

## Treatment and Prophylaxis of Catheter-Related Thromboembolic Events in Children

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**ABSTRACT** – Purpose. The therapeutic management of catheter-related thromboembolic events in children is still a challenge due to the large number of potentially effective pharmacological alternatives and the insufficient scientific evidence available. A bibliographic review was performed in order to identify the available pharmacological alternatives for the prophylaxis and therapeutic management of catheter-related thrombosis in children. Methods. A literature search was carried out on MEDLINE using the medical subject heading (MeSH) *central venous catheter thrombosis* and on Google Scholar. The search was limited to review papers, meta-analyses, clinical practice guidelines, and randomized controlled trials performed on pediatric populations until November 2011. Results. The different options for anticoagulation include unfractionated heparin, low molecular weight heparin and vitamin K antagonists. Thrombus resolution is stimulated more rapidly with thrombolytic agents than with anticoagulants, but the risk-benefit ratio must be considered. Streptokinase is not considered an optimal alternative due to the risk of anaphylactic reactions and has been replaced by urokinase, alteplase or the newer reteplase. Preventive strategies have been considered and most centers have protocols for routine flushing of the catheter with heparin or normal saline. Intraluminal application of urokinase and alteplase has also been studied. Conclusions. The wide range of options available for the pharmacotherapeutic management of catheter-related thromboembolism in children and the lack of strong evidence on the comparative efficacy and safety of the different therapeutic options, make its positioning rather difficult. Randomized controlled trials and national plans should be set up urgently.

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### INTRODUCTION

Central venous access devices (CVADs) are used in critically ill children and in children with chronic diseases for the administration of fluids, medications, total parenteral nutrition or blood products. The use of CVADs has tremendously improved the quality of care in these children. However, they may also cause several mechanical, infectious and thrombotic complications(1).

Catheter occlusion is defined as a partial or complete obstruction of the catheter that limits or prevents the ability to withdraw blood, flush the catheter, or administer parenteral solutions or medications(2). Thrombotic catheter occlusion accounts for 58% of all catheter occlusions and occurs when deposits of fibrin or blood within and around CVADs impede or disrupt flow through the catheter(3). It is also postulated that the localized vascular injury inflicted by the catheter induces a local prothrombotic state(4). Peripherally inserted central catheters (PICCs) lines may be more prone to thrombotic occlusion than non-PICC CVADs due to their longer length and smaller diameter(5).

Thrombotic catheter occlusion may delay or even interrupt infusion of therapy and may also contribute to the development of CVAD-related infection as the blood clot serves as a culture medium for bacterial growth(6). Potentially serious complications of deep vein thrombosis include recurrent thrombosis, loss of intravenous access, pulmonary embolism, post-thrombotic syndrome and death(7-12). Although the most commonly recognized complication of CVADs is infection(13-16), diagnosis of thrombotic events related to these devices is becoming increasingly prevalent.

Catheter occlusion can be treated in some cases, avoiding possible complications and cost of catheter replacement(5). Few clinical trials have studied prophylaxis of catheter-related thrombosis in children(17). Thromboembolic events in children are still relatively rare compared to adults and hence uniform recommendations regarding indications,

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drug of choice, route of administration and dosing regime are not well established(18). Dose regimes have often been extrapolated from adult guidelines, but the fibrinolytic system in children is a dynamic, evolving system with unique features that markedly influence the response to thrombolytic agents(19). In addition, the pathophysiologic mechanisms of thrombosis in children are very different from those in adults.

The presence of a CVAD is the leading cause for thromboembolic complications in children(20). In neonates, systemic infection is the most common risk after the presence of a catheter(21). A variety of inherited predisposing factors to the development of thrombosis have been described including genetic risk factors such as factor V Leiden, prothrombin 20201A, and protein C and S deficiencies(4). The reported frequency of catheter thrombosis in children ranges from 5%, including only symptomatic cases, to 50%, when patients are systematically screened for catheter-related thrombosis(1).

