

THE THROMBOEMBOLIC DISEASE IN CHILDREN (II) (TREATMENT AND MANAGEMENT)

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ABSTRACT

Thrombosis is the result of an imbalance between two complex systems: hemostasis and fibrinolysis. Although the incidence of thromboembolism is lower in children than in adults, the associated morbidity is clinically relevant. This paper summarizes the main risk factors, important to define effective strategies for primary thromboprophylaxis in children at risk, the diagnostic criteria and the optimal therapeutic approach, which, until now, have mostly been extrapolated from the adult's recommendations.

Keywords: thrombosis, child, anticoagulant therapy

The management of thromboembolism in children is complex and sometimes difficult, due to the lack of widely accepted specific protocol. Consequently, therapeutic decisions are based on the experience in adult pathology and on minor paediatric studies. Recent studies continue to demonstrate the differences in pharmacokinetics, dose-dependent response and monitoring tests for the anticoagulant therapy in children, as compared to adults (1).

The main goals of the antithrombotic therapy are removing the thrombus and reducing the risk of recurrence. Therapeutic options includes: heparin, oral anticoagulant and thrombolytic therapy, depending on the magnitude of thromboembolism. However, there is very limited available data on the efficacy and safety of therapeutic methods and doses used in paediatric practice (2).

PHARMACOLOGICAL TREATMENT

Anticoagulant therapy

While in adults' initial therapy with heparin followed by vitamin K antagonists therapy is the most common choice, in children, choosing agents depends on age, compliance and co-existing conditions (2).

Unfractionated heparin (UFH) is the most commonly used first-line therapy in paediatric patient (3,4). UFH is used as initial therapy when

rapid anticoagulation action is required. The action of heparin is based on the potentiation of antithrombin III action by binding to it, to inactivate thrombin and the factor Xa in the coagulation cascade (5).

The therapeutic range used for the treatment of thrombosis in children is extrapolated from the adult use. An initial bolus of heparin, not exceeding 75-100 U/kg, should be followed by continuous infusion at doses in accordance with the patient's age and weight (Table 1) (1). Continuous administration of heparin is therapeutically superior to intermittent administration every 4h.

The monitoring of UFH therapy is achieved by determining the activated partial thromboplastin time (aPTT). Modern tests are based on chromogenic anti-fXA tests that directly measure the inhibitory effect of heparin-antithrombin complex on fXA. Clinical guidelines recommend maintaining aPTT values 1.5-2.5 times higher than the control value, an equivalent level of anti-FXA 0,35-0,7U / ml (1,2).

Diaz R. (2015) suggested that antithrombin may be an adjunct to the treatment with UFH. Higher values of anti-fXA were recorded in children treated with this combination, unlike those receiving only heparin, but larger trials are needed so as to establish the stark benefits of using antithrombin together with heparin (6).

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TABLE 1. Heparin: doses and monitoring

	Unfractionated Heparin	LMWH			
		Enoxaparin (1 mg = 100 U)	Reviparin	Dalteparin	Tinzaparin
Loading dose	75 U/kg i.v. over 10 min Adolescents: 80 U/kg				
Maintenance dose	<1 year: 28 U/kg/h iv Children >1 year: 20 U/kg/h iv Adolescents: 18 U/kg/h	Age < 2 months: 1.5 mg/kg/dose each 12 h sc Age >2 months: 1 mg/kg/dose each 12 h sc	Weight <5 kg: 150 U/kg/dose each 12 h sc Weight >5 kg: 100 U/kg/dose each 12 h sc	129±43 U/kg/ dose each 24h	0-2 months: 275 U/kg/dose every 24h; 2-12 months: 250 U/kg/dose 1-5 years: 240 U/kg/dose 5-10 years: 200 U/kg/dose 10-16 years: 175 U/kg/dose
Prophylactic dose		< 2 months: 0.75 mg/ kg/dose q12 h sc >2 months: 0.5 mg/ kg/dose q12 h sc	<5 kg: 50 U/kg/ dose each 12 h sc >5 kg: 30 U/kg/ dose each 12 h sc	92±52 U/kg/ dose each 24h	
Target range - Monitoring	APTT between 60-85 sec. ! Repeating APTT after 4 hours of the initial loading dose and 4 hours after each change in the infusion rate.	Determine anti-factor Xa level 4-6 hours after subcutaneous administration Optimal level 0,5-1 U/ml anti-factor Xa			
Dose adjustments	APTT < 50 50-59 60-85 86-95 96-120 > 120	Dose + 10 % + 10 % 0 - 10% - 10% - 15%	Anti- fXa U/ml < 0.35 0.35-0.49 0.5-1.0 1.1-1.5 1.6-2.0 >2.0	Dose + 25 % + 10 % 0 - 20% Wait until anti-fXa < 1.0 U/ml, then - 30% Wait until anti-fXa <0.5 U/mL, then - 40%	
Duration of therapy	VTE: 5-10 days; PE: 7-10 days.	Initial therapy: 5-10 days Extended Treatment: First episode: 1. with reversible risk factor: 3-6 months 2. idiopathic: 6-12 months; 3. with chronic clinical risk factor: 12 month- lifelong. Recurrent episode: 1. with reversible risk factor: 6-12 months; 2. idiopathic: 12 month- lifelong; 3. with chronic clinical risk factor: lifelong.			

