Efficacy and safety of a single 2 mg dose or 4 mg double dose of alteplase for 50 occluded chest ports using a unique instillation technique

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PURPOSE: To evaluate the effectiveness and safety of a single 2 mg dose or a 4 mg double dose of alteplase for restoring function in occluded chest ports.

METHODS: A prospective, open-label, nonblinded study was performed on 40 enrolled patients with a total of 50 chest ports at the Henry Ford Hospital Interventional Radiology Department (Detroit, Michigan, USA). Alteplase (Cathflo Activase; Genentech, USA), a recombinant tissue plasminogen activator produced by recombinant DNA technology, was used to restore the function of 50 occluded chest ports. Occlusion was defined as the inability to withdraw blood freely from the port, or the inability to flush the port easily. A 2 mg (2 mL) dose of alteplase was injected into the port through a Huber needle, using a gentle push and pull technique, and was left to dwell for 30 min. If the port remained

occluded after the initial 2 mg alteplase treatment, an additional 2 mg alteplase treatment was administered with the same dwell time of 30 min. If a port had remained occluded despite the above regimen, this outcome would have been considered a failure and the chest port would have required surgical intervention. However, all ports were successfully treated, and no surgical intervention was required. The safety end points included minor or major hemorrhages, such as intracranial hemorrhages, or sepsis. Safety end points were determined by a 24 h follow-up telephone call.

RESULTS: Of the 50 chest ports (30 single ports and 10 double ports) treated with alteplase, 36 required 2 mg (72%) and 14 required 4 mg (28%). The efficacy end point was 100% for all chest ports treated, without any adverse events.

CONCLUSION: High efficacy and safety rates of restoring function in occluded chest ports were obtained with 2 mg or 4 mg doses of alteplase. Part of this high efficacy rate may be due to the gentle push and pull technique used in the present study.

Key Words: Alteplase; Chest port; Instillation; Occlusion

There has been a dramatic increase in the implantation of chest ports by interventional radiologists for long-term venous access (1). Interventional radiologists have achieved high rates of placement success and fewer complications primarily due to their experience with ultrasound and fluoroscopy. Referring physicians value the promptness in which the radiology department can perform the procedure, in contrast with surgical services that often have busy operating room schedules. The two most common complications associated with chest ports are occlusions and infections (2,3). Occlusion of chest ports can delay treatment and can be a source of frustration for the patient and caregiver. The standard treatments of port occlusion are revision, removal or replacement, all of which expose the patient to additional risks such as bleeding and infection. Therefore, finding non-invasive ways to salvage the ports is very important in minimizing the disruption of care. In the past, thrombolytic therapy was used as the standard of care to restore flow to occluded central lines and chest ports.

Before 1998, the only thrombolytic agent approved by the United States Food and Drug Administration for catheter clearance was human-derived urokinase (Abbokinase Open-Cath; Abbott Laboratories, USA). However, the product was withdrawn from the market in November 1998 (4). In

September 2001, the Food and Drug Administration approved the use of alteplase (Cathflo Activase, 2 mg/vial; Genentech, USA) for the indication of restoring function to central venous access devices, as assessed by the ability to withdraw blood from the device (5). The approval was based on the pivotal phase 3 Cardiovascular Thrombolytic to Open Occluded Line (COOL)-1 and COOL-2 trials (6,7).

The aim of the present study was to assess the efficacy and safety of a single 2 mg dose or a 4 mg double dose of alteplase for restoring function of occluded chest ports in a prospective, nonblinded, open-label clinical study using a gentle push and pull instillation technique.

METHODS

Study design

From November 2002 to February 2005, 40 patients with occluded chest ports (a total of 50 chest ports) were enrolled in the Henry Ford Hospital Interventional Radiology Department (Detroit, Michigan, USA). The present study was approved by the institutional review board. The study was prospective, open-label and nonblinded. Alteplase, a recombinant tissue plasminogen activator produced by recombinant DNA technology, was used to restore the function of the 50 occluded chest ports. Occlusion was defined as the inability

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TABLE 1
Broad categories of chest port patients

Category	Patients, n
Malignancy	
Blood	10
Lymphatic	4
Organs	11
Metastatic	6
Infections/analgesics	9

Infections/analgesics indicates a combined group that includes patients with infections and patients taking analgesics

to withdraw at least 5 mL of blood freely from the port, or the inability to flush the port easily.

