adding alteplase orders to care sets for the care and maintenance of CVADs.

The process of adding alteplase to the CVAD care and maintenance order set required approval from the pharmacy team. The cost of alteplase is approximately $100 a dose; because of cost concerns, the pharmacy committee recommended a review of the literature to ensure that alteplase was the current standard of care for declotting central catheters. As a result, an evidence-based practice team was formed to evaluate the literature on alteplase and restoring patency in non-HD CVADs. The team used the following PICO question to guide the literature search: In the adult patients with non-HD central lines, what medications currently are recommended to restore patency? OVID, EBSCO, and PubMed were searched using the key words "central line," "patency," "declotting," or "alteplase."

REVIEW OF LITERATURE

The original study guiding the project was conducted by Haire et al[5] and explored the use of a 2-mg dose of alteplase versus urokinase with a 2-hour dwell time to restore catheter patency. A sample of 50 patients with CVADs with radiography-confirmed tip location in the superior vena cava with occluded lumens was included in the study. Alteplase restored 25 of 28 catheters (89%), with urokinase restoring 13 of 22 catheters (59%). Haire et al[5] concluded that alteplase was significantly ($P = .013$) more effective in restoring catheter patency.

Davis et al[6] explored the use of a lower dosage of alteplase to restore patency to sluggish lumens. Patients with 58 catheters with 66 lumens were enrolled in the study. An initial dose of 0.5 mg alteplase IV with a 60-minute dwell time was instilled in each lumen for the first dose. If the lumen remained sluggish or without blood return, a second dose of alteplase 1 mg IV was instilled for another hour. If both doses did not restore patency, the prescriber was contacted for a third dose of alteplase 2 mg IV. The findings were that 50 catheters were cleared with 0.5 mg alteplase (86.2%), with 5 catheters requiring a second 1-mg dose of alteplase (8.6%) and 1 catheter escalated to 2 mg alteplase (1.7%).[6] Patency was unable to be restored to 2 lumens (3.5%). Complete occlusions were cleared more often than partial occlusions with alteplase 0.5 mg IV (64% versus 36%). It was also noted that partial occlusions were sluggish longer than total occlusions (11.3 days versus 1.9 days, $P = .001$).

Whigham et al[7] evaluated the average time between occlusive events. Patients with central catheters with 56 occlusive events were evaluated in an interventional radiology unit for fibrin sheath causing occlusion. The intervention included the infusion of 1 mg/mL alteplase IV followed by 0.4 mL sterile saline with a dwell time of 15 minutes. A venogram was then completed to assess the presence of a fibrin sheath. Alteplase 1 mg/1 mL was repeated up to 2 more times if needed. If the occlusion remained, the alteplase dose was allowed to dwell overnight with a repeat venogram in the morning. If the occlusion remained, the fibrin was removed by percutaneous fibrin stripping, or the catheter was replaced. The findings revealed that 52 of 56 occlusions cleared with alteplase 1 mg IV (92.9%). Eight occlusions required 1 mg total (14.3%), 23 required 2 doses (41%), 19 required 3 mg total (34%), and 2 lumens required 4 doses (3.5%). The dwell time with the first dose was 15 minutes. The average time to the second occlusion event was 38.5 days, with the third event 27 days with repeat alteplase restoring function without replacement of catheters.

Fink et al[8] explored the effectiveness of alteplase 1 mg and 2 mg in a randomized unblinded trial. The study included 45 patients, of whom 61 had occluded lumens. The patients received either 1 mg/mL or 2 mg/2 mL with 60-minute dwell time to each occluded lumen, with repeat dose 1 time if needed. The findings showed that 37 lumens used 1 mg/mL with success obtaining patency 81.1%, and 24 lumens used 2 mg/2 mL restoring patency 83.3%.[8]

The literature strongly supported the use of alteplase to restore patency to non-HD catheters.[5-8] The literature also suggested that the dosage could be reduced from 2 mg to 0.5 mg[5] to effectively restore patency, with the potential to decrease cost. This project then became an evidence-based project to implement and evaluate the use of low-dose alteplase to restore patency to non-HD CVADs. The EBP PICO question for this project was as follows: In adult patients with non-HD central lines, how does alteplase 0.5 mg IV compare with alteplase 2 mg IV in restoring patency?

IMPLEMENTATION

The stakeholders for the project included physicians, pharmacists, and nurses. Pharmacy proposed the project and change to multiple physician committees and received approval from all committees. The protocol recommended alteplase 0.5 mg IV with a 1-hour dwell time for the first dose. If the catheter remained without blood return, alteplase 1 mg IV with a 1-hour dwell time was recommended. If the first 2 doses were unsuccessful in restoring patency, alteplase 2 mg was recommended.

The next step included setting up the process for physicians ordering alteplase in the electronic health record. Automatic substitution orders were created within the system recommended on the project protocol. The pharmacy would automatically substitute alteplase 0.5 mg/1 mg IV for any order received for alteplase 2 mg IV for declotting non-HD CVADs.

