Intensive Care Med (2007) 33:1978–1984
DOI 10.1007/s00134-007-0718-8

PEDIATRIC ORIGINAL

Joe Bontadelli
Alexander Moeller
Markus Schmugge
Thomas Schraner
Oliver Kretschmar
Urs Bauersfeld
Vera Bernet-Buettiker
Manuela Albisetti

Enoxaparin therapy for arterial thrombosis in infants with congenital heart disease

Received: 21 November 2006
Accepted: 6 April 2007
Published online: 7 June 2007

J. Bontadelli · A. Moeller · M. Albisetti (✉)
University Children's Hospital, Division of Pediatrics,
Steinwiesstrasse 75, 8032 Zurich, Switzerland
e-mail: manuela.albisetti@kispi.unizh.ch
Tel.: +41-44-2667138
Fax: +41-44-2667171

M. Schmugge · M. Albisetti
University Children's Hospital, Division of Hematology,
Steinwiesstrasse 75, 8032 Zurich, Switzerland

T. Schraner
University Children's Hospital, Division of Radiology,
Steinwiesstrasse 75, 8032 Zurich, Switzerland

O. Kretschmar · U. Bauersfeld
University Children's Hospital, Division of Cardiology,
Steinwiesstrasse 75, 8032 Zurich, Switzerland

V. Bernet-Buettiker
University Children's Hospital, Division of Neonatology and Intensive Care,
Steinwiesstrasse 75, 8032 Zurich, Switzerland

Abstract *Objective:* To investigate efficacy and safety of enoxaparin for catheter-related arterial thrombosis in infants with congenital heart disease. *Design:* Prospective observational study. *Setting:* Pediatric Intensive Care and Cardiology Unit at the University Children's Hospital of Zurich. *Patients:* A cohort of 32 infants aged 0–12 months treated with enoxaparin for catheter-related arterial thrombosis from 2002 to 2005. *Measurements:* Dose requirements of enoxaparin, resolution of thrombosis by Doppler ultrasound, and bleeding complications. *Results:* Catheter-related arterial thrombosis was located in the iliac/femoral arteries in 31 (97%) infants and aorta in 1 infant, and was related to indwelling catheters and cardiac catheterization in 17 (53%) and 15 (47%) cases, respectively. Newborns required increased doses of enoxaparin to achieve therapeutic anti-FXa levels (mean 1.62 mg/kg per dose) compared with infants aged 2–12 months (mean 1.12 mg/kg per dose; $p = 0.0002$). Complete resolution of arterial thrombosis occurred in 29 (91%) infants at a mean of 23 days after initiation of enoxaparin therapy. Partial or no resolution was observed in 1 (3%) and 2 (6%) infants, respectively, at a mean follow-up time of 4.3 months. Bleeding complications occurred in 1 (3%) infant. *Conclusion:* Enoxaparin is efficient and safe for infants with congenital heart disease and catheter-related arterial thrombosis, possibly representing a valid alternative to the currently recommended unfractionated heparin.

Keywords Artery · Thrombosis · Low molecular weight heparin · Enoxaparin · Newborns · Infants

Introduction

Catheter-related arterial thrombi are increasingly recognized serious complications of advances in intensive care and cardiac catheterization techniques used for the treatment of congenital heart disease (CHD) in infants [1–3]. Untreated, catheter-related arterial thrombosis possibly increases long-term morbidity including early onset of occlusive peripheral arterial disease, leg-length differences, and loss of vascular access in those children

requiring repeated cardiac catheterizations; thus, optimal antithrombotic treatment is extremely important to restore arterial patency and avoid long-term sequelae.

