Prevention and Treatment of Thrombosis Associated With Long-Term Hemodialysis Catheters

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Soft, cuffed, central vein hemodialysis catheters are used in about 20% of chronic hemodialysis patients in the United States, because long-term arteriovenous blood access cannot be maintained in an aging patient population with a large proportion of diabetics. The most frequent complication of these catheters is thrombosis.

The treatment of catheter-related thrombosis is difficult and expensive; thus the emphasis should be on prevention. The preferred material for a long-term catheter is silicone rubber, since it is the least thombogenic. Anticoagulation should be more vigorous during "catheter dialysis" than during "fistula dialysis." Heparin is the least expensive and most convenient anticoagulant, suitable for over 99% of chronic dialysis patients. The dose of heparin for sufficient anticoagulation depends on many factors, varies widely, and should be established for each patient based on activated clotting time (ACT). ACT should be kept over 270 sec throughout dialysis.

Recently we introduced a method of locking catheter lumina with a predetermined amount of heparin; this heparin is not discarded before the next dialysis, but serves as a loading dose. This saves a number of connections/disconnections and decreases dialysis-associated blood losses. To prevent catheter thrombosis, over 60% of patients require warfarin in sufficient doses to keep the international normalized ratio (INR) between 1.5 and 2.5.

The most common catheter-related thrombus is a peri-luminal fibrin sleeve. Locking the catheter with urokinase to dissolve the clot is of little value, because the bulk of the thrombus is outside the catheter. We have found a high-dose (250 000 U or more) intradialytic urokinase infusion through the venous chamber to be a very efficient and convenient method for dissolving clots. Cumulative success of up to three infusions is over 99%. This obviates the need of catheter stripping or replacement, which is more cumbersome and expensive.

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Key words

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Introduction

Soft, cuffed, central vein catheters are increasingly used as permanent dialysis accesses because of deterioration of results with arteriovenous fistulas in aging dialysis populations with high proportions of diabetics (1,2). Even in patients with good blood vessels, intravenous catheters are implanted during maturation periods of arteriovenous fistulas or in patients with "needle phobia." According to the USRDS, in 1996, 18.9% of dialyses were performed using cuffed catheter access (3). In 1997, in our center, 22.4% of patients were dialyzed through permanent catheters (4).

The main advantages of catheters are simple, painless on/off dialysis procedures and no need for maturation before the first use. The main disadvantages include high risk of infection and catheter thrombosis. If a catheter does not provide the prescribed blood flow, the dialysis time has to be increased to provide adequate dialysis. Poorly functioning catheters trigger alarms, increase nursing labor, disrupt the dialysis schedule, and increase the cost of therapy. Poor blood flow may be related to insufficient diameters of lumina, malposition of the catheter tip, and thrombosis. To provide blood flow of 400–500 with prepump pressure no less than –350 mm Hg, a minimum inflow lumen diameter must be 2.0 mm at an average catheter length of 40 cm. The catheter tip should be located within a 50-mm range up or down from the superior vena cava/right atrium junction, preferably in the right atrium. Provided that the catheter lumina and tip location are appropriate, the most common reason for poor blood flow is catheter-related thrombosis.

Prevention of catheter-related thrombosis

Because treatment of catheter-related thrombosis is difficult and expensive, major efforts should be directed toward prevention. As early as the mid-19th century, Rudolf Virchow postulated that three factors predispose to phlebothrombosis: hypercoagulable state, vein wall damage, and blood stasis. These three factors are still judged to be the most important and have to be considered in planning preventive measures. With a foreign body in the blood vessel, an additional factor becomes important: the material from which this foreign body is made.

Material

Thrombogenicity of material is crucial in the speed of thrombus formation. Due to high thrombogenicity, prolonged catheterization was impossible with glass, polyethylene, and polyvinyl cannulas. Polyurethane is claimed to be less throm-

bogenic than tetrafluoroethylene. In animal studies, silicone rubber catheters showed the lowest thrombogenicity compared to catheters made of other materials (5). Silicone rubber is a preferred material to prevent catheter-related thrombosis.

