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Short Communication

Dabigatran *versus* Warfarin for the Treatment of Pediatric Thromboembolism: A Pilot Randomized Trial

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Abstract

Background: Venous thromboembolism (VTE) is still a problematic situation in children. Drugs like warfarin, enoxaparin, and heparin are current standard of care in childhood VTE. This study was designed to compare the efficacy of warfarin with dabigatran etexilate in children with VTE.

Methods: This randomized and active-controlled study was done in Amir-Kabir Hospital, Arak, Iran. Twenty-five children aged between 6 and 18 years with VTE were included. Study subjects were randomized 1:1 to enoxaparin 1 mg/kg twice daily and daily 0.2 mg/kg warfarin or enoxaparin 1 mg/kg twice daily and dabigatran etexilate twice daily. Enoxaparin therapy was continued for 5 days. Treatment with warfarin and dabigatran continued for 6 months. Patients were monitored for minor and major bleeding events, thrombus extension or recurrence, and death.

Results: A total of 23 patients presented with deep-vein thrombosis completed the study and followed up over the course of 6 months. Dabigatran had similar effects to warfarin with respect to the thrombus cure, which occurred in 10 patients in the dabigatran group (90 %) and 9 patients in the warfarin group (81%). There were no differences in the frequency of bleeds, either major or minor ($P > 0.05$). GI upset was the most common side effects seen in both groups, and the differences were significant ($P < 0.05$).

Conclusion: Our study suggests that a 6-month treatment with dabigatran and warfarin had similar effects in secondary prevention of VTE in children < 18 yr. Dabigatran therapy was associated with more gastrointestinal upset.

Introduction

Venous thromboembolism (VTE) is a problematic situation in children and the need for the anticoagulation is increasing. A 70% rise has been seen in overall annual incidence of VTE in the pediatric population per 10,000 hospital admissions.[1,2] Central venous access catheter (CV line), immobility, arterial catheter, paresis, and some medications are linked with the development of pediatric VTE.[3,4] It is noteworthy that there is an important difference in levels of haemostatic proteins between children and adults. During growing, this difference will be diminished and the proteins reach the adult range.[5] The developmental hemostasis may cause a significant difference in pharmacological responses between adults and pediatrics. Most of current standard of care in pediatric VTE are extrapolation of adult data. Unfractionated heparin (UFH), low molecular-weight heparins (LMWHs), and vitamin K antagonists (VKAs) are current choices in childhood VTE.[6,7] Parenteral administration of medications, frequent blood tests, dose adjustments, and several interactions are general disbenefits linked to these medications.[6-8] Direct oral anticoagulant drugs (DOAC) like rivaroxaban and dabigatran can inhibit coagulant factors with a predictable pharmacokinetic profile. DOACs are a unique anticoagulant class since they require no monitoring. They are used in a variety of conditions, including DVT prevention and treatment. They are also effective in preventing and treating pulmonary embolism. Low dose rivaroxaban plus aspirin can be used in cardiovascular events.[9,10] Among DOACs, dabigatran etexilate is gaining extensive use in adults, albeit having

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an unlicensed application in pediatrics. Dabigatran is the only FDA approved drug which is administered orally and can directly inhibit thrombin. Compared to VKA, it has important advantages; predictable pharmacokinetics, fixed dosing, predictable pharmacological responses, and no need for coagulation monitoring.[11] During recent years several works have been done to provide evidence for pharmacokinetics and safety assessment of dabigatran in children and infants. Due to lack of evidence for dabigatran effects in pediatric VTE, present study was designed. We aimed at comparing the efficacy of dabigatran etexilate with warfarin in children aged ≤ 18 years.