Little information is available on the optimal treatment of peripheral arterial thrombosis in children, and treatment guidelines are usually extrapolated from recommendations in adults [4]. This approach is not optimal for a several reasons. Firstly, the etiology of arterial thrombosis in children differs substantially from that of adults. In children, arterial thrombosis usually occurs after arterial catheterization procedures in otherwise normal vessels, reflecting a direct "cause-and-effect" relationship between risk factor and thrombotic event [3]. In contrast, the cause-and-effect relationship in adults is more indirect with risk factors that include hyperlipidemia, diabetes, hypertension, smoking, and obesity, which cause vascular occlusion by accelerating atherosclerosis [5]. Secondly, both the coagulation and fibrinolytic systems in children differ significantly from adults. Hemostatic differences likely affect not only the use of, but also the response to, anticoagulant and thrombolytic agents in children compared with adults [6, 7]. Thirdly, risk factors for bleeding complications during anticoagulant or thrombolytic therapy are age dependent, with neonates and infants being particularly at increased risk.

Current recommendations for the treatment of catheter-related arterial thrombosis in infants and children include the administration of therapeutic doses of intravenous heparin [4]. Information on the optimal duration of heparin therapy is not available. Unlike the frequent use in adults, thrombolytic therapy in children is usually only recommended for extensive arterial thrombosis causing threatened limb or organ viability [4]. The limited and cautious use of thrombolysis in children derives from data showing that thrombolytic therapy is associated with a weak benefit and a significant increased risk of bleeding, particularly in newborns and infants [8].

Low molecular weight heparin (LMWH) has important advantages over unfractionated heparin (UFH), including predictable pharmacokinetics, subcutaneous administration, minimal monitoring, and fewer adverse effects [9]. While recent studies have provided important information on the use of LMWH in children with venous thrombosis, little information is available on the use of this drug in the treatment of arterial thrombosis in the young [10, 11].

This study aims to investigate dose requirements, efficacy, and safety of enoxaparin for the treatment of catheter-related arterial thrombosis in newborns and infants with CHD.

Methods

Patient population

Infants aged 0–12 months with CHD, who received therapeutic doses of enoxaparin for the treatment of catheter-related arterial thrombosis at the University Children's Hospital of Zurich from January 2002 to December 2005, represent the cohort of this study. All included infants had clinical suspicion of arterial thrombosis confirmed by objective radiological tests including Doppler ultrasonography and/or angiography, and Doppler ultrasound examination on follow-up. Data concerning age at the time of thrombosis, weight, gender, type of cardiac catheter and duration of cardiac catheterization, hematocrit at the time of thrombosis, dosing of enoxaparin (initial dose, dose required to achieve target anti-factor (F) Xa and maintenance dose), anti-FXa levels, duration of therapy, resolution of thrombosis, and bleeding complications during enoxaparin therapy were collected in all infants from clinical, laboratory, and radiological records. Our practice regarding prophylactic anticoagulation during cardiac catheterization is to administer UFH at bolus doses of 100 and 50 U/kg in the first and second hours, respectively, followed by subsequent doses depending on the activated clotting time. This study conformed to the declaration of Helsinki, and was approved by the Research Ethics Boards of the University Children's Hospital of Zurich (Zurich, Switzerland).

Treatment with enoxaparin

Dosing and monitoring of enoxaparin therapy were performed following guidelines established by the hematology service at our institution in accordance to the "Sixth ACCP Consensus Conference on Antithrombotic Therapy" [12]. Enoxaparin was administered through a subcutaneous catheter (Insuflon, Unomedical A/S, Roskilde, Denmark) at a dose of 1.5 mg/kg every 12 h in infants aged 0–2 months, and 1 mg/kg every 12 h in infants aged 2–12 months. Doses of enoxaparin were considered therapeutic when anti-FXa levels of 0.5–1.0 U/ml were achieved in blood samples taken 4 h following a second or third subcutaneous injection. Dose adjustments and subsequent anti-FXa measurements were performed according to a validated nomogram [12].