Codes were created for the different doses of alteplase. The 2 different codes for alteplase 0.5 mg IV and 1 mg IV allowed for correct billing. The coding also allowed for tracking of dose, which allowed for evaluation of efficacy of lower-dose alteplase. Coding of the doses identified the

effectiveness of 1 dose of alteplase 0.5 mg IV and how often a repeat dose of alteplase 1 mg IV was required to restore patency.

Pharmacy assessed the usage of alteplase to be 150 to 180 doses a month. With the large volume and cost per dose, pharmacy recommended premixing and freezing the doses to assist in the process of the patient receiving the lower dose. A study by Grewing et al[9] found that alteplase did not lose efficacy up to 30 days frozen. For efficiency and cost effectiveness, pharmacy premixed the doses using 50-mg and 100-mg vials rather than the 2-mg single-dose vial.

Alteplase (0.5-mg dose) was prepared using the 50-mg vial. Alteplase 50 mg was reconstituted, then drawn up into 100 (0.5-mg) doses. Alteplase (1-mg dose) was prepared using the 100-mg vial. Alteplase (100 mg) was reconstituted, then drawn up in 100 (1-mg) doses. Once reconstituted, each dose was drawn up into single-dose syringes. The syringes selected were 10-mL syringes to prevent extreme pressure on any CVAD when the medication was instilled into the catheter.

A critical component of this project was the dose and dilution of the medication. The decreased doses of alteplase were reconstituted in multidose vials with less diluent compared to the 2-mg dose. The 0.5 mg- and 1 mg-dose vials were reconstituted in 50 mg/50 mL and 100 mg/100 mL dose vials, while the 2-mg dose was reconstituted in single dose 2 mg/2 mL vials. Once reconstituted, the 0.5-mg and 1-mg dose was 0.5 mg/0.5 mL and 1 mg/1 mL. The 2-mg dose is diluted into 2.2 mL of sterile water, which assists in the fill volume of most central catheters. Questions arose regarding the amount of drug dose and diluent recommended for declotting CVADs.

The recommended treatment for declotting non-HD CVADs is based on dosage rather than fill volume. For example, with the 2-mg dose, if a catheter had a fill volume of more than 2 mL, extra fluid could be mixed with the alteplase to obtain the fill volume needed for the catheter. For example, with a 3-mL fill volume catheter, 2 mg would be mixed with 2.2 mL sterile water, then an extra 1 mL of saline could be added to the medication for a dose of 2 mg/3 mL. With the 0.5-mg and 1-mg dose, it was decided to add extra saline to have a fill volume of 2 mL. For example, the 0.5-mg dose would have 1.5 mL saline added, for a dose of 0.5 mg/2 mL. The 1-mg dose would have 1 mL saline added, for a dose of 1 mg/2 mL. Once this was completed by pharmacy, the doses were labeled, marked for 30-day expiration, and frozen.

Education regarding the practice change was developed for pharmacy, physicians, and nursing. Education for pharmacy was done by the lead pharmacist through the use of flyers and through staff meetings. Educating and communicating with 1500 nurses is a challenge. Education for nurses included multiple means of communication, which included flyers, announcement in staff meetings, newsletters, and announcement by leadership at early morning huddles. The education was implemented 1 month before the start date, with weekly reminders.

INITIAL OUTCOMES

In June 2012, the new protocol using the lower dose of alteplase was implemented. A total of 1185 doses were instilled to restore patency to non-HD CVADs between July 2012 and March 2013 for evaluation of the project. One thousand forty-five doses were reviewed for efficacy following the protocol of 0.5 mg first dose, followed by 1 mg repeat dose if needed. One hundred forty doses were removed from initial review because 1 mg was documented as the first dose without the first dose of 0.5 mg. These doses are reviewed and discussed later in the article.

Alteplase 0.5 mg/2 mL IV restored patency to non-HD CVADs 92.9% (n = 976) successfully with 1 dose. A total of 69 lumens remained without blood return. Alteplase 1 mg/2 mL restored patency in the remaining 98.6% (n = 68), with 1 failed attempt.

One Hundred Forty Doses Reviewed

A review of the 140 doses of 1 mg alteplase when the 0.5 mg alteplase was skipped identified barriers in coding and practice. A common practice was administering alteplase 0.5 mg in both lumens. The dose was coded by pharmacy as a 1-mg second dose, but was a first 0.5-mg dose for the second lumen (n = 37).

Coding issues also included the following:

- Dose was identified as 1 mg but documented as 0.5-mg dose in MAR (n = 58).
- First dose given on previous day, and following 1-mg dose incorrectly identified as given as 1 mg (n = 11).
- Alteplase was ordered as 1 mg IV for a second dose (n = 12); it was not administered and not required, but not returned to the pharmacy for a credit.
- Alteplase was ordered as 0.5-mg dose, but 1-mg dose sent up by pharmacy and administered (n = 17).
- Alteplase was ordered as 1-mg dose and administered because 0.5-mg dose was not on MAR (n = 5).