Inclusion criteria

Patients were eligible for the present study if they had an occluded chest port, were older than 18 years of age, had the ability to provide written consent and were willing to comply with study requirements.

Exclusion criteria

Patients were excluded from the present study if they met any of the following criteria: any evidence of mechanical, non-thrombotic occlusion of the port; patients younger than 18 years of age, known hypersensitivity to alteplase or any component of the formulation; patients who received any fibrinolytic agent within 24 h of enrollment; patients with known right-to-left shunt, patent foramen ovale, or atrial or ventricular septal defects; patients considered to be at high risk for bleeding or an embolic event (eg, recent pulmonary embolism, deep vein thrombosis, endarterectomy); patients with internal bleeding, superficial bleeding from a venous cutdown or arterial puncture; and pregnant patients. The presence of mechanical occlusion was evaluated by review of a recent chest radiograph. Nonthrombotic occlusion, such as the presence of a fibrin sheath, was suspected if the chest port could be infused but not aspirated.

Treatment protocol

The chest ports were treated with 2 mg (2 mL) of alteplase per dose, to a maximum of two doses. Injections were delivered through a Huber needle. The indwell time for the first dose was 30 min. If at this time the port remained dysfunctional (the inability to freely withdraw at least 5 mL of blood from it), then a second 2 mg dose of alteplase was administered and the chest port was reassessed after an additional 30 min (60 min from the time of administration of the first dose). This was considered a secondary outcome measure. A third dose was not part of the study and was not used. The safety end points included all minor or major hemorrhagic events, such as intracranial hemorrhage, and sepsis. Safety end points were determined by a 24 h follow-up telephone call.

Statistics

For the present study, it was assumed that each port was independent. The success rate was estimated, along with its 95% CI, assuming an exact binominal distribution.

Figure 1) Reconstitution of recombinant tissue plasminogen activator 2 mg with 2.2 mL of sterile water in a 3 mL syringe

Study population

The patient population included 21 men (52.5%) and 19 women (47.5%). The ages ranged from 27 to 81 years. The mean age was 54.4 years. Body weight varied from 46.8 kg to 129.5 kg. The average body weight was 80.5 kg. There were 28 white patients (70%) and 12 black patients (30%). The length of time the chest ports were in place at the time of treatment ranged from 0.1 to 132 months. The average length of time the chest ports were in place was 16.1 months. The majority of patients had chest ports placed for chemotherapy (77.5%) with the following conditions: glioblastoma multiforme, acute myelogenous leukemia, multiple myeloma, non-Hodgkin's lymphoma, breast cancer, rectal cancer, ovarian cancer, Kaposi's sarcoma, nasopharyngeal carcinoma, squamous cell carcinoma, appendiceal adenocarcinoma and chronic myelogenous leukemia. The population also included patients with sickle cell disease and bilateral lung transplants (Table 1).

RESULTS

A port was considered patent if 5 mL or more of blood could be withdrawn freely following lytic instillation. Patency was established successfully in 50 chest ports – an efficacy rate of 100% (95% CI 92.8% to 100%). Of the 50 chest ports (30 single ports and 10 double ports) treated with alteplase, 36 required 2 mg (72%) and 14 required 4 mg (28%). The success rate for one dose of alteplase (2 mg) was 72.0% (95% CI 57.5% to 83.8%). An average of 1.3 doses of alteplase were administered to the 40 enrolled patients. There were no adverse effects cited.

DISCUSSION

High efficacy and safety rates can be obtained in restoring the function of occluded chest ports with a 2 mg or 4 mg dose of alteplase. Part of this high efficacy rate may be due to the gentle push and pull technique used by the interventionalists in the present study.

