MANAGEMENT OF ANTITHROMBOTIC PROPHYLAXIS AND TREATMENT

THROMBOSIS IN CHILDREN

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International registries reported an annual incidence of venous thromboembolism (VTE) of 0.07-0.14 per 10,000 children in the general population; this incidence was 5.3 per 10,000 hospital admissions in children, 0.24 per 10,000 neonatal admissions to intensive care units, and 0.51 per 10,000 births in neonates.[1-3] The peak of the thrombotic risk was evidenced in the age group less than one year of age and during adolescence. The mortality directly attributable to VTE was 2.2%, and the morbidity was 8.1% for recurrence of VTE and 12.4% for postphlebitic syndrome.[2] There is evidence that the primary thrombotic risk is much lower in children in comparison with adults. Idiopathic VTE is indeed rare, and by converse seriously associated conditions are often present in children with VTE. Central venous lines (CVL) are the most common risk factors for VTE in children with an incidence of clinically evident thrombosis of 3.5 per 10,000 paediatric hospital admissions.[4] The presence of CVL is the sole reason of an increased frequency of VTE in the upper venous system in children (80% of deep venous thrombosis (DVT) in newborns, and 60% in older children) in contrast to adults in whom less than 2% of DVT are in the upper venous system.[5] The diagnosis of CVL-related DVT is strongly dependent upon the diagnostic test. The PARKAA multicenter clinical trial performed in children with acute lymphatic leukemia treated with asparaginase evidenced an ultrasound sensitivity of 37% in the upper venous system, where the vein compressibility cannot be performed, and a venography sensitivity of 79% as consequence of its low sensitivity in the jugular veins that are preferred for placement of CVL in children. Echocardiography detected 10% of clots that were not detected by venography. These findings suggest that a combination of venography, ultrasound and echocardiography may be used for a complete evaluation of the upper venous system in children.[6] Umbilical vein catheters are associated with clots in the inferior vena cava and portal vein that may remain clinically silent and are a cause of portal hypertension later detected.[7]Doppler ultrasound and venography may be the required diagnostic methods. Pulmonary embolism is a serious secondary complication of a thrombotic event in children. Its incidence in paediatric patients is unknown but is increasing as a result of an improved survival rate in children with previously lethal disease with an incidence of 8.6 per 100,000 hospital admissions of children between 1 month and 18 years of age 1. CVL and extracorporeal circulation techniques are the most important risk factors for PE in children. The clinical symptoms of PE are often confused with the clinical symptoms of the underlying disorders in ill children with an underestimation of the diagnosis. Prophylactic antithrombotic therapy is not routinely indicated in children because the incidence of VTE is too low to warrant the bleeding risk. However antithrombotic prophylaxis may be considered in pediatric patients in certain circumstances as Fontan operation, the concomitant presence of congenital prothrombotic disorders and high-risk situation, sick children with multiple risk factors. Primary anticoagulant prophylaxis in children with CVL is not yet recommended and need further evaluation.[8] Arterial catheterisation is the most common risk factor for arterial thromboembolism in children, and includes peripheral or umbilical arterial catheterisation and cardiac catheterisation. Prophylaxis with unfractionated heparin can be recommended to prolong patency of peripheral arterial catheters, and reduces from 40% to 8% the incidence of thromboembolism in children less than 10 years of age following cardiac catheterisation.[9] Arterial ischemic stroke in children is very rare with an estimated incidence between 12 per 100,000 children per years in neonates and 0.5 to 6 per 100,000 in children aged more than 1 year 10-11. Its incidence is similar to the incidence of brain tumor. Congenital heart malformations (atrial septal defects, patent foramen ovale), peri-natal asphyxia, infections, arterial abnormalities, and dissections are the most frequent predisposing conditions for ischemic cerebrovascular accidents in children. As the non-specific clinical symptoms neonatal stroke is detected in the acute phase only in rare cases and the diagnosis is made later, following the presentation of neurological impairments. Computerized tomography or magnetic resonance imaging are useful in the acute situations; magnetic resonance angiography or conventional angiography should be considered for visualization of small and medium cerebral arteries, when dissection has not been excluded and for unexplained recurrence.[12] Results of outcome studies in children evidenced that 35% of children remained normal neurologically after an ischemic stroke, and that 42% had a moderate or severe neurological deficit. In neonates, a normal outcome was reported in approximately 50% of patients. The risk of recurrent ischemic stroke in children has been found to be approximately 20% with a mortality rate that ranges from 6 to 14 %.[13] Cerebral sinovenous thrombosis in children is a rare but increasingly diagnosed disorder with an estimated incidence of 0.67 per 100,000 children with a predominance of neonate and young infants.[14] Risk factors for sinovenous thrombosis are age related: in neonate, the most common risk factors are dehydration and sepsis, whereas in older children they are haematological disorders, cardiac disease, connective tissue disorders and head and neck infections. Magnetic resonance imaging is the technique of choice for the diagnosis of sinovenous thrombosis.[15] Thrombophilia in children The frequency of congenital prothrombotic disorders in children with VTE varies in the available study between 13 and 60%; these results reflect the different clinical characteristics of the populations evaluated in each study (only VTE or both VTE and arterial and cerebral events, only spontaneous VTE).[16-18] The prevalence of thrombophilia in children with recurrent VTE was 46.9% in the German study, and 27 and 12% in the Dutch and in Canadian registry, respectively. According to results obtained at our study center in different settings of children, carriers of thrombophilia identified as family members of symptomatic probands when exposed to the common triggering factors for VTE exhibit a thrombotic risk that is definitely lower than that observed in adults.[19]