Modified after Guyatt et al. (2012), Dijk et al. (2012) and Seth (2009).

The advantages of using UFH are its fast coming into effect and its short half-life. The disadvantages include the need for continuous venous administration and the impossibility of establishing an optimal dose with clinical response, due to heparin binding to plasma proteins (3). Compared with low molecular weight heparin (LMWH), the disadvantages are related to the route of administration (intravenous, opposed to the subcutaneous LMWH), the need to frequently monitor and its poor bioavailability (2).

The major effect of UFH therapy is primarily bleeding, whose rate of occurrence is 2 to 18%, followed by heparin-induced thrombocytopenia (HIT) (5). HIT appears in the 6th-12th day of treatment, with platelet returning to normal after about 4 days after treatment interruption. It is recommended to

stop the treatment with any form of heparin and other anticoagulant molecules, such as danaparoid, hirudin or argatroban (7). The pathogenic mechanism of thrombocytopenia consists of forming antibodies against heparin-platelet F4 complex (or heparan sulfate platelet-F4), resulting in an immune complex which reacts with platelet Fc receptors. This causes increased platelet destruction and activation of platelets (risk of thrombosis) (8).

Bleeding requires cessation of UFH, which, due to its short half-life, quickly disappears from circulation. If the bleeding requires more prompt intervention, the antidote to be administered is protamine sulfate. The dose must be proportional with that of UFH, 1 mg of protamine sulfate inactivating about 100 units of heparin (5, 9).

Other side effects that may occur are: a fall in the levels of antithrombin, osteoporosis, mineralocorticoid deficiency, allergic reactions, abnormal liver function tests, skin necrosis (1).

Low molecular weight heparins (LMWH) are obtained by chemical or enzymatic polymerization of heparin (3). Unlike unfractionated heparin, their activity is specific for the inactivation of factor Xa rather than thrombin, having twice as long a half-life, and a subcutaneous bioavailability 3-4 times greater (10,11). LMWH advantages include lower probability of heparin-induced thrombocytopenia, more convenient methods of administration (subcutaneous), the possibility of ambulatory using, lack of interaction with other drugs or with the patient's diet (4,12). In practice, LMWH are increasingly preferred as first-line therapy instead of UFH and represent the most commonly used anticoagulants for prophylaxis of thrombosis in children (4). LMWH is the preferred therapy in children under 1 year of age (2).

Therapeutic ranges for LMWHs are extrapolated from adults. Subcutaneous doses of LMWH in children were assessed for *enoxaparin*, *reviparin*, *dalteparin* and *tinzaparin* (Table 1). The monitoring of LMWH treatment is based on anti-fXa levels, the target is 0.5-1 u/ml anti-factor Xa 4-6 hours after subcutaneous administration (1). APTT should not be used for monitoring of LMWH therapy, because they do not significantly alter or prolong aPTT (thrombin dependent test), having a predilection for inactivating factor Xa. The therapy with LMWH should be interrupted if platelets fall below 100,000/mm³ (11).

The most common complication that occurs with the use of LMWH is bleeding, but its occur-

rence is lower than in cases treated with UFH (0-10%, depending on the study) (5). HIT also has a lower incidence, and if chronic use, osteoporosis is a rarer event (5,13).

The pathological conditions that absolutely contraindicate heparin therapy are: active bleeding, malignant hypertension, coagulation disorders due to hypocoagulation disorders, heparin allergy, shock, active peptic ulcer, active tuberculosis (9).

For long-term anticoagulation treatment, starting from the 5th day of heparin therapy, vitamin K antagonists are administered together with heparin for 3-5 days, until an optimal INR or PT is obtained (1 2).

Oral anticoagulants

Coumarins or vitamin K antagonists (VKAs), among which the most commonly used are **acenocoumarol** and **warfarin**, aim to inhibit the production of coagulation factors which are dependent on vitamin K (factors II, VII, IX and X), and protein C and S (anticoagulant molecules), with minor procoagulant effect (14).

