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Perioperative thromboembolism prophylaxis in children – is it necessary?

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Abstract

Perioperative antithrombotic prophylaxis in adults is widely recommended. In the past, it was believed that this does not concern the paediatric population. Recently, however, there has been growing evidence that the incidence of venous thromboembolism (VTE) in children is increasing and is probably underestimated. This is a result of advances in treatment of previously lethal conditions, wide use of central venous catheters, and improved awareness and diagnosis of VTE complications. However, large clinical trials assessing the efficacy and safety of antithrombotic treatment in children have not been conducted and there are not widely accepted protocols of perioperative prophylaxis. At the same time, there is a growing awareness of its sequelae: compartment syndrome, pulmonary embolism, pulmonary hypertension, post-thrombotic syndrome, cost, length of hospital stay, and mortality. Local recommendations based on observational studies, individual experience, and extrapolation from data of adults have emerged.

Key words: venous thromboembolism, paediatric surgery, thromboembolism prophylaxis, perioperative thromboembolism.

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Perioperative antithrombotic prophylaxis in adults is widely recommended because venous thromboembolism (VTE) is a significant comorbidity in hospitalised patients. In the past, it was believed that this was not an issue in the paediatric population. However, there is growing evidence that the incidence of venous thromboembolism in children is increasing and is probably underestimated. This may be a result of advances in treatment of previously lethal conditions, wide use of central venous catheters, and improved awareness and diagnosis of VTE complications. However, large clinical trials assessing the efficacy and safety of antithrombotic treatment in children have not been conducted, and there are no widely accepted protocols of perioperative prophylaxis. At the same time, there is a growing awareness of thrombosis sequelae: compartment syndrome, pulmonary embolism, pulmonary hypertension, post-thrombotic syndrome, or neurologic deficit leading to increased morbidity, cost, length of hospital stay, and mortality. Local recommendations based on observational studies, individual experience, and extrapolation from data of adults have emerged.

The article presents current knowledge on epidemiology, risk, consequences, and prophylaxis of perioperative thromboembolism in children.

EPIDEMIOLOGY

The incidence of paediatric VTE is relatively low, which can be related to developmental haemostasis [1]. In comparison to adults, children are protected from hypercoagulation due to the following: reduced capacity to generate thrombin, increased capacity of $\alpha 2$ macroglobulin to inhibit thrombin, lower plasma prothrombin concentration, the presence of circulating anticoagulant at birth, and enhanced antithrombotic potential of the vessel wall. Additionally, in contrast to adults, the child's healthy endothelium is not damaged by hypertension, diabetes, or hypercholesterolaemia and is not exposed to smoking.

In the 1990s, the incidence of VTE in children was estimated between 0.07 and 0.14/10,000 children in the population and 5.3/10,000 hospital admissions [2, 3]. Since that time, a series of reports have been published suggesting dramatic increase in VTE recognition. In 2007 Raffini *et al*. reported that between 2001 and 2007 the incidence of paediatric VTE increased 7 to 10 fold – 34–58 new cases/10,000 hospital admissions per year [4]. Similar trends were observed by Sandoval in a Children's Hospital in Indianapolis: the incidence of thromboembolic cases increased from 0.3 in the years 1992–1995 to 28 new cases of VTE/10,000 hospital admis-

sions in 2005 [5]. In a Swedish survey concerning thromboembolism in children from 2000 to 2015 the incidence was estimated at 0.8/10,000 children in the population [6].

PATHOPHYSIOLOGICAL FEATURES

In 1856 Virchow described three main groups of factors leading to thrombus formation: altered blood flow, endothelial injury and hypercoagulable state. Over the last decade, growing evidence suggests a role of the process of inflammation as a major contributor to the pathophysiology of VTE as well [7]. Activation of endothelial cells, platelets, leukocytes, and release of cytokines triggers the coagulation system through induction of TF (tissue factor). Probably the key event in thrombus formation is vein wall inflammation. The probable associations between VTE and pro-inflammatory cytokines – interleukin (IL)-6 and TNF-α – have been demonstrated. Extracellular DNA fibres extruded from neutrophils in response to infection stimulate fibrin formation and platelet adhesion. Excessive complement activation leads to thrombosis, while the specific interactions between the complement and coagulation systems lead to pathological thrombus formation. The significant interplay between inflammation and coagulation is responsible for thrombotic complications in sepsis, inflammatory bowel disease, systemic lupus erythematous, surgery, trauma, and even obesity [8].