Table 1 Demographic and clinical characteristics of newborns and infants

Characteristics	Infants < 1 month ($n = 21$)	Infants 2–12 months ($n = 11$)
Gender		
Male	13	7
Female	8	4
Age at the time of thrombosis		
Mean	10 days	3.6 months
Median	7 days	3.1 months
Congenital heart disease		
Non-cyanotic		
Atrial and/or ventricular septal defect	1	4
Coarctation of the aorta	2	1
Aortic stenosis	2	1
Anomalies of the aortic arch	3	0
Bland–White–Garland syndrome	0	1
Cyanotic		
Tetralogy of Fallot	1	1
Pulmonary/tricuspidal atresia	1	0
Transposition of the great arteries	6	1
Anomalous pulmonary venous return	1	0
Hypoplastic left heart syndrome	2	1
Single ventricle	2	1
Arterial catheter		
Umbilical	1	0
Femoral	12	4
Cardiac	8	7
Location of thrombosis		
Aorta	1	0
Iliac artery[a]	11	3
Femoral artery[a]	14	8

[a] Five infants < 1 month of age developed thrombosis in both the iliac and femoral arteries

Table 2 Dose requirements of enoxaparin. *F*-factor; *CI* confidence interval

Variable	Infants < 1 month	Infants 2–12 months
Initial dose (mg/kg per dose)		
Mean (95% CI)	1.48 (1.34-1.62)	1.12 (0.96-1.28)
Median	1.50[a]	1.04[a]
Range	0.74–1.98	0.88–1.70
Dose to achieve target anti-FXa (mg/kg per dose)		
Mean (95% CI)	1.62 (1.45-1.78)	1.12 (0.95-1.28)
Median	1.61[b]	1.04[b]
Range	0.74–2.47	0.86–1.70
Maintenance dose (mg/kg per dose)		
Mean (95% CI)	1.59 (1.39-1.80)	1.12 (0.96-1.28)
Median	1.69[c]	1.04[c]
Range	0.65–2.47	0.88–1.70

The *p*-values indicate significant differences in median dose requirements between infants under 1 month of age and infants between 2 and 12 months of age: [a]$p = 0.002$; [b]$p = 0.0002$; [c]$p = 0.001$

Due to the lack of evidence-based recommendations regarding the optimal duration of therapy, the practice at our institution was to treat catheter-related arterial thrombosis with LMWH from the time of diagnosis until clinical and radiological resolution of thrombosis occurred, and for a maximal duration of 3–4 weeks. In infants with persistent thrombosis on ultrasonographic follow-up after this period of time, heparin therapy was changed to anti-platelet therapy with aspirin for 3–6 months. Depending on the clinical conditions of the infants, therapy with enoxaparin was performed in the hospital or at home.

Outcome

Efficacy of enoxaparin therapy was determined by resolution or extension of the arterial thrombus using Doppler ultrasonography performed by three experienced pediatric

radiologists trained in Doppler ultrasonography. Resolution of arterial thrombus was defined as complete if the thrombus was no longer detected and/or the blood flow had returned to normal, as partial if only a reduction of the thrombus and/or a still reduced blood flow was detected, and as no resolution when no changes in size or volume of the thrombus and/or no changes in blood flow were observed. Once radiological resolution occurred, no attempt was made to perform radiological follow-up in the absence of clinical signs of recurrence. In infants showing partial or no resolution, Doppler ultrasonography was performed at regular bases, usually during cardiological follow-up for ≥ 3 months.

Safety of enoxaparin therapy was determined by major and minor bleeding associated with treatment. Major bleeding included hemorrhage into internal organ sites, in the retroperitoneum, in the central nervous system, or a hemorrhage of any source requiring blood-product transfusion. Minor bleeding included mucosal bleeding and bleeding from vascular puncture sites.

Laboratory methods

Blood samples for the determination of anti-FXa were drawn from peripheral veins 4 h following a subcutaneous injection. Blood samples were collected into tubes containing 0.106 mol/l trisodium citrate solution (1.4 ml final volume). The volume of trisodium citrate was adjusted when hematocrit values were > 0.55. Anti-FXa was measured by a chromogenic assay (STA Rotachrom Heparin, Roche Diagnostics, Rotkreuz, Switzerland). For calibration, STA-Calibrator HBPM/LMWH kits (Diagnostica Stago, Asnieres, France) were used.