The treatment is monitored by checking the INR (International Normalized Ratio) or the prothrombin time (PT). The target is INR between 2 and 3 and prothrombin time 1.5-2 times higher than the witness time. The dose is adjusted according to INR values (Table 2) (1,2). Patients with liver disease, malnutrition, as well as those taking antibiotics – conditions reducing endogenous synthesis of vitamin K – should receive lower doses, as they have higher sensitivity to the treatment. In children, it is difficult to monitor the treatment, as the levels of vitamin K vary depending on their dietary intake, on medication and on pre-existing pathology

TABLE 2. VKA doses and monitoring in children

Vitamin K antagonists	Loading dose	Maintenance dose	Monitoring	Duration of therapy
Acenocoumarol Warfarin	Day 1: 0,1 - 0,2 mg/kg orally (maximum 10 mg/day) Day 2-4: INR 1,1-1,3: repeat initial loading dose; INR 1,4-1,9: 50% of initial loading dose; INR 2-3: 50% of initial loading dose; INR 3,1-3,5: 25% of initial loading dose; INR>3,5: hold until INR<3,5, then restart at 50% decreased dose. Maximum dose for older children: 10-15 mg/day (warfarine), 4 mg/day (acenocoumarol)	Z5: 0,05 mg/kg/day Adjusted depending on INR INR 1,1-1,4: increase by 20% of dose; INR 1,5-1,9: increase by 10% of dose; INR 2-3: no change; INR 3,1-3,5: decrease by 10% of dose; INR >3,5: hold administration until INR<3,5 then begin with 20% from last dose. Maximum dose for older children: 5-7,5 mg/day (warfarine), 2 mg/day (acenocoumarol).	- INR , TP -Therapeutic target: INR between 2-3 - Daily INR monitoring in first 5 days, then 3 times a week for 4 weeks; After reaching optimal dosage - monthly check up.	First episode 1. with reversible risk factor: 3-6 months; 2. idiopathic: 6-12 months; 3. with chronic clinical risk factor: 12 months-lifelong; Recurrent episode: 1. with reversible risk factor: 6-12 months; 2. idiopathic: 12 months-lifelong; 3. with chronic clinical risk factor: lifelong.

Modified after Guyatt et al. (2012), Dijk et al. (2012).

(e.g. malabsorption) (3,4). Another impediment to the use of these molecules is their presentation form; as insoluble tablets, they are difficult to convert into liquid preparations suitable for pediatric patients, leading to poor control of the dose of the administered active substance (15). Cessation of treatment, if necessary, will be gradual, with the dose being reduced over 3-4 weeks.

In case of overdose and adverse effects of coumarin, oral anticoagulant treatment is interrupted and vitamin K is administered (iv/orally), with doses of 30 µg/kg up to 5 mg being reported as effective (16). Blood transfusions, frozen plasma and/or concentrated Factor VII, IX, X may be associated if heavy bleeding occurs.

Antiplatelet agents

Aspirin, a cyclooxygenase irreversible inhibitor, causes platelet dysfunction, while indobufen, flurbiprofen, sulfinpyrazone and triflusal produce reversible inhibition of cyclooxygenase. Aspirin is the most used antiplatelet agent in the pediatric population. The dosage in children is 1-5 mg/kg/day, single dose (1).

Dipyridamole leads to a decrease in platelet aggregation, by inhibiting phosphodiesterase. The usual dose of dipyridamole is 3-6 mg/kg/day, with a maximum of 75-100 mg/day to adolescents (17).

Ticlopidine and *clopidogrel* are molecules with independent action of the cyclo-oxygenase, preventing the binding of ADP to the platelet surface (additional effect to aspirin). The safe and effective dose of clopidogrel in children is 1 mg/kg/day. There are no studies on the use of ticlopidine in children, the usual dose being 10 mg/kg/day (17).

GP IIb/IIIa antagonists (abciximab, eptifibatid, tirofiban), a new class of potent platelet aggregation inhibitors, interact with fibrinogen to occupy the platelet receptor, which results in the reduction of the thrombastenic platelet functions. There is no data on the safety usage of these compounds in children (17).

New anticoagulant molecules have recently been approved in adults. They are factor Xa inhibitors, such as *fondaparinux*, and thrombin inhibitors, like *bivalirudin* and *argatroban*. They are currently recommended for HIT and percutaneous coronary intervention. According to adult pathology, studies have shown that fondaparinux can be successfully used both in preventing and in treating thrombosis. This substance has a greater half-life than LMWH, requires monitoring once a day and does not affect bone metabolism. Studies on its usage in children are still needed, so as to establish its efficacy and appropriate dose (15).