RISK FACTORS

In contrast to adults, in whom VTE is idiopathic, in about 31%, 96 to 98% of children have identifiable risk factors that arise in connection with hospitalisation [3, 9]. Most children exhibit two or more risk factors [2]. The age groups at greatest risk are infants and teenagers [2, 10].

In 2014 Takemoto *et al*. performed a retrospective analysis of patients (up to 21 years old) hospitalised at the Johns Hopkins Hospital from 1994 to 2009 [11]. They found 270 episodes of hospital-associated VTE in 90,485 admissions (30 per 10,000 admissions). Young adults (18 to 21 years of age) and adolescents (14 to 17 years of age) had significantly increased rates of VTE compared with children (2 to 9 years of age). A central venous catheter (CVC) was present in 50% of patients, and a surgical procedure was performed in 45% of patients before VTE diagnosis. For patients without a CVC, trauma was the most common admitting diagnosis. CVC-related VTE was diagnosed most frequently in infants (< 1 year old) and in patients with malignancy. Renal disease and congenital heart diseases were associated with the highest rates of VTE (51 and 48 per 10,000, respectively). The incidence of VTE was significantly higher among those with ≥ 4 medical conditions compared with those with a single medical condition.

At the same time, the International Society for Thrombosis and Haemostasis Paediatric/Neonatal Haemostasis and Thrombosis Subcommittee for the Scientific and Standardisation Committee convened a working group to develop recommendations for standardisation of paediatric risk assessment models [9]. The group conducted a meta-analysis identifying risk factors for VTE in the paediatric population based on a literature search via PubMed (1946–2014) and Embase (1980–2014). Data on risk factors and risk-assessment models were extracted from case-control studies, registries, large (n > 40) retrospective case series, and cohort studies. In conclusion, they defined four most common risk factors of paediatric VTE: intensive care unit stay (more than four days), central venous catheter, mechanical ventilation, hospital length of stay (more than seven days).

Recently, the Children's Hospital-Acquired Thrombosis (CHAT) registry, collecting data from seven large paediatric centres, was developed [12]. The primary aim of this case cohort study was to identify clinical risk factors that can predict hospital-acquired (HA) VTE in children. The interim results were published in 2018. VTE events were diagnosed in 621 children from five hospitals – the incidence ranged from 12 to 37 cases per 10,000. The majority of the subjects were male (57%), with a median age at the time of VTE diagnosis of three years. A diagnosis of congenital heart disease (27%) and cancer (13%) were the most prevalent comorbidities in these subjects. Fifty-seven per cent of subjects were in an intensive care unit (neonatal, paediatric, or cardiac) at the time of VTE diagnosis, and the median time to diagnosis was 10 days after admission. Eighty per cent of VTEs were associated with a CVC. Fourteen per cent of subjects had an infection prior to their VTE, of which 92% were due to bacteria. Forty-three per cent of patients had surgery prior to diagnosis, and 62% of subjects were intubated prior or during the time they were diagnosed with a VTE. Thirty-one per cent of subjects were on steroids at the time of VTE diagnosis.

Biss *et al*. analysed risk factors for VTE in adolescents based on data from eight tertiary centres in the UK [13]. Between 2008 and 2014, 76 cases were diagnosed. The identified risk factors were as follows: reduced mobility – 45%; thrombophilia – 24%; malignancy – 20%; surgery – 18%; combined oral contraceptive pill – 12%; and congenital venous anomaly – 5%. Twenty-eight patients (37%) had no significant underlying diagnosis and no provoking event. Patients who were post-pubertal or over 15 years old are at higher risk of developing VTE after major trauma assessed as Injury Severity Score > 25 [14–17].