Materials and Methods

Study design

This randomized, active-controlled, open-label, parallel-group, and single center study was done in Amir-Kabir Hospital, Arak, Iran. The clinical trial registry number was IRCT20180711040431N1. Sealed envelopes with an enclosed assignment were used for allocation concealment, and simple randomization method was used. Children who aged between 6 years and 18 years with diagnosed Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) were included. VTE was defined as a combination of deep-vein thrombosis and pulmonary embolism which may be fatal or nonfatal. Diagnosis of VTE was done using bilateral Doppler sonography or venography, angiography, lung scanning, and computed tomography of pulmonary arteries. Included patients received initial treatment with enoxaparin (Sanfoi, France) for 5 days. They were randomized 1:1 to 0.2 mg/kg warfarin (Orion, Finland) dabigatran etexilate twice daily (Boehringer Ingelheim, Germany). According to Hayton's scaling method, dose calculation was done using a normogram based on weight and age of children. Treatment with warfarin and dabigatran continued for 6 months. Warfarin therapy was started concurrently with enoxaparin to achieve and maintain the International Normalized Ratio (INR) between 2.0 and 3.0. Dabigatran was initiated after discontinuation of enoxaparin. Participants were excluded if they had active bleeding, surgery, history of major bleed with any cause, hypersensitivity to study drugs, pregnancy, hepatic diseases with aminotransferase exceeding 3 times the upper limit of normal range, and renal failure (estimated Glomerular Filtration Rate of less than 30 ml/min). Patients were discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation.

Efficacy measures

Incidence of symptomatic recurrent VTE was the primary efficacy outcome. Recurrent VTE diagnosis was established like the initial diagnosis. Patients were visited daily for 7 days and then were visited monthly for 6 months. Parents and older patients were trained for possible adverse effects of warfarin and dabigatran and also symptoms of VTE. They were asked to call the clinic immediately in case of any problem.

Safety measures

Patients were monitored for bleeding. Major bleeding was defined as overt bleeding with 2 g or more per deciliter fall in hemoglobin requiring transfusion of 2 or more units of red cells. Non-major bleeding was defined as overt bleeding without criteria of major bleeding. Hepatic and renal functions were evaluated as well. For assessment of adverse effects of the drugs, patients were monitored weekly for dyspepsia, any bleed, and signs of hypersensitivity including rash, urticarial, and pruritus. Recombinant factor VIIa, Vitamin K, and FFPwere our therapeutic choices for reversal of warfarin and dabigatran overdoses.

Data analysis

Shapiro-Wilk was used to test normality of data. We used x^2 and Fisher's exact test to study the associations between variables. $P < 0.05$ was considered as statistical significance. Analysis was carried out using SPSS software version 18.0, Chicago, USA.

Results

Baseline characteristics

Of the 25 patients who were included 2 patients did not receive the treatments (1 did not use the medications, and 1 met the exclusion criteria). No patient was lost to follow up and all 23 participants were observed over the course of 6 months. Table 1 shows the clinical characteristics of study participants.

Table 1. Characteristics of patients at baseline in two groups.

Characteristics	Warfarin (n=12)	Dabigatran (n=11)	P value
Age, y	11.4 ± 4.3	12.1 ± 2.1	0.5
Age (range)	7-15yr	6-14yr	0.5
Female	7 (58)	6 (54)	0.7
Male	5 (42)	5 (45)	0.8
Body weight (Kg)	11 ± 3.7	13 ± 3.9	0.6
Admission diagnosis			
Pneumonia	1 (8.3)	1 (9)	0.5
Sepsis	2 (16.6)	1 (9)	0.5
Trauma	4 (33.3)	3 (27.2)	0.5
Surgery	4 (33.3)	5 (45.4)	0.6
Cancer	1 (8.3)	1 (9)	0.4
Platelets, 10^9/L	253 ± 110	254 ± 109	0.6
VTE			
DVT	7 (58.3)	7 (63.3)	0.4
PE	3 (25)	2 (18.1)	1.0
DVT + PE	2 (16.6)	2 (18.1)	0.2
Total WBC count,10^9/L	7.7 ± 3.3	6.8 ± 2.1	0.7
ALT range (U/L)	5-49	5-48	0.6
AST range (U/L)	12-32	13-38	0.7

Data are shown as mean ± SD or number (%). x^2 and Fisher's exact text were used. VTE: venous thromboembolism, DVT: deep venous thrombosis, PE: pulmonary embolism, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

The mean age was 12 ± 2.9 years with an excess of females (56 % vs 44 %). No significant differences in patients' characteristics were seen at baseline. All patients had

normal range of liver aminotransferases and normal renal function. Surgery and trauma were the most common causes of hospital admission. Previous history of DVT was the most common event in both groups; two patients in both groups had history of DVT with PE. Participants' flow through is shown in Figure 1.

Efficacy

All patients received enoxaparin for 5 days. During the observation 10 % of patients receiving warfarin were below the therapeutic range of INR and 11% were above it. As shown in Table 2, two patients experienced recurrent DVT in warfarin group and no children had recurrent DVT in dabigatran group (P > 0.05). There was no case with recurrent PE in both groups and no patient died due to VTE or its complications.