THROMBOLYTIC THERAPY

It is recommended only for situations which require rapid reperfusion. American College of Chest Physicians (ACCP) recommends the thrombolytic therapy in children with venous thromboembolism (VTE) only for life-threatening thrombosis or limb thrombosis. It should be taken into account for patients with massive pulmonary thromboembolism with hemodynamic instability, where there are no contraindications (3). It may also be considered in case of thrombosis involving the superior and inferior vena cava or intracardiac locations (2). In children with VTE, systemic thrombolysis or catheter thrombolysis is recommended, in accordance with the doctor's experience.

The most commonly used thrombolytic agents are urokinase, streptokinase and tissue plasminogen activator (tPA). These molecules act by converting endogenous plasminogen to plasmin, leading to the destruction of fibrin (3) and thus providing a faster way to unblock thrombosed vessel than other therapeutic methods. On the other hand, it is associated with a higher risk of bleeding. In pediatric patients, the first thrombolytic agent is the tissue plasminogen activator (tPA), due to its low immunogenicity and based on the results of some studies conducted in vitro, which proved it to be more efficient than other molecules (18). The recommended dose of tPA according to the clinical trials is 0.1-0.6 mg/kg/hour for 6 hours (19). Urokinase may be administered systemically with a loading dose of 4,400U/kg, followed by a maintenance dose of 4,400 U/kg/h for 6-12 hours (12). Streptokinase is not used because of the allergic risk and the development of antibodies. *Since there are no studies in children proving the efficacy and safety of the therapy, they are not indicated for routine treatment of thrombosis.*

SURGICAL THERAPY

Surgical thrombectomy is rarely used in children; it is reserved for cases of inferior vena cava thrombosis associated with intravascular extension of Wilms tumor, severe intracardiac thrombosis after cardiac surgery, prosthetic valve thrombosis, septic thrombosis and peripheral arterial thrombosis secondary to vascular access in newborns (10). Studies have reported performing thrombectomy after cardiac intervention (1). There are no specific guidelines for using thrombectomy in children.

We review some of the main recommendations of international guidelines regarding indications and span of treatment, which depend on the location of thrombosis and its associated risk factors:

Pediatric patients with idiopathic thromboembolism generally require initial anticoagulant therapy with UFH/LMWH, then oral therapy with VKA for at least 6 months and up to 12 months.

In case of secondary thromboembolism, anticoagulation with VKA should be maintained for at least 3 months, if risk factors have been removed.

Idiopathic recurrent thromboembolism requires therapy indefinitely with therapeutic or prophylactic dose of VKAs or LMWH, if oral anticoagulation is too difficult.

In case of VTE associated with a central venous catheter (CVC), the removal of the catheter is recommended. The CVC could be maintained if it is necessary and functional, and consequently anticoagulant therapy is required.

Thromboembolism associated with antiphospholipid syndrome requires lifelong anticoagulation.

In cerebral sinovenous thrombosis without significant intracranial hemorrhage, as well as in embolic stroke, initial anticoagulation is administered with UFH/LMWH, followed by LMWH or VKA for minimum 3 months; in case of intraventricular brain hemorrhage, anticoagulation is not recommended (1,2).

THROMBOPROPHYLAXIS

Generally speaking, thromboprophylaxis is done until the risk factors disappear and the patient can be included into a minimal risk category.

General preventive measures involve hydration, early removal of CVC and cessation of oral contraceptive therapy in teenagers who require surgery. Preventive physical measures, such as elastic stockings, are recommended for older children and adolescents with an increased risk of VTE (2). In children, particularly teenagers, with multiple risk factors for VTE, LMWH thromboprophylaxis may be imposed (2). In case of congenital deficits of coagulation factors with procoagulant hyperactivity, prophylaxis is for life. The implant devices for therapeutic and prophylactic purposes require continuous treatment (e.g. heart valves, endovenous filters, stents) (4).

CONCLUSIONS

The anticoagulant therapy remains within the spectrum of medical challenges, due to the differences in pharmacokinetics, the dose-dependent effect, as well as the specifics of the monitoring tests. International guidelines devise the dose and the length of anticoagulant treatment according to etiology of the thromboembolism, the approaches determined by location, and thromboprophylaxis. Given that most of the therapeutic recommendations for the thrombotic disease in children have been extrapolated from adult therapy, studies on larger groups of children are required. The treatment must be chosen depending on the patient's hemodynamic stability, comorbidities and the balance between risks and benefits.

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