Statistical analysis

Data are described as means, medians, with ranges and 95% confidence intervals (CI) as appropriate. Statistical significant differences between groups were calculated by using the Mann–Whitney U-test. To assess for relations between different variables (age, type of CHD, hematocrit, initial anti-FXa, time gap between diagnosis of thrombosis and initiation of enoxaparin therapy, type of arterial catheter, duration of cardiac catheterization, and type of cardiac catheterization) and resolution of thrombosis, the Fisher's exact test was used. Differences with p-values ≤ 0.05 were considered significant. Analysis was performed using GraphPad InStat for Windows (GraphPad Software, version 3.05, San Diego, Calif.).

Results

Patient population

A total of 56 newborns and infants with CHD were diagnosed with catheter-related arterial thrombosis. Of these 56 patients, 24 (43%) had to be excluded from the present analysis. Reasons for exclusion were no treatment with enoxaparin due to renal insufficiency ($n = 2$), treatment with UFH in infants with unstable clinical conditions possibly requiring rapid on/off anticoagulation ($n = 7$), treatment with dalteparin ($n = 1$), treatment with aspirin only ($n = 3$), no confirmation of arterial thrombosis by radiological tests ($n = 8$), loss to follow-up ($n = 2$), and no parental consent to access patient records for study purposes ($n = 1$). The remaining 32 (57%) patients constitute the cohort for this analysis.

Demographic and clinical characteristics of patients are depicted in Table 1. Of the 32 patients, 21 were newborns, and 11 were between 2 and 12 months of age at the time of arterial thrombosis. The mean gestational age and birth weight of newborns were 38.6 weeks (median 39.2 weeks, range 33.3–41.1 weeks) and 3034 g (median 3020 g, range 2020–4130 g), respectively. Arterial thrombosis occurred at a mean of 3.8 days (median 2 days, 95% CI 1.19–6.57) following the placement of an indwelling arterial catheter, and 0.8 days (median 1 day, 95% CI 0.27–1.32) following cardiac catheterization ($p = 0.01$). From the 15 cardiac catheterization procedures, 8 were diagnostic and 7 were interventional. Cardiac catheterization was performed using a 4-F sheath for vascular access in 14 infants, and a 6-F sheath in 1 infant. Clinical signs of catheter-related thrombosis included the presence of a cool and pale extremity in 15 infants (47%), loss of a palpable arterial pulse in 29 infants (90%), and decreased blood pressure measured by Doppler in 12 infants (37.5%). None of the infants presented severe life-threatening limb viability.

Treatment with enoxaparin

Overall, enoxaparin therapy was started at a mean of 1.9 days (median 0.5 day, 95% CI 0.85–2.96) following diagnosis of arterial thrombosis. Initiation of enoxaparin therapy was significantly delayed in infants less than 1 month of age (mean 2.66 days, median 1 day, 95% CI 1.18–4.14) as compared with infants aged 2–12 months (mean 0.45 days, median 0 day, 95% CI –0.46–1.37; $p = 0.02$).

Dose requirements of enoxaparin in both infants less than 1 month of age and infants aged 2–12 months are

presented in Table 2. Median initial dose, median dose to achieve target anti-FXa, and median maintenance dose were significantly higher in infants less than 1 month of age as compared with infants aged 2–12 months. Although not statistically significant, a trend of increased dose requirements to achieve and maintain anti-FXa as compared with initial dose requirements was observed in infants less than 1 month of age (Table 2). Mean anti-FXa level within the target range was 0.65 U/ml (median 0.57 U/ml, 95% CI 0.55–0.75 U/ml) in infants less than 1 month of age, and 0.64 U/ml (median 0.57 U/ml, 95% CI 0.52–0.75 U/ml) in infants aged 2–12 months.