Table 2. Efficacy measure of two treatments.

Characteristics	Warfarin (n=12)	Dabigatran (n=11)	P value
Symptomatic DVT	2 (16.6)	0	0.09
Symptomatic PE	0	0	0.1
Death	0	0	0.1

Data are shown in number (%), Fisher's exact test was used, DVT: deep venous thrombosis, PE: pulmonary embolism.

Safety

The study was not stopped before the 6 months due to severe adverse effects of treatments and no patient died. Adverse effects are shown in Table 3. One patient had major gastrointestinal bleeding in spite of normal INR values in warfarin group, and no patient on dabigatran had major GI bleeding (P > 0.05). Two patients receiving warfarin had minor bleeds and 1 patient in dabigatran group experienced minor bleeds (P > 0.05). In addition, 2 patients in warfarin group and 1 patient in dabigatran group had elevation in alanine aminotransferase and aspartate aminotransferase which were not exceeding 3 times the upper limit of normal.

Table 3. Safety measure of two treatments.

Characteristics	Warfarin (n=12)	Dabigatran (n=11)	P value
Major bleed*	1 (8.3)	0	0.06
Minor bleed	2 (16.6)	1(9.0)	0.5
Rise in ALT†	0	0	0.1
Rise in AST†	0	0	0.1
Gastrointestinal upset	1 (8.3)	3 (27.2)	0.03

Data are shown in number (%), Fisher's exact test was used. * Gastrointestinal hemorrhage, †three times upper limit of normal, ALT: alanine aminotransferase, AST: aspartate aminotransferase

The between group differences were not significantly different (P > 0.05). Three patients in dabigatran group and 1 patient in warfarin group had mild gastrointestinal upset (P < 0.05). No case with renal dysfunction was observed.

Discussion

This study provided the first evidence on dabigatran and warfarin comparison in childhood VTE. In this randomized trial we compared effects of dabigatran with warfarin during the 6 months of treatment and we found that dabigatran is as effective as warfarin for the prevention DVT/PE in children. Of note, we observed 2 cases of recurrent DVT in patients who received warfarin. It should be taken into account that our sample size was quite small and it is difficult to interpret the present results. This was hypothesis-generating study and confirmatory investigations are needed. However, small studies can test the hypotheses and avoid spending a considerable amount of resources. Regarding this limitation and various difficulties to recruit and follow up children, we tried to conduct a well-designed small size trial. Dabigatran is a small molecule which directly inhibits free thrombin. In addition, it can inhibit clot-bound thrombin. Bioavailability of dabigatran is 3-7 % and the half-life is about 15 hours. Renal excretion is the main route of elimination. In patients with moderate

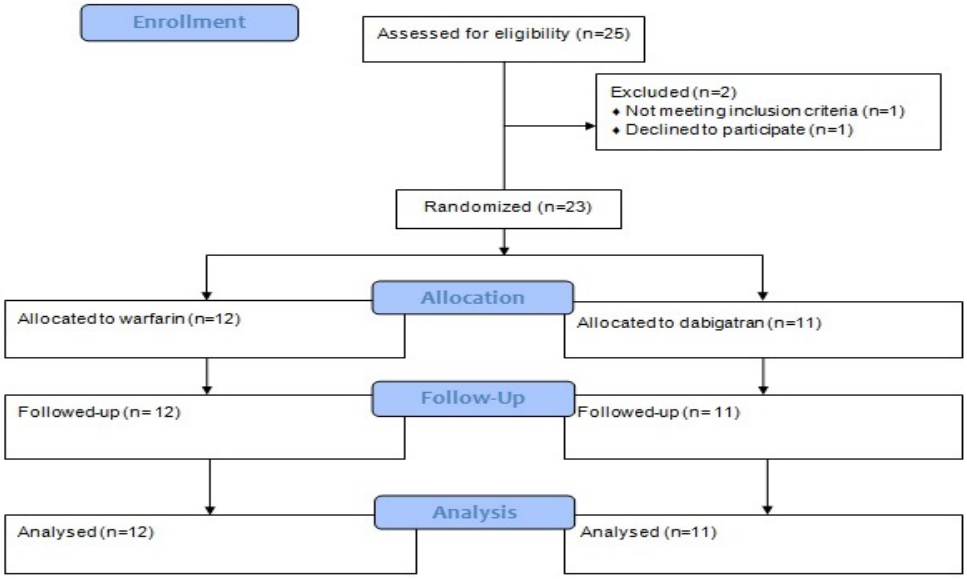

Figure 1. Consort diagram detailing study subject.