Insertion site

The repeated damage to the intima seems to be crucial in thrombosis of cannulated veins. A strong argument for this mechanism is more frequent and massive thrombosis seen with left-sided cannulation where the vein path is more tortuous (6). In the series of Hoshal *et al*. (7) mural thrombi usually formed at the points where the catheter pressed on the vessel wall, particularly where the tip touched on the intima. In choosing the insertion site, these factors should be kept in mind. The jugular route, particularly on the right side, is advantageous since the course of the catheter to the right atrium is almost a straight line, minimizing trauma to the intima. The path from the left jugular vein is more tortuous. Subclavian veins are least favorable because of the tortuous course, particularly on the left side. Besides, the narrow space between the first rib and the clavicle, where the subclavian vein passes, predisposes to vein wall trauma when the catheter is squeezed by movement of the upper extremities.

Heparin

During a hemodialysis procedure, blood comes into contact with the catheter lumina, tubings, drip chambers, and the dialyzer membrane. All these surfaces activate the intrinsic coagulation cascade and, if not counteracted, will cause clot formation in the blood circuit, including the surface of the catheter. Heparin is the least expensive and the most convenient anticoagulant. It prevents coagulation by bonding to antithrombin III, which then complexes with serine proteases of coagulation factors II, IX, X, XI, and XII, resulting in rapid inactivation of theses factors (8). The degree of anticoagulation during dialysis is monitored by measuring the whole blood partial thromboplastin time or the activated clotting time (ACT). The ACT test uses siliceous earth to accelerate the clotting process. Devices that automatically tilt or rotate the tube and detect clot formation facilitate reproducibility of the results. In our center we use the Hemochron (International Technidyne Corporation, Edison, NJ, U.S.A.) to measure the ACT. The device is approved by CLIA for outpatient use in our clinic. Several different anticoagulation targets are used in different centers, but the most common in routine heparin protocol for "fistula dialysis" is to keep the ACT between 200 and 250 sec during dialysis and 170 and 190 sec at the end of dialysis (9). In the "tight" heparin protocol, the ACT is kept between 170 and 190 sec during the entire dialysis (9).

Anticoagulation in "catheter dialysis" must be more vigorous than in "fistula dialysis." Activation of the coagulation system during dialysis predisposes to clot formation on the catheter surface. "Catheter dialysis" requires continuation of efficient anticoagulation until the end of dialysis to prevent deposition of clots on the catheter at that time. Moreover, there is no risk of bleeding from the puncture sites after dialysis as is the case in "fistula dialysis."

If there are no contraindications to systemic anticoagulation, the following protocol is observed in our center. At the start of the first hemodialysis after catheter implantation the patient receives 1000 U of heparin and the ACT is checked within 15 min. The dose of heparin is then given according to the sliding scale:

ACT (sec)	Heparin (U)
>270	None
241–270	1000
221–240	2000
201–220	3000
181–200	4000
161–180	5000
140–160	6000
<140	7000

The ACT is checked every 30 min, and heparin is given according to the sliding scale. The loading dose of heparin for the second dialysis equals the sum of heparin given during the first half of the first dialysis. The ACT is checked every hour and the heparin dose given according to the sliding scale. The loading dose for the third dialysis is adjusted (if needed) to equal the sum of the total dose of heparin during the first half of the second dialysis. ACT is measured every hour during the third dialysis. For the fourth dialysis the loading dose of heparin equals the total dose given during the first half of the third dialysis; the dose at half time equals the sum of doses during the second half of the third dialysis. Four dialyses usually suffice to establish the loading and half-time doses of heparin.

Loading with locked heparin

Traditionally, each catheter lumen is locked with 5000 or 10 000 U of heparin after dialysis. At the start of the next dialysis session, this heparin is aspirated with a small amount of blood and discarded. Discarding the locked heparin results in wastage of about 2.2 mL blood per dialysis session assuming that approximately 3 mL of total volume is aspirated from each lumen. The amount of blood loss may vary depending on the catheter type, but some inadvertent blood wastage occurs. If 3 mL is aspirated per lumen, cumulative blood loss amounts to 340 mL per patient year for thrice-weekly dialysis. If daily hemodialysis is performed, the blood loss would amount to 800 mL. The resultant elemental iron loss and increased requirement of erythropoietin are not inconsequential.

Our recently published study indicates that the locked heparin does not lose more than 15% of the activity up to 72 hours (10). Thus the locked heparin may be used as a loading dose. Our recommended protocol is as follows: after determining the required loading dose of heparin, each lumen

is locked with the half loading dose plus 15%. Before the next dialysis, using 10-mL syringes filled with 7 mL of sterile normal saline, the locked heparin is aspirated but not discarded. This step helps assess catheter function. The locked heparin-saline-blood mixture is injected through each lumen and dialysis is started.