Since CVADs are increasingly common in the pediatric population, it is of paramount importance to be aware of new information regarding thromboembolic complications of these devices. The objective of this study is to review the literature in order to identify different pharmacological strategies available for prophylaxis and therapeutic management of catheter-related thrombosis in children, and their positioning in clinical practice. This article focuses on the potential indications, efficacy and safety profiles of different therapeutic options. Concentration, reconstitution/dilution and stability of the main anticoagulant and thrombolytic drugs were also considered. We believe this is the first review that analyzes the quality of the existing evidence and grades of recommendation for each therapeutic option in treatment and prophylaxis of catheter-related thromboembolic events in children.

## METHODS

A search was performed on MEDLINE, through PubMed, using the medical subject heading (MeSH) *central venous catheter thrombosis* and on Google Scholar. The search was initially limited to meta-analysis, practice guidelines, randomized controlled trials and review papers performed on pediatric populations up to November 2011. Pertinent articles from reference lists of related papers were also taken into consideration as well as non-randomized controlled trials and series of cases when no information of higher-level evidence was available. In addition, summaries of product characteristics for each drug, the Drugdex medicines database from Thomson Micromedex Healthcare Series and Lexi-Comp ONLINE™ were also reviewed. Quality of the scientific evidence found in literature and associated grades of recommendation were given for each therapeutic option (Table 1).

## RESULTS

### Treatment

The available options for treatment of venous thromboembolism are anticoagulation, thrombolysis and surgery.

### Anticoagulation

The optimal therapy for acute and symptomatic catheter-related thrombosis is prompt removal of the catheter(1, 17). If the catheter cannot be removed, anticoagulation should be initiated at full dosage for 3 months followed by prophylaxis until the device is removed(7, 12). The aims of initial anticoagulation are to prevent extension of the thrombus and subsequent pulmonary embolism(22).

**Table 1.** Quality of the scientific evidence and associated grades of recommendation(84)

#### Classification of evidence levels

- Ia: Evidence obtained from meta-analyses of randomized controlled trials
- Ib: Evidence obtained from at least one randomized controlled trial
- IIa: Evidence obtained from at least one well-designed, non-randomized controlled study
- IIb: Evidence obtained from at least one well-designed, “quasi-experimental” study
- III: Evidence obtained from well-designed, nonexperimental descriptive studies such as comparative studies, correlation studies, and case reports
- IV: Evidence obtained from an expert committee or expert report and/or from the clinical experience of respected authorities

#### Categories of recommendation

- A: Based directly on evidence level I
- B: Based directly on evidence level II or recommendation extrapolated from level I evidence
- C: Based directly in the evidence level III or recommendation extrapolated from level I or II evidence
- D: Based directly in the evidence level IV or recommendation extrapolated from level I, II or III evidence

*Unfractionated heparin*

Unfractionated heparin (UFH) doses used in the treatment of catheter-related thrombosis are: a loading dose of 75 IU/kg in 10 minutes intravenously and maintenance doses of 28 IU/kg/h in children less than 1 year old and 20 IU/kg/h in children older than 1 year(12, 22). Evidence level Ib; Category of recommendation B. Commercially available heparins can be diluted with dextrose 5% or sodium chloride 0.9%. Once diluted, the solution is stable 24 h at room temperature (Table 3).

*Low molecular weight heparin*

Low molecular weight heparin (LMWH) therapy administered twice daily subcutaneously has more reliable pharmacokinetics and requires less monitoring in children than warfarin(17). In

addition, it is at least as effective as UFH and causes fewer bleeding complications(23). Enoxaparin is the most commonly used LMWH and recommended doses are 1.5 mg/kg/12h in children less than 2 months old and 1.0 mg/kg/12h in children older than 2 months with adjustment to achieve anti-factor Xa level of 0.5 to 1 unit/mL(12, 22). Evidence level Ib; Category of recommendation B.

The potential advantages of LMWH for pediatric patients include minimal monitoring requirements, lack of interference from other drugs or diet (compared to vitamin K antagonists), reduced risk of heparin-induced thrombocytopenia and probable reduced risk of osteoporosis with long term use compared to UFH(12).