Median duration of enoxaparin therapy was 12 days (range 3–93 days, 95% CI 10.03–27.01) in infants less than 1 month of age, and 16 days (range 4–91 days; 95% CI 9.10–51.44) in infants aged 2–12 months ($p = 0.51$). In three infants, enoxaparin therapy was continued for 3 months due to the presence of a concomitant venous thrombosis. Following discontinuation of enoxaparin therapy, a total of 17 (53%) infants received anti-platelet therapy with aspirin, and 2 infants (6%) oral anticoagulation with phenprocoumon. Indications for aspirin therapy included arterial thrombosis and conditions related to the congenital heart disease in 8 (47%) and 9 (53%), respectively, of the 17 infants. Indications for oral anticoagulation were related to the congenital heart disease in both cases.

Outcome

Overall, complete resolution of arterial thrombosis occurred in 29 (91%) of all 32 patients, including 20 (95%) of the 21 infants less than 1 month of age and 9 (82%) of the 11 infants aged 2–12 months. Complete resolution was observed on follow-up Doppler ultrasonography at a mean of 27 days (median 12.5 days, range 5–187 days, 95% CI 7.1–46.8) in infants less than 1 month of age, and 13.5 days (median 12 days, range 2–28 days, 95% CI 46.3–20.7) in infants aged 2–12 months after initiation of enoxaparin therapy ($p = 0.47$). Partial and no resolution of arterial thrombosis was observed in 1 (3%) and 2 (6%) of the 32 patients, respectively, at a mean follow-up time of 4.3 months after initiation of enoxaparin therapy. Age at the time of thrombosis, type of congenital heart disease, hematocrit, initial anti-FXa, time gap between diagnosis of thrombosis and initiation of enoxaparin therapy, type of arterial catheter, duration of cardiac catheterization, and type of cardiac catheterization were not related to resolution of arterial thrombosis.

Major bleeding complications occurred in 1 (3%) of the 32 infants. This 6-day-old boy presenting catheter-related arterial thrombosis following cardiopulmonary bypass for the repair of an interrupted aortic arch developed hemorrhagic pericardial effusion 2 days after initiation of enoxaparin therapy. The infant required cardiopulmonary resuscitation and surgery with the placement of a pericardial drainage due to cardiac tamponade. At the time of bleeding, the dose of enoxaparin was 1.5 mg/kg per dose, and the anti-FXa was 0.62 U/ml. No relevant minor bleeding complications were observed. No clinical signs of recurrence during the follow-up time were observed.

Discussion

Although catheter-related arterial thrombosis are well-known complications of indwelling arterial catheters or cardiac catheterization procedures in infants with CHD, limited information is available on the optimal treatment of these thrombotic complications. The present study is by far one of the largest cohort studies evaluating the use of enoxaparin in the treatment of catheter-related arterial thrombosis in infants with CHD. Results of this study demonstrate that enoxaparin represents an efficient and safe anticoagulation therapy for non-life-threatening catheter-related arterial thrombosis in these infants. Recommendations from the ACCP Consensus Conference on Antithrombotic Therapy for the treatment of femoral artery thrombosis following cardiac catheterization and peripheral arterial catheter-related thrombosis in children include therapeutic doses of intravenous UFH with or without thrombolysis, depending on the clinical situation [4, 12]. Since 2002 enoxaparin has been increasingly used at our institution for two major reasons. The first is that LMWH has important pharmacokinetic advantages and a more convenient clinical use compared with UFH. Minimal monitoring and subcutaneous administration are only two of the important benefits that spare the use of central venous lines in children with poor venous access, and possibly decrease the risk of central venous line-related thrombosis, which is known to occur at a high incidence in children with CHD; the second is the inferior outcome observed in a retrospective evaluation of infants with CHD treated with UFH and/or thrombolysis for non-life-threatening catheter-related arterial thrombosis at our institution between 1997 and 2001 [2]. In this study, complete and partial/no resolution was noted in 70 and 30% of cases, respectively. Bleeding complications occurred in 2% of patients treated with UFH and in 54% of patients receiving thrombolysis [2].