If laboratory tests are desired, a 30-mL syringe is used to aspirate locked heparin (total blood-heparin volume 30 mL) from the arterial side. The extra volume would reasonably avoid interference by heparin with blood test results. The arterial syringe is disconnected but not discarded. Then blood for laboratory work is drawn, and the 30-mL heparin-blood mix is reinfused via the arterial lumen.

Loading with locked heparin decreases the number of connections/disconnections and thus, theoretically, may decrease the risk of bacterial contamination. Administration of locked heparin as the loading dose results in a decrease in blood wastage. The decreased blood wastage should reduce the requirement of iron supplements and probably erythropoietin, leading to cost savings. Additional savings would accrue by avoidance of heparin wastage. At our center, where the usual practice is locking with 10 000 U heparin per lumen, the resultant annual cost saving is approximately $156 per patient for thrice-weekly dialysis. For daily dialysis the saving would increase to $365.

Warfarin

The majority of patients require warfarin to prevent catheter-related thrombosis. In 1997, in our center, of 104 patients dialyzed through catheters, 68 (65%) required warfarin therapy to maintain catheter patency (4). Some patients require only a minimal dose to maintain the international normalized ratio (INR) around 1.0 as recommended by Bern *et al.* (11) for infusion catheters; however, the majority of patients need a higher dose of warfarin to keep the INR between 1.5 and 2.5.

Treatment of catheter-related thrombosis

Types of catheter-related thrombi

There are three kinds of catheter-related thrombi: intraluminal, periluminal (fibrin sleeve, ball thrombus), and mural. Mural thrombi may be infected, causing thrombophlebitis. The clot may migrate to the lung causing pulmonary embolus. In clinical practice, usually the type of thrombus cannot be determined prospectively; however, there are sufficient data to suggest that the most common is a fibrin sleeve. Thus, if there is poor blood flow during dialysis and the catheter has a good tip position, it is prudent to assume the diagnosis of the sleeve thrombus and treat it accordingly (*vide infra).*

Intraluminal clot

Intraluminal clots are common, but may be prevented by locking the lumina with heparin and may be easily displaced or dissolved with thrombolytics. "Locking" of the catheter with urokinase has been a well-established practice to open occluded intravenous catheters for hemodialysis with success rates up to 95 % (12). In this method, 5000 U of urokinase is instilled to each lumen for 30 min and hemodialysis is attempted again (12). Urokinase instillation may be repeated several times (13). In our outpatient dialysis facility this method was used in the late 1980s and early 1990s with a success rate of 40%–50% in catheters occluded a few days or weeks after implantation; however, the catheters usually clotted again in a few days, and repeated "locks" were usually unsuccessful or only partially successful at providing better flow, but not restoring the desired flow. The success rate was markedly lower in catheters occluded several weeks or months after implantation. This method was very inconvenient, because the frequently repeated doses were required and dialysis time was wasted while the patient sat in a chair with a "locked" catheter.

Experience gained while removing catheters, either electively or because of obstruction, indicated that the intraluminal clot is not typically responsible for significant catheter obstruction. The intraluminal clot is usually easily sucked into a syringe after a catheter is removed. Such a clot should not interfere with the blood flow because it would easily be either aspirated into a syringe or pushed into the venous system. The intraluminal clot is probably attached to a clot formed outside the catheter. Such a clot is larger than the catheter lumen and, therefore, cannot be aspirated. The urokinase "lock" works temporarily, because the thrombolytic agent diffuses out of the lumen and dissolves part of the outside clot, but the clot extends to the catheter tip again in a short time.

Periluminal

Fibrin sleeve. Clot formation around the catheter was documented by Bonner in 5 of 18 autopsy cases in 1951 (14). These cases were probably the first documented description of what is known now as a "sleeve thrombus"(15) or "fibrin sleeve"(7). The fibrin sleeve is not visible when the catheter is pulled from the vein, because the sleeve is stripped and remains in the vein or migrates to the lung.

A fibrin sleeve may form within 24 hours after insertion. Hoshal *et al.* (7) found fibrin sleeves at autopsy on all 25 polyethylene and Teflon subclavian vein catheters examined. The sleeves extended from the insertion site up to the catheter tip. In one case the fibrin sleeve was found to persist intact, attached to the point of entrance, 23 days after catheter removal. Microscopically, the fibrin sleeve showed no evidence of endothelialization or organization, but subendothelial proliferation of the vein wall was present adjacent to the adherent fibrin sleeve. It is to be expected that a sleeve reaching the tip may act as a flap preventing blood inflow but allowing blood outflow until the continuing growth of the sleeve causes flow to cease completely.