TABLE 1. The most important risk factors of venous thromboembolism in hospitalised children mentioned in the literature (listed alphabetically due to current lack of expert consensus or data regarding relative risk contribution)

• Anticipated hospitalisation > 72 h
• Active cancer
• Central venous catheter
• Oestrogen therapy started within the last month
• Inflammatory disease (e.g. Crohn's disease, ulcerous colitis)
• Intensive Care Unit admission
• Mechanical ventilation
• Mobility decreased from baseline
• Obesity (BMI > 99th percentile for age)
• Post-pubertal age
• Severe dehydration
• Surgery > 90 min within last 14 days
• Systemic or severe local infection
• Trauma as admitting diagnosis

The analysis of a Swedish registry (164 cases of paediatric VTE in southern Sweden between 2001 and 2015) indicated that the most frequent acquired risk factors were: the hormonal therapy (34%), concomitant malignancy (21%), infection at the time of thrombosis (19%), or a CVL (central venous line) (15%). Genetic thrombophilia risk factors were found in 45 out of 164 (27.5%) [6].

There are minimal specific paediatric data concerning the other risk factors that are reported in the adult population. A retrospective, case-control study of 48 children with VTE identified increased risk in obese children but not in overweight children [18]. Tuckuviene et al. conducted an analysis of correlation between obesity and VTE in children with haematological malignancies but failed to prove an association [19].

Multiple studies have implicated prolonged immobility as a risk factor for paediatric HA-VTE without indicating the "risky' duration of immobilisation [9].

The contribution of congenital thrombophilia and the need for routine screening of children with VTE for genetic disorders remain controversial [20]. Most authors agree that thrombophilia testing should be considered in children with recurrent thrombosis, spontaneous, and non-provoked VTE, and in children with VTE who have a family history of thrombosis or a close relative diagnosed with inherited thrombophilia [21].

In a Dutch survey, 56 children out of 115 diagnosed with VTE were tested for genetic disorders. The inherited problem was confirmed in: factor V R506Q mutation – four cases, protein S deficiency – three cases, protein C deficiency – one case, factor II G20210A mutation – one case, and hyperhomocysteinaemia – one case. One child had a combination of protein S deficiency and factor V R506Q mutation [3]. Data from southern Sweden showed that genetic thrombophilia risk factors were found in 45 out of 164 children with VTE (27.5%); the most common were Factor V Leiden (FVL) in 35 cases (21%), Factor II mutation in four cases (2%), and double heterozygosity for FVL and FII mutation was found in two patients (1%). Plasma deficiency of protein S was found in five cases, protein C deficiency in six cases, and antithrombin deficiency in one patient (who had three episodes of VTE) [6].

Thrombosis was also confirmed in acquired prothrombotic disorders as nephrotic syndrome [3], or those accompanied by the presence of antiphospholipid antibodies (APLAs). The incidence of VTE in children with APLAs due to systematic lupus erythematous ranges from 21 to 57% [20].

SURGERY AS A RISK OF THROMBOEMBOLISM IN CHILDREN

It is estimated that almost 40 to 46% of paediatric VTE episodes occur in coincidence with surgery [11]. Humes published analysis of data from UK hospitals from 2001 to 2011 [22]. Among 15,637 surgical patients, six cases of VTE were recognised, i.e. 0.4 cases per 1000 surgical patients versus 0.04 per 1000 children in the population. No incidence of VTE was observed in children after inguinal hernia repair and one-day surgery. The American College of Surgeon's National Surgical Quality Improvement Program-Paediatric (NSQIP-P), revealed that the risk of VTE event among 218,432 surgical patients between 2012 and 2015 was 0.11% in general but 0.2% for inpatient surgery [23]. In total 305 patients (0.20%) developed 296 venous thromboses and 12 pulmonary emboli. Median time to VTE was nine days. Most VTEs (81%) occurred pre-discharge. Subspecialties with the highest VTE rates were cardiothoracic (0.72%) and general surgery (0.28%). No differences were seen for elective vs. urgent/emergent procedures. All-cause mortality of VTE patients was 1.2% vs. 0.2% in patients without VTE [24]. Urological surgery was connected with an incidence of 0.12% VTE complication, and the risk was greater for hospital surgery versus ambulatory: 0.2 vs. 0.012% [25]. Baker *et al*. queried the same database for patients undergoing an orthopaedic surgical procedure between 2012 and 2013 [26]. Of 14,776 cases, 15 patients (0.10%) experienced postoperative VTE. Deep vein thrombosis (DVT) occurred in 13 patients (0.09%), and pulmonary embolism developed in two patients (0.01%). The procedure with the highest VTE rate was surgery for infection (1.2%). Patient factors associated with the development of VTE included hyponatraemia, abnormal partial thromboplastin time, elevated aspartate transaminase level, and gastrointestinal, renal, and haematological dis-