Outcomes Updated

Based on the analysis of the 140 doses of alteplase, it was determined that 95 doses were added back in the overall analysis of the effectiveness of the 0.5-mg dose as a result of coding and documentation error. Twenty-six doses of 1-mg alteplase were given off protocol and so were removed from this analysis, but are discussed later. The total number of doses for analysis included 1147. After review, alteplase 0.5 mg/2 mL IV restored patency to non-HD CVADs 93.4% (n = 1071) successfully with 1 dose. Alteplase 1 mg/2 mL restored patency in the remaining 98.6% (n = 68), with 1 failed attempt. Alteplase 1 mg/2 mL restored patency in the remaining 98.8% (n = 80), with 1 failed attempt.

COST ANALYSIS

Cost analysis includes the process of using alteplase 2-mg vials, 50-mg vials (100 doses), and 100-mg vials (100 doses). Cost

may vary per facility, but the team was given cost estimates for a 2-mg vial of alteplase ($89.05) and a 50-mg vial of alteplase ($1211). Once reconstituted and drawn up into 100 doses of 0.5 mg each, the cost for one 0.5-mg dose was equal to $12.11. A 100-mg vial of alteplase ($2577) reconstituted and drawn up into 100 doses of 1 mg each was estimated to cost $25.77.

The cost analysis was estimated for the 1147 doses given in this project. The cost for the 2-mg dose was $102 140.35 (1147 × $89.05). The 0.5-mg alteplase dose was successful in restoring patency in 93.4% of the CVADs that were not patent (n = 1071) at a cost of $12 969.81 (1071 × $12.11). For the catheters that needed a repeat dose, alteplase of 0.5 mg was given without success, with a repeat dose of the 1-mg dose administered in 76 doses. The cost for the 0.5 mg and 1 mg for the repeat dose was $12 969.81 (1071 × $12.11) + $920.36 (76 × $12.11) + $1958.52 (76 × $25.77) = $2878.88. The total cost for the decreased dosing was $12 969.81 (0.5 mg doses) + $2878.88 (0.5 mg and 1 mg repeat dose) = $15 848.69. This resulted in a cost savings of $86 291.66 ($102 140.35 − $15 848.69).

Cost analysis was also conducted on the 80 repeat doses that were administered for failed first attempt. If the initial 80 doses were administered at the original recommended 2 mg of alteplase, the cost would have been $7124.00 (80 × $89.05). When administering the 80 doses under the new protocol with 1 mg of alteplase, after the failed 0.5 mg of alteplase, the total costs were $2061.60 (80 × $25.77). Thus, the cost savings equaled $5062.40 ($7124.00 − $2061.60). The combined total cost savings for the entire project was estimated at $87 465.14 ($82 402.74 + $5062.40).

DISCUSSION

A review of the implementation process identified barriers with outpatient and procedural areas. Within the outpatient service, patients arrive to the area for treatment. One barrier for the outpatient is extended procedure time in the outpatient area with the time needed to obtain alteplase from the pharmacy rather than immediate dispensing of alteplase from an electronic dispensing system. The patient's CVAD is assessed for patency, and when not patent, an order was received to administer alteplase. Normally, the nurse would obtain alteplase from the electronic storage area, mix, and administer immediately. The new method required sending the order to pharmacy and requesting the medication STAT.

The vast size of the campus and the amount of orders the pharmacists received caused varying times of response in receiving the medication for administration. The outpatient areas would receive the dose as soon as the pharmacy could send it, sometimes up to 2 hours later, thus delaying declotting, lengthening the treatment time for the patient, and decreasing productivity. This was a dissatisfier for both the patient and the nurse. Options for the areas included ordering a medication freezer for storage of this medication and having 1 dose on standby on the unit for the shift for patients who might require the medication.

Another point of discussion of the efficacy of the reduced dose is the overall effectiveness of the medication. For example, the reduced dose worked 93.4% of the time, but how often did the lower dose need to be repeated in the following days compared with the 2-mg dose? For example, did the lower dose need to be repeated more frequently compared with the 2-mg dose of alteplase? These data were not officially tracked during this pilot but were reviewed after data collection.

The data were reviewed for repeat doses before and after the implementation of the lower-dose alteplase. A review of the amount of doses of alteplase did not show an increase in number when converting from 2 mg to 0.5 mg. The vascular access team also reviewed activity for declotting CVADs and did not notice an upward trend in call for declotting CVADs.

The project was presented to the system pharmacy team and recommended for implementation for the system as a best practice. The reduced dose of alteplase was added to a CVAD care set for care and maintenance of a CVAD. On insertion of a CVAD, the order for alteplase is not routine, but the order for alteplase in a decreased dose is now on an order set ready for implementation with an order from a physician.

CONCLUSIONS

A decreased dose of alteplase is effective in restoring patency to nonpatent non-HD CVADs. The cost of restoring patency to a nonpatent non-HD CVAD with a decreased dose proved to be an effective cost savings.

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