Because of poor results with the locking method, and considering that the real reason of catheter failure is usually

sleeve thrombus, systemic urokinase infusions were gradually introduced in our outpatient clinic in 1993 following encouraging reports in the literature (16,17). Six-hour (40 000 U/hour) urokinase infusions were used successfully in central-vein infusion catheters after unsuccessful trials of 5000-U boluses by Haire and Lieberman (16). Uldall *et al.* (17) developed a method to restore the patency of double lumen hemodialysis catheters by infusing 250 000 U of urokinase. The authors considered it a safe method to be administered to outpatients provided that heparin is not given simultaneously. A method similar to that of Haire and Lieberman (16), but for hemodialysis catheters, was used by Lund *et al.* (18) and Trerotola *et al.* (19). In catheter failure (flow less than 200 mL/min), if a 5000-U bolus of urokinase was unsuccessful, an infusion of urokinase, 20 000 U per lumen per hour over 6 hours was implemented. Hemodialysis was not carried out during the infusion. The results were similar to those reported by Uldall *et al.* (17). Lund *et al.* (18) reported a 79.5% success rate with single infusion. Trerotola *et al.* (19) reported a 55% success rate with single infusion with duration of patency of 8–70 days (mean 31±22 days) after successful infusion.

In 1993 and 1994 we adopted the method of Uldall *et al.* (17). In cases of a nonpositional catheter malfunction, instead of "locking" the lumina we infused 125 000 U of urokinase over 2 hours through one lumen and then 125 000 U over 2 hours through the other lumen. No dialysis was performed, and no heparin was used during urokinase infusion. The patient was then dialyzed on the next shift. Although this method was more convenient and successful than the "locking" method, the difficulties in scheduling dialysis sessions and patient transportation were still present. If the infusion was given on the evening shift, the patient had to return for dialysis the next morning.

In November 1995 we introduced a new method: high-dose intradialytic urokinase infusion. If there were no contraindications, high-dose (250 000 U) urokinase was infused into the venous chamber over 3 hours during dialysis. Infusion began after heparin had already been administered, and the routine dose of heparin was continued during hemodialysis.

Between November 1995 and April 1997, blood flow was inadequate in 286 of 7179 catheter dialyses (4.0%), and various protocols of urokinase infusion were used. High-dose intradialytic infusions were repeated up to three times if the first infusion was not completely successful. The results of the retrospective analysis of the urokinase treatment have been recently published (4).

In 9 cases where blood could be aspirated or the flow was less than 100 mL/min, high-dose urokinase was used without dialysis with restoration of blood flow in 7 (78%). The number of high-dose intradialytic infusions totaled 231. Cumulative success rate with full restoration of blood flow was achieved in 81% of cases after the first infusion, 95% after the second infusion, and 99.5% after the third infusion. Only one catheter could not be opened after the third infusion. In this case the catheter patency was restored by an interventional radiologist who stripped the fibrin. High-dose urokinase was given after stripping to remove the remnants of the clot.

Catheter stripping as a method of fibrin sleeve treatment was introduced by Knelson *et al.* (20). In this procedure a snare is advanced via the femoral vein up through the inferior vena cava and right atrium to the occluded catheter. The snare is looped over the catheter, tightened, and pulled down to strip the sleeve from the catheter. The sleeve is not recovered, but is taken by the blood flow to the lungs.

The cost of a vial of 250 000 U of urokinase in our outpatient dialysis center is $358.47 and is reimbursable. The remaining cost of administration (syringes, infusion lines, nursing time, etc.) is negligible and is included in the composite rate for dialysis. Catheter stripping or replacement is markedly more expensive and less convenient than the high-dose intradialytic urokinase. In our medical center the charges for catheter stripping total $2433 ($1233 hospital charges plus $1200 professional fee). Catheter replacement by an interventional radiologist averages $1300 (19). Surgical catheter replacement is the most expensive. In our medical center the charges for operating room, supplies, recovery room, and professional fees average $3060. This cost does not include rescheduling of dialysis treatments, transportation, or hospitalization. Moreover, convenience, avoidance of discomfort, and continuation of regular dialysis schedule all favor intradialytic urokinase over radiological or surgical methods of restoring catheter function. Catheter stripping or replacement does not preclude the recurrence of the problem. Haskal *et al.* (21) reported good initial results of the stripping in 24 procedures with recurrence of poor flow rates by the fifth hemodialysis session. They did not use either warfarin or urokinase after successful stripping. High-dose urokinase probably dissolves the remnants of the fibrin sleeve and may help to lyse a potential pulmonary embolus after catheter stripping.