orders. Complications associated with VTE included prolonged hospitalisation, pneumonia, unplanned intubation, urinary tract infection, and central line-associated bloodstream infection. No patients with VTE have died.

The incidence of VTE in paediatric orthopaedic and spinal surgery is very low. Georgopoulos *et al*. analysed the data from 44 USA hospitals: among 143,808 children admitted for orthopaedic surgery 74 thromboembolic events (6.3 per 10,000 patients) were identified, and four children (5.4%) have died [27]. The authors excluded patients with infection, malignancy, trauma, and coagulopathies. The most important risk factors in this analysis were: in-patient versus out-patient surgery, metabolic disorders (dehydration, hypernatraemia, hyperosmolarity, obesity), and complications of implanted devices or surgical procedure. As far as the type of surgery is concerned, the risk for VTE was the greatest for spinal surgery – 18.1/10,000 admissions. Shore made a retrospective analysis of 4583 children with neuromuscular complex chronic conditions, who had undergone an elective spine and lower-extremity surgery between 2005 and 2009 at six centres. He excluded patients with pre-existing central vein catheter. He found only two cases of VTE complication – both in children with a known coagulation disorder. He concluded that there was no antithrombotic prophylaxis in this type of surgery unless other known risk factors are present [28]. In a survey of Scandinavian scoliosis centres between 1963 and 1976, deep venous thrombosis was reported in eight out of 1229 cases (0.65%), with only three cases between ages 15 and 18 years [29]. In a recent article, 40 successive adolescents undergoing surgery for scoliosis underwent regular ultrasonography to look for deep venous thrombosis. Two minor transient thromboses were identified, which resolved spontaneously, so the authors concluded that there are no grounds for routine antithrombotic prophylaxis [30].

The overall risk of thromboembolism in children is still very low compared to its incidence in adults, where data indicate an incidence of between 104 and 184 per 100,000 persons per year in Europe [31], but the consequences for children with VTE and the burden for the healthcare system are significant. The VTE complication in a child requires 8.1 days longer hospitalisation and the total additional hospitalisation cost amounts to $27,686, compared to $17,848 for adults [32]. Additionally, mean expenditures for children with secondary VTE are five times higher than for children with idiopathic VTE [33]. Post-thrombotic syndrome is diagnosed in 20–63% children with VTE [34, 35]. The exact incidence of pulmonary embolism is unknown, although it is reported between 8.6 to 57 per 100,000 hospitalised children and 0.4 to 0.9 per 100,000 children in the population [2, 3, 36], with a mortality rate of 8% [37]. A relatively high incidence of pulmonary embolism was registered in Sweden – 21 cases of PE per 164 children with thromboembolic complications in the years 2001–2015 [9]. Nevertheless, this data can be underestimated. In Buck's study the pre-mortem diagnosis was considered only in 15% of cases diagnosed at autopsy [38]. Basing on Paediatric Health Information 2001–2014, in the USA the incidence of pulmonary embolism in children increased from one (2001) to six (2014) per 10,000 children discharged from the hospital – which indicates a 200% increase [39].

The mortality rate due to VTE is assessed as 11.4 per 1000 child-years (Canadian data) [40] or 1.73% (Dutch analysis) [3].

In 2012, the Children's Hospitals Solutions for Patient Safety (a collaborative of 33 children's hospitals dedicated to implementing HAC [hospital-acquired conditions] best practice prevention bundles) acknowledged VTE as the second most common cause of preventable harm in the 80 paediatric hospitals currently associated with this network [41].

The question arises of whether a child needs antithrombotic prophylaxis in the perioperative period.