In the present study, complete resolution of arterial thrombosis occurred in 91% of all infants at a mean of 23 days following initiation of enoxaparin therapy, whereas bleeding complications occurred in only 3%. As compared with studies on infants with predominantly venous thrombosis, enoxaparin in our cohort was more effective and associated with a comparable low risk of bleeding complications [13, 14]. No studies on infants with exclusively arterial thrombosis treated with LMWH are available for comparison. It is evident, however, that compared with our retrospective data, the introduction of

enoxaparin at our institution has provided a rapid, more efficient, and safer alternative to UFH or thrombolysis for the treatment of non-life-threatening catheter-related arterial thrombosis [2]. The increased efficacy of enoxaparin compared with UFH and thrombolysis is possibly related to the composition of arterial thrombi, which develop in high flow conditions and are composed mainly of platelet aggregates bound together by thin fibrin strands [15]. Increasing evidence suggests that the anticoagulant effect of UFH is impaired by platelets to a greater extent than LMWH, and that platelet interaction is much more inhibited by LMWH than UFH [16–18]. In addition, animal models have shown that platelet-rich thrombi are particularly resistant to thrombolysis, and that platelets and fibrin still accumulate on lysing thrombi during effective thrombolytic therapy [19].

Previous studies in infants and children have demonstrated that doses of enoxaparin to achieve adult therapeutic anti-FXa levels of 0.5–1.0 U/m are age dependent, with preterms and newborns having increased requirements compared with older infants and children [12–14, 20–23]. Possible explanations for the increased requirements of LMWH in newborns include a faster clearance of LMWH due to a larger volume of distribution, and decreased plasma concentrations of antithrombin in newborns compared with older children [10]. While confirming these findings, a trend of increased dose requirements to achieve target anti-FXa as compared with published initial dose recommendations was observed in our infants less than 1 month of age. Of particular interest was the finding that anti-FXa levels remained close to the lower limit of the target range despite increased doses of enoxaparin in most of the cases. This finding, together with the high resolution rate, raises the question of whether the therapeutic anti-FXa range will be lower than that for adults.

Forty-three percent of infants who developed catheter-related arterial thrombosis were not included in this study mostly due to no treatment with enoxaparin, and the lack of radiological confirmation of thrombosis. Catheter-related arterial thrombosis usually occurs in critically ill infants with serious underlying diseases. When CHD is concerned, these infants usually require intensive care following cardiopulmonary bypass or cardiac catheterization, are often in hemodynamically unstable conditions, possibly require urgent re-operation, or develop complications such as renal insufficiency. Due to the longer half-life of LMWH and the fact that LMWH are cleared principally by the renal route, treatment of arterial thrombosis with UFH instead of enoxaparin is preferable in these infants. While allowing a bedside, non-invasive examination compared with contrast angiography, which is considered the gold standard, Doppler ultrasound in small infants is not always feasible, and radiological diagnosis of thrombosis becomes a major issue; thus, several infants with typical clinical signs of arterial thrombosis treated with enoxaparin had not been included in this study due to the lack of confirmation of thrombosis by Doppler ultrasound.

Conclusion

In conclusion, results of this study show that enoxaparin is an efficient and safe form of anticoagulation for newborns and infants with CHD and non-life-threatening catheter-related arterial thrombosis, possibly representing a valid alternative to the currently recommended intravenous UFH. Multicenter randomized clinical trials are required to properly define efficacy and safety of LMWH over UFH for the treatment of catheter-related arterial thrombosis in children. Further studies are also required to determine pediatric anti-FXa therapeutic range and optimal duration of enoxaparin therapy for catheter-related arterial thrombosis in children, as well as to assess the long-term benefit of the use of enoxaparin in the studied population.