Repeated urokinase infusions also do not solve the problem indefinitely. Those patients who form the fibrin sleeve probably have some form of thrombophilia. Without warfarin, these patients tend to repeatedly form a fibrin sleeve. We do not know whether agents preventing aggregation of platelets and release of platelet granules, like aspirin or ticlopidine, may be useful in preventing catheter clotting.

After the retrospective analysis of the results with high-dose intradialytic urokinase was completed (4), we introduced a few changes in the protocols. In cases where blood cannot be aspirated or the flow is less than 100 mL/min, 250 000 U of urokinase is dissolved in 100 mL of normal saline and infused over half an hour through one lumen; then dialysis is started and infusion is continued during dialysis if a flow higher than 100 mL/min can be achieved. If the flow is less than 100 mL/min, urokinase infusion is continued without dialysis for another half hour, then the dialysis is attempted again. Dialysis is prolonged to compensate for the lost efficiency. In cases where 250 000 U of intradialytic urokinase

does not restore blood flow after three infusions, the dose of urokinase is doubled (500 000 U) and infused over 3 hours during the next dialysis and eventually the subsequent dialysis. In the meantime, the dose of warfarin is adjusted to keep the INR as needed for maintaining the patency of the catheter.

Ball thrombus. Ball thrombus is a large clot adherent to the catheter tip but not to the vessel wall. Such a thrombus is difficult to dissolve. Caruana *et al.* (22) could not dissolve such thrombi with streptokinase and/or urokinase; however, they used rather low doses of thrombolytic agents. Ball thrombus can be removed by stripping. Whether the ball thrombus can be dissolved with high-dose urokinase is not known. Some of the cases of difficult to treat fibrin sleeves in our series could in fact be cases of undiagnosed ball thrombus.

Mural thrombus

A mural thrombus is a large clot adherent to both the catheter and the vessel walls causing partial occlusion of the vessel. Clinical manifestations are rare and occur in 0%–4.8% of cases (23). The patient presents with ipsilateral swelling of the neck and/or arm, venous distention, and pain in the neck and anterior chest wall. Radiologically detectable mural thrombi occur in 20%–30% of patients with soft, cuffed catheters used for chemotherapy or parenteral nutrition. Catheter removal and systemic anticoagulation have been recommended as the treatment of choice (24). Successful attempts have been made to treat mural thrombi without catheter removal. Seigel *et al.* (25), using heparin and urokinase infusion at 25 000 to 120 000 U/hour for 12–24 hours, were able to achieve complete lysis of mural thrombi in 36 of 38 patients with catheters used for chemotherapy (31 cases), antibiotic therapy (4 cases), and parenteral nutrition (3 cases). Moss *et al.* (26), using streptokinase infusion, restored function in six of seven dialysis catheters where venograms showed ipsilateral subclavian vein thrombosis.

Thrombophlebitis

The combination of sepsis and thrombosis may lead to the development of suppurative thrombophlebitis. The clinical features suggesting this diagnosis include: (1) persistent bacteremia after catheter removal despite appropriate antibiotic therapy; (2) absence of evidence of endocarditis; (3) phlebographically demonstrated central venous thrombosis; and (4) clinical and bacteriological response with institution of heparin therapy (27). Lewis *et al.* (28) reported a case of silicone catheter-related sepsis in which antibiotics could not clear the infection, but addition of streptokinase to the antibiotic regimen dramatically changed the course of infection and saved the catheter used for parenteral nutrition.

Pulmonary embolism

Asymptomatic pulmonary embolism must be extremely common with so many thrombotic events associated with chronic catheters. Most of the clots are probably dissolved efficiently in the pulmonary circulation without clinical manifestation because reports on pulmonary embolism are rare (29,30). Bismar *et al.* (31) studied 60 long-term indwelling catheters using fluoroscopy and noted that most of the sleeve thrombi peeled off during catheter removal and were carried away by the blood stream. Most of these emboli were asymptomatic, but there were three instances of clinically symptomatic pulmonary emboli. Winn *et al.* (32) reported a case of significant pulmonary embolus with *Citrobacter freundii* and coagulase-negative *Staphylococcus* sepsis after the stripping of a large fibrin sheath.