Hospital-acquired thromboembolism is preventable in adults – multiple randomised controlled trials have shown the superiority of pharmacologic prophylaxis, compared to placebo, in reducing the incidence of VTE in high-risk patients. There is also a consensus that risk assessment markedly reduces the rate of VTE in hospitalised adults [42].

In children the safety and efficacy of perioperative thromboprophylaxis is controversial due to the low incidence of the problem, bleeding risk, and lack of high-quality randomised controlled trials. There are no widely accepted evidence-based recommendations concerning perioperative prophylaxis. Nevertheless, there is consensus that universal thromboprophylaxis cannot be recommended and only high-risk children can benefit from prophylactic treatment, so the risk assessment is a key issue in VTE prevention. Based on published or local data and individual experience, some local recommendations emerged. Padhye published a Canadian prophylaxis algorithm for paediatric surgical orthopaedic patients, which was developed after a literature review, consultation with national and international experts, as well as using a consensus development conference [43]. Based on available literature, age > 14 years, body mass index (BMI) > 30 kg m^{-2}, limited or altered mobility for > 48 hours, cardiovascular flow anomalies, metabolic syndromes, central venous catheter, prolonged surgery (defined herein as surgery > 120 minutes), as well as repeat and complicated surgery (at the discretion of the surgeon)

TABLE 2. Risk factors of paediatric thromboembolism defined by the Association of Paediatric Anaesthetists of Great Britain and Ireland – for children age 13+

Patient related
• Central venous catheter
• Active cancer or cancer treatment
• Dehydration
• Known thrombophilia
• Obesity (BMI > 30 kg m^{-2})
• One or more significant comorbidities (e.g. congenital or low output heart disease, metabolic or inflammatory condition)
• Personal history of venous thromboembolism first-degree relative with a history of venous thromboembolism age < 40 years
• Use of oestrogen-containing contraceptive therapy
Admission related
• Significantly reduced mobility for 3 days or more
• Severe trauma with injury severity score (ISS) > 9
• Spinal cord injury with paralysis
• Total anaesthetic + surgical time > 90 minutes
• Acute severe sepsis
• Surgery involving pelvis or lower limb with total anaesthetic + surgical time > 60 minutes
• Critical care admission intubated and ventilated
• Severe burns

were accepted by consensus as risk factors for VTE. In all patients, early ambulation and passive motion exercises are encouraged. In patients with three and more risk factors, the use of mechanical prophylaxis is recommended. The presence of four risk factors defined patients at high risk for VTE and prompted a haematology consultation and consideration of pharmacological prophylaxis [43].

In 2018, the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) Guidelines Working Group on Thromboprophylaxis in Children, based on a thorough review of the literature, produced national guidelines on perioperative thromboembolism prophylaxis in children [44]. According to the guidelines, perioperative prophylaxis is not recommended in younger children. Because adolescents are at slightly higher risk of VTE, all children over 13 years old should be assessed for risk factors. The risk factors defined by the APA are listed in Table 2. The authors recommend mandatory stepwise management in all children over 13 years of age, especially if immobilisation for more than 48 hours is expected, to ensure proper hydration and quick mobilisation, and to reduce risk factors (e.g. removing CVC as quickly as possible). If a child presents with up to two risk factors, the authors recommend consideration of mechanical prophylaxis. In children with more than two risk factors, bleeding risk assessment is recommended, and if there are not risk factors, low molecular weight heparins (LMWH) should be considered.

Interesting and straightforward advice towards perioperative VTE prophylaxis was presented in Australia [45]. Clinicians of the Royal Children's Hospital of Melbourne developed local recommendations for post-pubertal children admitted for prolonged surgery (defined as lasting more than four hours). In children without additional risk factors, the guidelines recommend early ambulation, calf compression, and the use of elastic compression stockings. In children with any of risk factors (obesity, oral contraceptive, central venous access devices, immobilisation for more than four days, dehydration, sepsis, family history of or known thrombophilia) enoxaparin subcutaneously once daily is recommended.

Many other local protocols have been proposed [46]. All of them concern postpubertal children, and all of them consider immobilisation as an important determinant of VTE, but interestingly there is significant variability in the other risk factors considered. Mechanical prophylaxis is generally recommended for low- and moderate-risk patients, while pharmacological treatment is reserved only for high-risk children. Which risk factors are of greatest importance and how many of them constitute high risk is still an open question.