Although data on the role of thrombophilia in children with VTE are conflicting, there is evidence that thrombophilia is associated with spontaneous VTE and with recurrent VTE. Before systematically implementing thromboprophylactic strategies, larger prospective studies are needed to investigate the true role of thrombophilia in children with additional risk factors and in those with underlying medical diseases. Accordingly, the routine screening for thrombophilia may be recommended in children with spontaneous or recurrent VTE, while it seems unjustified in otherwise healthy children belonging to families with inherited thrombophilia. The prevalence of prothrombotic disorders in children with ischemic stroke or sinovenous thrombosis is 38-68%.[20-21] Factor V Leiden may represent a risk factor for cerebral events in children, while the risk in carriers of the prothrombin variant G20210A appears weak. Recurrent thromboembolism does not seem common in children with neonatal arterial ischaemic stroke, but the presence of prothrombotic risk factors may increase the risk.[22] Available data suggests the search for thrombophilia in children with cerebral thrombosis in particular in "idiopathic" subgroup.[23]

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THE IMPROVE REGISTRY

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Background and Aim of the Study. Evidence-based guidelines recommend that hospitalized medical patients at risk of venous thromboembolism (VTE) should receive prophylaxis. However, physicians' practices for providing VTE prophylaxis to these patients remain poorly characterized. To assess clinical practices for VTE prophylaxis in these patients, the International Medical Prevention Registry on Venous Thrombo-embolism (IMPROVE), funded by Sanofi-Aventis, was organized. *Patients and methods.* Participating hospitals enrolled the first 10 consecutive eligible acutely ill medical patients each month. Patient management was determined by the treating physicians and hence the data reflect 'real-world' practices. *Results.* From July 2002 to September 30, 2006, 15,156 patients were enrolled from 52 hospitals in 12 countries. In total, 50% of patients received thromboprophylaxis, either pharmacological or mechanical, but practices varied considerably among the different countries, and especially between

USA and the rest of the world. The preferred thromboprophylaxis modality in the USA was intermittent pneumatic compression (IPC), which was applied to 22% of patients, followed by unfractionated heparin (UFH), which was administered to 21% of patients, low molecular weight heparin (LMWH), which was given to 14%, and elastic stockings (ES), which were applied to 3%. In all other countries combined, the most commonly used thromboprophylaxis modality was LMWH, which was administered to 40% of patients, followed by UFH (9%), ES (7%), and IPC, which was applied only to the 0.2% of patients. In the USA and other participating countries, 52% and 43% of patients, respectively, should have received prophylaxis according to guideline recommendations from the American College of Chest Physicians (ACCP). Of these patients who met the ACCP criteria, 61% received thromboprophylaxis, either pharmacological or mechanical. *Conclusions*. Our data suggest that physicians' practices for providing VTE prophylaxis to acutely ill hospitalized medical patients are suboptimal, and that huge practice variations exist among different countries, particularly between USA and the rest of the world.

HOW A PHARMACY-DRIVEN, PHYSICIAN-CHAMPIONED PROGRAM CAN IMPROVE RATES OF APPROPRIATE VTE PROPHYLAXIS IN A HOSPITAL

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Venous thromboembolism prevention in the hospitalized patient: a focus on the US JCAHO National Patient Safety Goal on Anticoagulation, current state VTE measures, and Future VTE Performance measures. Venous thromboembolism (VTE) continues to be a primary focus of many of the United States' Quality Organizations. The Leapfrog Group, Agency for Healthcare Research and Quality (AHRQ), Center for Medicare/Medicaid Services (CMS), Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and National Quality Forum (NQF) are a small number of these organizations. Currently, CMS and JCAHO are partnered in the Surgical Care Improvement Project (SCIP) initiative to improve surgical VTE Prophylaxis rates and outcomes within US hospitals. In January 2008, JCAHO's new National Patient Safety Goal (NPSG) focusing on dedication to appropriate management of anticoagulants in the hospital setting came into force. In 2006 and 2007, JCAHO and NQF piloted 8 measures in 55 hospitals throughout the U.S. These quality measures have been slightly modified to seven measures and are now in the final NQF endorsement phase. Recommendations for risk-assessment and appropriate prophylaxis are based off of the 7th ACCP guidelines. One of the VTE measures is for prophylaxis initiation within 24 hours of admission OR documentation of a legitimate VTE Prophylaxis Contraindication. A mirrored measure applies to patients transferred to the ICU. In order to meet these quality measures, US hospitals will have to designate a method and approach to risk-assessing all admitted patients and patients transferred to critical care units (i.e. ICU's). The Lovelace Medical Center was one of these pilot hospitals and initiated a clinical pharmacist-driven, physician-championed VTE prophylaxis program. "Appropriate" VTE prophylaxis is a new concept in the US that takes into account correct type, dose and duration of therapy for hospitalized patients. Initial studies in the US show that *appropriate* VTE prophylaxis rates are much lower than expected. Studies measuring appropriate prophylaxis in US hospitals will be reviewed. In addition, methods of implementation and execution of a clinical-pharmacist-driven program, as well as the program's effect on VTE prophylaxis rates will be will be reviewed.