**Table 2.** Summary of different therapeutic strategies and their evidence level for treatment and prophylaxis of catheter-related thromboembolic events in children

Objective	Therapeutic options	Evidence level	
Treatment	Anticoagulation	Unfractionated heparin	Ib
		Low molecular weight heparin	Ib
		Oral anticoagulants	III
		Streptokinase	III
	Thrombolysis	Urokinase	Ib
		Alteplase	Ib-III
		Reteplase	III
		Surgery	IV
Prophylaxis	Anticoagulation	Normal saline flushes	IV
		Unfractionated heparin	Ia-Ib
	Thrombolysis	Low molecular weight heparin	Ib-IIa
		Oral anticoagulants	Ib-III
		Ib-IIa	

**Table 3.** Concentration, reconstitution/dilution and stability of main anticoagulant and thrombolytic drugs(37, 43, 85-87)

	Concentration	Reconstitution/dilution	Stability
<b>Heparin sodium</b>	1-200 IU/mL depending on indication	Dilution: dextrose 5% or sodium chloride 0.9%	Dilution: 24 h at room temperature
<b>Urokinase (UK)</b>	Maximum concentration not established	Reconstitution: water for injection Dilution: sodium chloride 0.9%	Dilution: 24 h at room temperature
<b>Alteplase (rt-PA)</b>	0.2-1 mg/mL depending on indication	Reconstitution: water for injection Dilution: sodium chloride 0.9%	Reconstituted vial: instant use Dilution: 24 h at room temperature Freezing solutions: -0.25 mg/mL: 1 year at -70°C -0.5, 1 and 2 mg/mL: 14 days at -70 and -25°C Once defrost, no more than 48 h at 2°C

### *Oral anticoagulants*

Treatment with vitamin K antagonists can be initiated together with UFH or LMWH. The duration of this initial therapy should be a minimum of 5 days and heparin can be withdrawn when the international normalized ratio (INR) remains stable and  $>2$ (22). The choice of anti-vitamin K (warfarin, acenocoumarol or phenprocoumon) depends on availability in each country. Safety and efficacy in pediatric patients have not been established in randomized controlled clinical trials, although the use of warfarin for the treatment or prophylaxis of thrombosis is well documented(24). Andrew *et al.*(25) demonstrated that 0.12 to 0.28 mg/kg/day of warfarin to achieve an INR of 1.4 to 1.8 helped the dissolution of the thrombus and increased the catheter lifespan. Evidence level III; Category of recommendation C.

### *Thrombolysis*

Thrombus resolution is stimulated more rapidly with thrombolytics than with anticoagulants, particularly if the clot is relatively acute(26). However, the risk-benefit ratio must be carefully analyzed in each situation since bleeding risk is higher with thrombolytics than anticoagulation alone. Therefore, systemic thrombolysis in infants should be restricted to life, limb or organ-threatening thrombosis, where the benefit of rapid clot resolution outweighs the risk of major hemorrhage. If the catheter is still functioning, the therapy can be directed at the thrombus through the catheter with less systemic toxicity(12, 27). Monagle *et al* (12) suggest against thrombolytic therapy for neonatal venous thromboembolism unless major vessel occlusion occurs; in these cases recombinant tissue-type plasminogen activator (rt-PA) should be used rather than other thrombolytics. The use of thrombolytic therapy in pediatrics has increased despite no established indications for thrombolysis due to the lack of well designed clinical studies(18).

### *Streptokinase*

Streptokinase (SK) is a polypeptide produced by Group C  $\beta$ -hemolytic streptococci(28). Its half-life ranges from 18 to 30 min(29-31). Apart from bleeding, SK can cause immunogenicity leading to allergic reactions such as serum sickness-like reaction, fever, hypotension, urticaria and bronchospasm(32, 33). Therefore, SK is not considered an optimal alternative due to this risk of life-threatening anaphylaxis. In the small number of patients described in literature, doses of 1,000-2,000 IU/kg/h have been

administered(34, 35). Evidence level III; Category of recommendation C.