Conclusions

The most common cause of nonpositional malfunction of the intravenous hemodialysis catheters is a pericatheter fibrin sleeve. In these cases, high-dose intradialytic urokinase is safe and more effective than locking the catheter with urokinase. The higher cost of high-dose intradialytic urokinase as compared to the catheter "lock" is offset by the high probability of positive results, saving of nursing and patient time, and saving on transportation expenses. The cost of urokinase is reimbursable. Intradialytic urokinase infusion is clearly preferred to catheter stripping or catheter replacement in terms of cost and convenience. Opening of the catheter does not solve the problem indefinitely, since the recurrence of poor flow rates is the rule in those patients who required high-dose urokinase. Without warfarin, these patients tend to deposit fibrin sleeve repeatedly.

Appendix

Urokinase protocol to restore patency of a nonpositional catheter malfunction

As of April 1998 the following protocol has been used in our outpatient clinic:

Low-dose urokinase

Day 1 to 3 postcatheter implantation or other surgery. If blood cannot be aspirated or the flow is diminished, the lumina are filled with urokinase in sufficient quantity to reach the tip of the catheter but avoiding injection into the systemic circulation (5000 U per 1.6 mL for PermCath). After 60 min the urokinase is aspirated. The urokinase injection may be repeated up to two times if needed. For repeated injections, 9000 U of urokinase dissolved in normal saline (NS) is used.

Days 4 to 6 postcatheter implantation or other surgery. If blood cannot be aspirated, 10 000 U of urokinase is diluted in 5 mL of NS and injected into each lumen. Depending on the catheter capacity, this results in injection of 13 000 to 15 000 U of diluted urokinase into the systemic circulation. After 30 min dialysis is attempted without aspirating urokinase from the lumens. If flow is intermittent and/or triggers alarms, hemodialysis is stopped and urokinase injections are repeated up to two times.

If dialysis can be started but flow is less than intended, 18 000 or 20 000 U of urokinase is injected into systemic circulation (through the venous drip chamber) and dialysis is continued. An additional bolus of 18 000 to 20 000 U of urokinase may be injected into systemic circulation.

High-dose urokinase

This protocol is used in patients who are more than 6 days postimplantation or surgery (other than intracranial).

No blood flow or intermittent flow less than 100 mL/min. If blood cannot be aspirated or the flow is less than 100 mL/min, 250 000 U of urokinase is dissolved in 100 mL of NS and infused over half an hour through one lumen; then dialysis is started and infusion is continued during dialysis if flow higher than 100 mL/min can be achieved. If flow is less than 100 mL/min, urokinase infusion is continued without dialysis for another half hour; then the dialysis is attempted again. Dialysis is prolonged to compensate for the lost time. If flow is still less than 100 mL/min, urokinase infusion is continued without dialysis and the patient is dialyzed on the next shift.

Prophylactic/Therapeutic high-dose urokinase. If poor blood flow is noted, but stable and at least 100 mL/min, 250 000 U of urokinase is dissolved in 100 mL of NS and infused slowly to the venous chamber over 3 hours. A pump blood flow of 400 mL/min, with inflow (prepump, arterial line chamber) pressure not lower than –350 mm Hg, is considered adequate. The infusion is repeated during the next treatment and the following treatment until a desired flow is achieved. In cases where 250 000 U of intradialytic urokinase does not restore blood flow after three infusions, the dose of urokinase is doubled (500 000 U) and infused over 3 hours during the ensuing dialysis and eventually the subsequent dialysis.

Patients who require high-dose urokinase treatments are started on warfarin anticoagulation; failure to do so results in repeated catheter failure. Typically the INR is kept between 1.5 and 2.5. We have found it convenient and more reliable to give warfarin in the clinic after dialysis for patients who do not take warfarin as prescribed at home.

Contraindications to high-dose systemic urokinase

Absolute contraindications

- Active internal bleeding
- Recent (within 10 days) intracranial or intraspinal surgery, intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent severe trauma
- Severe uncontrolled hypertension

Relative contraindications

- Left heart thrombus
- Subacute bacterial endocarditis
- Catheter-related sepsis
- Pregnancy
- Cerebrovascular disease
- Hemorrhagic retinopathy
- Recent surgery (other than intracranial or intraspinal)
- Recent biopsy or puncture of noncompressible vessel

Monitoring of adverse reactions

Vital signs (pulse, respirations, and blood pressure) are monitored every 15–30 min.

Patients are also observed for possible allergic reactions (skin rashes and bronchospasm) and bleeding.

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