In this technique, 2 mg of alteplase is reconstituted with 2.2 mL of sterile water in a 3 mL syringe (Figure 1). The Huber needle is then inserted into the chest port (Figure 2). A three-way stopcock is attached to the Huber needle hub, an empty

Figure 2) Insertion of the Huber needle into the chest port

Figure 4) Aspiration with a 10 mL syringe until the plunger is at the 8 mL or 9 mL mark. This step may be repeated to create greater negative pressure

Figure 3) (A) Attachment of a three-way stopcock into the Huber needle hub with the stopcock to the port turned off. **(B)** Attachment of an empty 10 mL syringe to the remaining stopcock port opposite the chest port. The top port is then turned off

10 mL syringe is attached to the stopcock port opposite the chest port and the remaining stopcock port is turned off (Figures 3A and 3B). A 10 mL syringe is then aspirated until the plunger is at the 8 mL or 9 mL mark to create negative pressure; the stopcock is then turned off (Figure 4). This step

Figure 5) Attachment of the 3 mL syringe with the recombinant tissue plasminogen activator (rt-PA) to the top port of the three-way stopcock. Using a gentle push and pull technique, rt-PA is instilled into the port. A small amount (0.1 mL to 0.2 mL) of rt-PA in the port is enough to start the process of clot lysis, allowing additional space for further instillation of rt-PA to a total dose of 2 mg (2 mL)

may be repeated to create greater negative pressure. In our experience, the placement of a 10 mL syringe in this location facilitates the production of negative pressure in a stable and safe manner. A 3 mL syringe with 2 mg alteplase is attached to the top port of the three-way stopcock. Using a gentle push and pull technique, alteplase is instilled into the port. A small amount (between 0.1 mL and 0.2 mL) of alteplase in the port is enough to start lysis and allow additional space for instillation of alteplase to a total dose of 2 mg (Figure 5). After instillation, the stopcock to the port is turned off, allowing the alteplase to dwell in the port for 30 min without interruption (Figure 6). The top port of the stopcock is turned off, and the port is aspirated with a 10 mL syringe to check for at least 5 mL of blood return (Figure 7). If there is no blood return, an additional 2 mg alteplase is instilled into the port. After an additional 30 min, patency is once again assessed. If patency is restored, 5 mL of blood is aspirated to clear the port of

Figure 6) After instillation of the recombinant tissue plasminogen activator (rt-PA), the stopcock to the port is turned off, allowing the rt-PA to dwell in the port for 30 min without interruption

alteplase. The port is then flushed with 10 mL of normal saline using a pulsing method. This is followed by 500 units of heparin (5 mL). The syringe is detached while infusing the last 1 mL of heparin and applying continuous positive pressure.

We believe that the administration of alteplase into the chest port with a gentle pull and push technique is responsible for the high efficacy rates seen in our study. The efficacy may be the result of the negative pressure created that allows a small amount of lytic agent into the port to start lysis. Since the present study, we have restored the function of several occluded chest ports that had failed alteplase treatment attempted by the nurses from our chemotherapy clinic.

In our study, patients received either 2 mg or 4 mg of alteplase in the port and catheter. A small amount of alteplase may have been administered into the systemic circulation. If alteplase is administered according to the study protocol, the circulating plasma level is not expected to reach pharmacological concentrations (8). The most frequent complication of systemic thrombolysis is bleeding. There was no incidence of

Figure 7) The stopcock to the top port is turned off and the line is aspirated to check for at least 5 mL of blood return. Steps 5 to 7 are repeated if there is no return of blood, or return is sluggish. If patency is restored, 5 mL of blood are aspirated to clear the line of recombinant tissue plasminogen activator. The line is then flushed with 10 mL of 0.9% weight/volume normal saline twice, using a 10 mL syringe, by a pulsing method. The flush is followed with 500 units (5 mL) heparin. The syringe is detached while infusing the last 1 mL of heparin and applying continuous positive pressure

bleeding with 2 mg or 4 mg of alteplase in our study, which only included patients with a low risk of bleeding. Thus, one or two doses (2 mg per dose) of alteplase are highly effective and safe in restoring the function of occluded chest ports when administered using a gentle push and pull technique.

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