ANTIPLATELET AGENTS IN CORONARY STENTING

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Over the last years, it has been demonstrated that drug-eluting stents (DES) reduce significantly angiographic and clinical restenosis after percutaneous coronary interventions. These results are consistent across several clinical randomized controlled trials comparing these new devices with bare metallic stents (BMS), which have already markedly improved the results obtained with balloon angioplasty in the early days of this method of myocardial revascularization. Current percutaneous coronary intervention is attempting more aggressively to treat difficult lesions and patient cohorts with a high procedural success rate. Double antiplatelet therapy with aspirin (ASA) and thienopyridine is the best current treatment to reduce the risk of coronary stent thrombosis. Due to the lower incidence of side-effects compared to ticlopidine, clopidogrel should be the thienopyridine of choice in association with ASA in the double antiplatelet regimen. However, the combination of delayed healing with DES and the increasing complexity of the stent implantation raises more demanding safety concerns about the dosage and duration of dual antiplatelet therapy. The routine off-label use of DESs has been associated with a higher prevalence of stent thrombosis in clinical practice than was previously suggested. Consequently, the early identification of patients at risk for stent thrombosis has become a major goal in cardiology. Current data show that the premature discontinuation of dual-antiplatelet therapy is an important risk factor for DES thrombosis, but the occurrence of stent thrombosis in patients adhering to this drug regimen suggests that some patients are nonresponsive to clopidogrel therapy. Patients with high platelet reactivity to adenosine diphosphate (ADP) during dual-antiplatelet therapy may be at increased risk for adverse ischemic events, including stent thrombosis. Preliminary data suggest that there may be a threshold of platelet reactivity, as measured by light transmittance aggregometry after ADP stimulation, that predicts an increased risk for stent thrombosis. Similar data may be obtained with point-of-care devices. Large prospective studies designed to identify which patients are at risk for stent thrombosis on the basis of platelet function testing are under way and may eventually lead to personalized antithrombotic therapy. Beyond stent thrombosis a similar approach could help to reduce

long term complications in stented patients. New antiplatelet agents have been developed and are currently under evaluation as possible alternative to clopidogrel.

POSTERS

COMPARISON OF WHOLE BLOOD COAGULATION ASSESSMENT USING THROMBOELASTOMETRY (ROTEM®) BETWEEN HUMAN AND CYNOMOLGUS MONKEYS

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Introdction. Microvascular thrombosis, due to activation of clotting cascade, is a key feature of the rejection process that takes place when pig organs are transplanted into primates. To date, little is known about qualitative characteristics of clot formation in primates. The present study is aimed at better understanding the differences in blood coagulation between primate and human using thromboelastometry (ROTEM®). *Matherials and Methods*. We studied ROTEM profiles in 40 naïve cynomolgus monkeys from Mauritius, China and Philippines and in 52 healthy human volunteers. Thromboelastometry (InTEM®, ExTEM®, FibTEM®, NaTEM®) was performed from whole blood with the ROTEM® coagulation analyser (Pentapharm, Munich, Germany).The main parameters obtained were clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), Area Under Curve (AUC) and Alpha (α) angle. Statistical analysis was performed using unpaired t-student test. *Results.* Data obtained in cynomolgus monkeys were reproducible and consistent with the normal range observed in human healthy subjects. Some important differences were, however, observed in primate blood. In monkeys ROTEM® profiles showed a hypercoagulable profile as compared to humans. Mean CT and mean CFT were significantly lower in primates (–25.7% and –55.5%, respectively) than in humans. MCF, α angle and AUC were significantly higher in primates than in humans (+23%, +21.5% and +32%, respectively). Similar distribution and range in human and monkey platelets were observed. In addition, fibrinogen levels in monkeys were lower than in humans (145.4 mg/dL *vs.* 289.9 mg/dL). *Conclusions*. Primate clot formation studied by ROTEM®, a technology to study whole blood coagulation, is consistent with a higher prothrombotic profile in primates as compared to humans. These differences do not appear to be related to higher platelet counts or fibrinogen levels in monkeys. Together these data suggest that, with regard to coagulation, xenotransplantation in cynos represent a much more difficult situation than xenotransplantation in humans.