### *Urokinase*

Urokinase (UK) is a serine protease isolated from human urine and fetal kidney cell cultures(36) and its half-life varies from 9 (administration as a bolus) to 16 minutes (administration as a continuous infusion)(37).

UK has been the drug of choice for treating thrombotic catheter occlusions restoring its patency with a single dose of 5,000 IU/mL in a volume to fill the catheter (2 mL/lumen in CVADs or 3 mL in Port-A-Caths)(18). After 2-4 h an attempt to infuse and withdraw samples is performed. A second attempt may be considered if the first one is unsuccessful. Evidence level Ib; Category of recommendation A. Thrombus dissolution with local UK infusion has been effective in some patients, but not in others requiring multiple rounds of UK infusion, with rates of success ranging from 0 to 88.9%(38).

The standard regime for thrombolysis includes a bolus of 4,400 IU/kg followed by a continuous infusion of 4,400 IU/kg/h during 6-12 h(26, 39). Longer courses have also been administered in clinical practice. However, there are numerous dosing strategies for UK used in pediatrics and doses vary if administered systemically [bolus of 7,000 (4,400-50,000) IU/kg and infusion of 5,500 (2,000-50,000) IU/kg/h] or catheter-directed [bolus of 4,400 (4,000-10,000) IU/kg and infusion of 5,000 (2,000-120,000) IU/kg/h](18). In a more recent review a 3-h infusion dose of 1,000 IU/kg/h has also proved to be effective(40). To date insufficient evidence is available to recommend catheter-directed administration over systemic thrombolytic therapy, even if increased lytic success rates and decreased risk of bleeding complications may occur with catheter-directed administration.

UK is still available in Europe, but has been replaced in the United States by the recombinant urokinase (r-UK), which has been proved to be safe and effective in reestablishing patency of occluded CVADs in both pediatric and adult patients(41). In this multicenter study 5,000UI/mL r-UK was administered intracatheter. Commercially available UK vials must be reconstituted with water for injection and diluted to the desired concentration with sodium chloride 0.9%. This solution is stable 24 h at room temperature (Table 3).

### *Recombinant tissue-type plasminogen activator*

Recombinant tissue-type plasminogen activator (rt-PA) or alteplase is a serine protease produced by endothelial cells(42) with a half-life of 4-5

minutes(43). Some studies have analyzed the use of rt-PA to restore CVADs patency with doses varying from 0.5 to 2 mg in 2 mL for a dwell time of 20 to 240 minutes(44-47). A second attempt can be considered if necessary(18). Evidence level III; Category of recommendation C.

Protocols for local instillation of alteplase to restore patency have been recently published(2, 12, 48). In a double-blinded randomized trial published by Haire WD *et al.*(49) which included adults and children, 2 mg of rt-PA resulted more efficient than UK in restoring catheter patency. Evidence level Ib; Category of recommendation A. Two rt-PA dosing regimens are frequently used for systemic thrombolytic therapy(50, 51). The high-dose regime may be used when rapid clot resolution is necessary, i.e, in life or limb-threatening events. It consists of a continuous infusion of 0.5-0.6 mg/kg/h and an assessment of the thrombus after 6 h. A second 6-h infusion may be administered if the response is not adequate. Evidence level III; Category of recommendation C. The low-dose regimen can be administered for a longer period of time (48-96 h). The starting dose in this second option is 0.03 mg/kg/h, with an hourly maximum dose of 2 mg(52, 53). Evidence level IIa; Category of recommendation B. Venous thromboembolisms may respond better to this low-dose regime, as the thrombus can be lysed slowly(50, 54, 55). Increasing evidence suggests that the low-dose regime may be at least as effective as standard doses and related to fewer bleeding events(18, 55). As in the case of UK, reported doses of rt-PA in literature also vary if administered systemically [bolus of 0.2 (0.0-0.8) mg and infusion of 0.435 (0.01-3.75) mg] or catheter-directed [bolus of 0.5 (0.0-0.5) mg and infusion of 0.08 (0.015-0.2) mg](18).