METHODS OF THROMBOPROPHYLAXIS

Mechanical methods may reduce lower limb venous stasis and increase blood velocity. Anti-embolism stockings reduce venous distention and direct superficial venous return to the deep system, thus increasing flow. Intermittent pressure compression boots (IPCs) – inflatable garments that wrap around the legs and provide pulsatile compression – prevent venous stasis in the deep leg veins and promote fibrinolysis [47]. Systematic reviews have shown their efficacy in preventing thromboembolism in adults [48, 49]. Unfortunately, similar studies have not been conducted in the paediatric population. Nevertheless, based on experience and evidence from the adult population, they are widely recommended for all patients 13 years of age or older, who are expected to have a surgical procedure lasting over 60 minutes [44, 46]. They should be started following induction of anaesthesia. The use of mechanical methods is limited to older and larger children, teenagers, and those weighing > 40 kg. Contraindications include massive leg oedema or pulmonary oedema (congestive heart failure), severe peripheral vascular disease or neuropathy, local conditions as dermatitis, recent skin graft/poor tissue viability, leg wound infection, and extreme limb deformity.

In children, LMWH is the preferred anticoagulant drug. However, controversies exist over the current

optimal dosages and safety in children because recommendations are based on small observational studies and case reports, and are largely extrapolated from adult data. The use of LMWH in children has recently been widely reviewed by Klaassen *et al*. [50]. The authors evaluated all published studies between 1980 and October 2017 concerning dosage, safety, or efficacy of LMWH in neonates and children up to 19 years of age. The most commonly used drugs include enoxaparin and dalteparin. Neonates need a higher mean dose of enoxaparin than older children because of the interaction between the drug and age-dependent plasma proteins and pharmacokinetic parameters: increased volume of distribution and faster renal clearance. The mean dose required to reach prophylactic anti-Xa levels is about 0.5 mg kg^{-1} per 12 h for children from 0 to 18 years of age. In the prospective dalteparin cohort study, the mean prophylactic dose to reach prophylactic target range was 95 IU kg^{-1} per 24 h in 12 children from 0 to 18 years of age [51]. In another multicentre prospective trial using dalteparin subcutaneously twice daily for acute VTE in children, median (range) therapeutic doses by age group were as follows: infants 180 IU kg^{-1} (146–181 IU kg^{-1}); children 125 IU kg^{-1} (101–175 IU kg^{-1}); and adolescents 100 IU kg^{-1} (91–163 IU kg^{-1}) [53]. 2.2% of patients experience a new VTE during dalteparin therapy [52].

The major bleeding rate for prophylactic use of LMWH is low. In a review of 18 studies by Klaassen *et al*., including 1286 children, bleeding events were reported only in eight children receiving prophylactic dosages of LMWH [50]. Two neonates experienced frontal lobe subdural haematoma whilst receiving enoxaparin after single ventricle heart surgery. A single patient had a postoperative gastrointestinal bleed, another one developed a major bleed during surgery, and one experienced an intracranial haemorrhage. Three patients had minor bleeding.

Although until now most of the studies have been retrospective cohort studies and data from randomized controlled trial are lacking, LMWH seems to be safe and effective for the prevention of VTE in children.

CONCLUSIONS

The incidence of perioperative thromboembolic events in the paediatric population is generally very low, so standard anti-thrombotic prophylaxis is not recommended. Nevertheless, there is growing evidence that this incidence is increasing and that in certain groups of patients it can have serious sequelae. Due to a lack of high quality RCTs, there are no widely accepted guidelines concerning perioperative thromboprophylaxis in children. However, there is a consensus that the risk of VTE should be routinely assessed in adolescent children. Which risk factors are of greatest importance and co-occurrence of how many of them constitutes high risk remain open questions. The same controversies concern pharmacological anti-thrombotic therapy. What we can safely do is ensure hydration, encourage prompt mobilisation and passive exercise, and quick withdrawal of CVC. Additionally, in some children with many risk factors mechanical prophylaxis and anti-thrombotic treatment can be a good choice.

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