References

1. Monagle P (2003) Thrombosis in pediatric cardiac patients. Semin Thromb Hemost 29:547–555
2. Albisetti M, Schmugge M, Haas R, Eckhardt BP, Bauersfeld U, Baenziger O, Hug MI (2005) Arterial thromboembolic complications in critically ill children. J Crit Care 20:296–300
3. Price V, Massicotte MP (2003) Arterial thromboembolism in the pediatric population. Semin Thromb Hemost 29:557–565
4. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD (2004) Antithrombotic therapy in children. Chest 126:645S–687S
5. Hirsh J, Crowter MA (2000) Arterial thromboembolism. In: Hoffman R, Benz EJ, Shattil SI, Furie B, Cohen HJ, Silberstein LE, McGlave P (eds) Hematology: basic principle and practice, 3rd edn. Churchill Livingstone, Philadelphia, pp 2089–2096
6. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L (1992) Maturation of the hemostatic system during childhood. Blood 80:1998–2005
7. Albisetti M (2003) The fibrinolytic system in children. Semin Thromb Hemost 29:339–347
8. Albisetti M (2006) Thrombolytic therapy in children. Thromb Res 118:95–105
9. Weitz JI (1997) Low-molecular-weight heparins. N Engl J Med 337:688–698
10. Albisetti M, Andrew M (2002) Low molecular weight heparin in children. Eur J Pediatr 161:71–77
11. Bontadelli J, Moeller A, Schmugge M, Kretschmar O, Bauersfeld U, Schraner T, Bernet-Buettiker V, Albisetti M (2006) Use of enoxaparin in the treatment of catheter-related arterial thrombosis in infants with congenital heart disease [Abstract]. Cardiol Young (Suppl) 16(2):27
12. Monagle P, Michelson AD, Bovill E, Andrew M (2001) Antithrombotic therapy in children. Chest 119:344–370S

13. Streif W, Goebel G, Chan AKC, Massicotte MP (2003) Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. Arch Dis Child Fetal Neonatal Ed 88:F365–F370
14. Michaels LA, Gurian M, Hegyi T, Drachtman RA (2004) Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. Pediatrics 114:703–707
15. Baumgartner HR (1973) The role of blood flow in platelet adhesion, fibrin deposition and formation of mural thrombi. Microvasc Res 5:167–179
16. Hirsh J, Levine MN (1992) Low molecular weight heparin. Blood 79:1–17
17. Mirshahi M, Soria J, Neuhart E, Steg PG, Jacob P, Combe S, Soria C (1992) Effect of heparin and enoxaparin on platelet interaction with fibrin clots. Thromb Res 65:187–191
18. Serra A, Esteve J, Reverter JC, Lozano M, Escolar G, Ordinas A (1997) Differential effect of a low-molecular-weight heparin (dalteparin) and unfractionated heparin on platelet interaction with the subendothelium under flow conditions. Thromb Res 87:405–410
19. Jang IK, Gold HK, Ziskind AA, Fallon JT, Holt RE, Leinbach RC, May JW, Collen D (1989) Differential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi to lysis with recombinant tissue-type plasminogen activator. A possible explanation for resistance to coronary thrombolysis. Circulation 79:920–928
20. Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M (1996) Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. J Pediatr 128:313–318
21. Punzalan RC, Hillery CA, Montgomery RR, Scott JP, Gill JC (2000) Low-molecular-weight heparin in thrombotic disease in children and adolescents. J Pediatr Hematol Oncol 22:137–142
22. Dix D, Andrew M, Marzinotto V, Charpentier K, Bridge S, Monagle P, de Veber G, Leaker M, Chan AKC, Massicotte P (2000) The use of low molecular weight heparin in pediatric patients: a prospective cohort study. J Pediatr 136:439–445
23. Ho SH, Wu JK, Hamilton DP, Dix DB, Wadsworth LD (2004) An assessment of published dosage guidelines for enoxaparin. J Pediatr Hematol Oncol 26:561–566