Although systemic thrombolysis with rt-PA appears to achieve a slightly higher response rate, an increased risk of bleeding complications, especially with the high-dose regime, has been observed as compared to SK or UK(18). Therefore, it is essential to use this drug with caution in patients with bleeding disorders or who are at risk of bleeding(2). Commercially available alteplase vials must be reconstituted with water for injection and diluted with sodium chloride 0.9%. This solution is stable 24 h at room temperature, but can be stored for a longer period of time if frozen (Table 3).

#### *Retepase*

Retepase is a new recombinant tissue plasminogen activator similar to rt-PA but with some structural domains missing(2, 22). This structure results in improved thrombus penetration. Efficacy and safety of this new drug

have been studied in children with cancer(56). The dose of reteplase was started at 0.1 IU and increased incrementally by 0.1 IU to a maximum dose of 0.4 IU. Evidence level III; Category of recommendation C. Reteplase seems to have similar efficacy as rt-PA, but requires shorter dwell times. However, prospective randomized trials are necessary to confirm this hypothesis.

#### **Surgery**

Surgical clot removal and vessel reconstruction may be indicated if life or limb threatening arterial thromboembolism or massive venous thrombosis occur(57). Evidence level IV; Category of recommendation D. With regard to the genetic predisposing factors, for neonates with clinical presentations of homozygous protein C deficiency, administration of fresh frozen plasma (10-20 mL/kg every 12 h) or protein C concentrate, when available (20-60 IU/kg) are recommended until resolution of clinical lesions(12). After initial stabilization, long-term treatment with vitamin K antagonists, LMWH, protein C replacement or liver transplantation are suggested.

#### **Prophylaxis**

To decrease the incidence of catheter-related thrombosis and subsequent complications, many preventive strategies have been studied. However, clinical studies of prophylaxis for catheter-related thrombosis are inconclusive and no definitive recommendations can be made(1).

Decisions regarding the use of prophylactic anticoagulation must be based on the prothrombotic risk associated with a specific condition and the morbidity resulting from a thrombotic event(58).

#### *Normal saline flushes*

Using a normal saline flush before and after administration of blood, blood products, and medications; before and after blood sampling; and at each tubing change is recommended to minimize catheter-related occlusions(59). Evidence level IV; Category of recommendation D.

#### **Anticoagulation**

##### *Unfractionated heparin*

Most centers have protocols for routine flushing of the catheter with UFH or normal saline, but no studies have shown a difference in effectiveness between these two approaches(60-62). A recent study in pediatric oncology patients showed no difference in the incidence of catheter-related thrombosis between the two study arms: once weekly flushing with saline solution via a

positive-pressure cap and twice-weekly flushing with 200 IU/mL UFH via a standard cap(63). However, more catheter-occlusions and catheter-infections occurred in the normal saline arm. Evidence level Ib; Category of recommendation A. The use of 100 IU/mL heparin flush is not recommended for use in neonates(24). With regard to heparin-bonded catheters, in a study with 50 children in an intensive care unit, which compared a heparin-bonded vs a standard femoral venous catheter, the first approach was far more effective(64). These results were consistent with a study published by Pierce CM *et al.*(65), but not with the randomized controlled trial carried out by Anton N *et al.*(66). The use of heparin-bonded catheters in children for prolonging patency seems promising, but further studies are warranted(67). Evidence level Ia; Category of recommendation A.

In a meta-analysis mainly based on adults and conducted by Randolph *et al.*(68) to assess the benefit of heparin in central venous and pulmonary artery catheters, systemically and catheter-bonded heparin was beneficial in preventing catheter occlusion. Evidence level Ia; Category of recommendation A. In neonates, Shah PS *et al.*(69) proved that a heparin infusion at 0.5 IU/kg/h prolonged the duration of peripherally inserted central venous catheter usability compared to placebo. Evidence level Ib; Category of recommendation A. On the other hand, in the recent work carried out by Schroeder AR *et al.*(70) a continuous infusion of heparin at 10 IU/kg/h was safe but did not succeed in reducing catheter-related thrombus formation in infants. Evidence level Ib; Category of recommendation A.