to severe renal impairment, dabigatran dose should be reduced. Few drug interactions, wide therapeutic window, no food interaction, and no drug monitoring are notable advantages of dabigatran.[12-15] It is of note that current data about pediatric use of dabigatran is very limited. Halton's study provided the first evidence for pharmacokinetic and safety profile of dabigatran in 18 children.[16] Authors in this single arm study reported no recurrent VTE in children aged < 12 yr. In addition, it found no case with major or minor bleed in spite of receiving dabigatran. Mild respiratory tract infection, ear pain, and back pain were reported in patients which might be irrelevant to dabigatran. All of these effects were recovered. Another work by Halton proved that dabigatran had no serious adverse effects including bleeding events or death even in infants. However, one case of aortic stenosis was reported which might not be related to dabigatran effects. The study showed that dabigtran had predictable PK/PD properties which was similar to adults.[17] To gain more reliable and valid data, all new drugs must be authorized by regulatory agencies like Food and Drug Administration (FDA) or European Medicines Agency (EMA) and must have Pediatric Investigation Plan (PIP). Notably a quite recent work by Brandão showed an acceptable safety profile of dabigtaran in 200 children with VTE. This was a single arm investigation to study safety of dabigatran in secondary prevention of VTE. Minor bleeds were the most common untoward effects of dabigatarn seen in 18% of included children.[18] At present, warfarin is the anticoagulation of choice in pediatric VTE particularly in patients who need long period of treatment. Warfarin interrupts the hepatic synthesis of clotting factors by inhibition of vitamin K epoxide reductase complex 1(VKOR1). Bioavailability of warfarin is 90% and the half-life is about 40 hours. Warfarin needs dose reduction in subjects with severe hepatic impairment. Slow onset, frequent blood sampling, interaction with other drugs and foods, risk of bleeding, unpredictable pharmacokinetics, and slow offset are main problems of warfarin.[19-21] Among them, frequent vascular access is challenging in children. The use of warfarin is particularly difficult in infants due to vitamin K intake through milk. In practice, warfarin is a very effective drug with several difficulties particularly in children. As previously mentioned, no trials have been implemented to compare warfarin with DOACs in children. Schulman's study demonstrated that dabigatran is as effective as warfarin for treating acute VTE in adults.[22] This study reports similar safety profile for both drugs. Moreover, RE-LY trial showed that both warfarin and dabigatran were effective in atrial fibrillation, however, rate of bleeding was higher in patients received warfarin.[23] In our study, except mild gastrointestinal upset which had higher rate in dabigtran group and one case of major bleeds which was reported in warfarin group, both drugs had same safety profile without affecting the liver and renal functions. It is noteworthy that dabigatran was prescribed after initial treatment with enoxaparin. Of note, there are some issues to officially authorize DOACs for children. One of challenges is limited number of patients with VTE. Although the incidence of pediatric VTE is increasing, it is still a problem to recruit children. Severe underlying diseases, lack of parental permissions to test new drugs, low level of cooperation, and finally unwillingness of practitioners to test new drugs in children are main limitations of clinical trials in children. Such issues may explain why several drugs including cardiovascular agents have not been officially authorized in children. Of special note is cost of these 2 treatments; warfarin is inexpensive and cost-effective in many parts of the world. As an important study limitation, it should be noted that due to small sample size, our findings are preliminary and large investigations should be done to provide more insights into efficacy, safety, and interactions of dabigatran. Of note potential drug interactions of dabigatran and its correlation with adverse effects of treatments should be focused by future works. This study was was a preliminary trial and we used all available and evaluable patients, therefore, we had no power- based sample size calculation.

Conclusion

Our study suggests that a 6-month treatment with dabigatran and warfarin had similar effects in VTE prevention in children ≤ 18 years. Of note, dabigartan therapy was associated with more GI upset. Our findings are from a hypothesis-generating study and large trials should be done to verify our results.

Ethical Issues

Ethics Committee approved the study (IR.ARAKMU.REC.1397.082) and written informed consent was obtained from parent(s) or legal representative.

Data Sharing

Applicants can obtain data by contacting the corresponding author.

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Conflict of Interests

The authors claim that there is no conflict of interest.

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