The addition of 1 IU/mL heparin to the parenteral nutrition (PN) solution is controversial, since there are studies with a high evidence level, but with contradictory results. A randomized controlled trial demonstrated no benefit in preventing thrombosis(71). However, a recent study published by Uslu S *et al.*(72) concluded that in neonates with CVADs, low-dose continuous infusion of 0.5 IU/kg/h within the PN is an effective measure to reduce catheter occlusion. Evidence level Ib; Category of recommendation A. A disadvantage of heparin is potential appearance of heparin induced thrombocytopenia and loss of bone mineral.

#### *Low molecular weight heparin*

In pediatric oncology patients, Mitchell *et al.*(73) concluded that LMWH (1 mg/kg/24 h enoxaparin) may help to prevent catheter-related thrombosis in high-risk patients. Evidence level IIa; Category of recommendation B. Monagle *et*

*al.*(12) recommend prophylactic doses of enoxaparin of 0.75 mg/kg/12h in children less than 2 months old and 0.5 mg/kg/12h in children older than 2 months. However, they warn against the use of routine systemic thromboprophylaxis for children with CVADs. Evidence level Ib; Category of recommendation B.

#### *Oral anticoagulants*

Very low doses of warfarin (1 mg daily beginning 3 days before catheter insertion and continuing for 90 days) have been shown to be effective in reducing catheter-related thrombosis in adult patients(74). Evidence level Ib; Category of recommendation A.

In a study with children on home PN, warfarin increased the patency of the catheter from 161 to 351 days and no new thrombosis and major bleeding episodes occurred(75). Evidence level III; Category of recommendation C. The main drawback of this work was the small sample size, only 8 patients. The pharmacokinetics of chemotherapeutic agents, antibiotics and other medications may be greatly affected by the administration of warfarin(76-78). Recent studies of low-dose warfarin do not support its use in prophylaxis of catheter occlusions(79). Evidence level III; Category of recommendation C. Prophylactic flushes with heparin or saline are the standard of care to maintain the patency of CVADs(2). New oral anticoagulants, such as direct factor Xa or thrombin inhibitors, which can be given in fixed doses with little monitoring in comparison with the conventional oral anticoagulants, may be promising.

#### *Thrombolysis*

Children receiving intraluminal application of UK (10,000 IU in each catheter lumen for 4 h) once a week showed a decreased rate of catheter occlusion compared to children without prophylaxis, and no hemorrhagic complications were observed(80). Evidence level IIa; Category of recommendation B. In the prospective study published by Dillon PW *et al.*(81) 5,000 IU/mL of UK every two weeks significantly decreased the rates of occlusive events compared to 100 IU/mL of heparin. Evidence level Ib; Category of recommendation A.

With regard to rt-PA, in a randomized controlled trial comparing alteplase vs heparin for maintaining the patency of paediatric central venous haemodialysis lines(82), 1 mg/mL of alteplase was significantly more effective than 5,000 IU/mL of heparin in preventing clot formation. Evidence level Ib; Category of recommendation A.

**Other strategies**

Jacobs BR *et al.*(83) failed to demonstrate that a nitroglycerin infusion reduced the incidence of catheter-related thrombosis in children. Evidence level Ib; Category of recommendation A.

**DISCUSSION**

Catheter thrombotic occlusions and catheter-related thrombosis in pediatric patients have become increasingly prevalent in the last years. However, present data are inconclusive and further research is necessary for more clearly defined guidelines and recommendations as regards both treatment and prophylaxis of catheter-related thromboembolism in pediatric patients. Due to the wide variety of options available for the pharmacotherapeutic management and until more evidence on the comparative efficacy and safety of the different drugs is found, therapeutic positioning is based on the authorized indications, commercial availability of the different agents, clinical experience, associated costs and patient specific characteristics, i.e., age or bleeding risk. Randomized controlled trials and national plans should be set up urgently.

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