STUDENTS' CORNER
RESEARCH ARTICLE

Rivaroxaban for Venous Thromboembolism (VTE) in Paediatric Patients: An institutional retrospective observational study from the Low/Middle Income setting in Pakistan

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Abstract

Objective: To evaluate bleeding events, mortality, recurrence and prescribing practices in paediatric and adolescent patients of venous thromboembolism using direct acting oral anticoagulants (DOACs).

Method: The descriptive, retrospective study was conducted from November 2021 to May 2022 at the Aga Khan University Hospital and comprised data from 2017 to 2021 of patients from birth to 18 years who received DOACs for prophylaxis or treatment purposes of venous thromboembolism. Data was analysed using STATA MP.15.

Results: Of the 45 patients, 37(82.2%) were males and 8(17.8%) were females. The overall median age was 16 years (interquartile range: 12.5-18 years). Of the total, 33(73.3%) patients were treated for acute venous thromboembolism, while 12(26.7%) received anticoagulants as prophylaxis. Complete thrombus resolution was achieved in 15(45.5%) patients, partial resolution in 3 (9.1%), and no resolution in 4(12.1%). Recurrence of venous thromboembolism occurred in 2(6%) patients. Enoxaparin was prescribed in 24(53.3%) cases, rivaroxaban in 14(31.1%) and heparin in 7(15.6%). There were 13(28.9%) deaths in the cohort.

Conclusion: Rivaroxaban may be safe in the management of paediatric venous thromboembolism, with no major bleeding complications observed in our study.

Keywords: Rivaroxaban, Direct oral anticoagulants, Paediatric, Low middle-income country. (JPMA 75: 851 2025)

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Introduction

Venous thromboembolism (VTE) has been established as a cause of significant morbidity and mortality in paediatric patients.[1] Most children have underlying complex medical conditions, such as paediatric cancers, congenital heart diseases, and inherited metabolic and congenital disorders, that put patients at risk for thromboembolic events.[2] This may be due to the use of central venous catheters and surgical procedures, both of which are associated with an increased risk of thrombosis.[3-6] Estimates of the annual incidence of paediatric VTE range from 0.07 to 0.49 per 10,000 children of all ages. VTE incidence is notably higher in hospitalised patients, up to 4.9-21.9 per 10,000 hospital admissions, with the highest risk in children aged <12 months and in adolescents aged 11-18 years.[7-10] As one of the leading causes of hospital-acquired morbidity for children, VTE, especially when acquired in hospitals, are associated with not only an increase in mean hospital costs, but also the mean length of hospital stay (LOS).[11]

Treatment decisions remain challenging because of the lack of high-quality paediatric evidence and are often extrapolated from adult studies and/or based on expert consensus opinion. The American Society of Haematology (ASH) published guidelines in 2018 for the treatment of paediatric VTE, but most recommendations are based on very little evidence.[12,13] Historically, anticoagulant treatment in children has often required parenteral administration of heparins (low molecular weight and unfractionated heparin), necessitating frequent blood sampling for laboratory monitoring.[14,15] In recent years however, a newer class of drugs, known as direct oral anticoagulants (DOACs), has seen a rise in usage among the paediatric population. Rivaroxaban, a DOAC, is the first oral factor Xa inhibitor (FXaI) introduced to clinical practice.[14] This agent has a rapid rate of absorption and high bioavailability. Rivaroxaban has a plasma half-life of 5-9 hours in younger adults, and of 11-13h in older patients, and has a low number of drug-drug interactions.[14,16,17]

The safety, efficacy and success of DOACs for VTE requires further assessment in the paediatric population, particularly in the setting of low- and middle-income countries (LMICs). The safety and efficacy profile of DOACs

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to treat VTE in children has been recently published by two large phase 2 and phase 3 clinical trials.[18-21]

The current study was planned to review retrospective data regarding the use of DOACs, particularly rivaroxaban, in the paediatric population, with the aim of highlighting the safety profile, adverse events, such as bleeding, mortality, VTE recurrence after cessation of DOACs, and the difference in cost between using low molecular weight heparin (LMWH) and DOACs.

Materials and Methods

The descriptive, retrospective study was conducted from November 2021 to May 2022 at the Aga Khan University Hospital (AKUH) and comprised data from 2017 to 2021 of inpatients from birth to 18 years of age who received DOACs for prophylaxis or treatment purposes of VTE. After approval from the institutional ethics review committee, data was retrieved, including demographic variables as well as pertinent laboratory, imaging and medication history. Outcome variables included adverse events linked to DOACs and the recurrence of VTE after the discontinuation of DOACs.

Data was analysed using STATA MP.15. Data was presented as median and interquartile range (IQR) or as frequencies and percentages, as appropriate.

Results

Of the 45 patients, 37(82.2%) were males and 8(17.8%) were females. The overall median age was 16 years (IQR: 12.5-18 years). Of the total, 33(73.3%) patients were treated for acute VTE, while 12(26.7%) received medication as prophylaxis. Major underlying conditions associated with VTE included malignancy 20(44.4%), trauma 10(22.2%) and infection 10(22.2%). There were 15(33.3%) patients with a peripherally inserted central catheter (PICC), and 13(86.6%) of them developed a VTE. There was no documented family history of thrombosis in the cohort. Activated protein C resistance was observed in 8(17.8%) patients, and 1(12.5%) of them experienced a recurrence of thrombosis after the cessation of therapy.

Immediate anticoagulation was performed using enoxaparin in 24(53.3%) cases, rivaroxaban in 14(31.1%) and heparin sodium in 7(15.6%). The median duration of therapy was 8 days (IQR: 7-201 days). Complete thrombus resolution was achieved in 15(45.5%) patients. Out of these patients, 4(26.7%) received rivaroxaban, 8(53.3%) received enoxaparin and 3(20%) were treated with heparin sodium. Partial resolution of thrombus was achieved in 3(9.1%) patients, and all 3(100%) were given enoxaparin. No thrombus resolution was identified in 4(12.1%) patients. and 3(75%) of them were given enoxaparin, and 1(25%)

Table: Data regarding population demographics, primary diagnoses, thromboembolic events, and resolution.

Variables	n (%)
Age (years)	
<4	1 (2.2)
4-6	1 (2.2)
7-12	10 (22.2)
13-18	33 (73.3)
Gender	
Male	37 (82.2)
Female	8 (17.8)
Primary Diagnosis	
Malignancy	20 (44.4)
Trauma	10 (22.2)
Infections	10 (22.2)
Others*	5 (11.1)
Hereditary hypercoagulable state (n=15)	
Yes	15 (100)
Antithrombin III deficiency	3 (20.0)
Protein C deficiency	3 (20.0)
Protein S deficiency	6 (40.0)
Homocysteinaemia	3 (20.0)
PICC line usage	
Yes	15 (33.3)
No	27 (60.0)
Unknown	3 (6.7)
Primary immediate Anti-Coagulation Used	
Rivaroxaban	14 (31.1)
Heparin	7 (15.6)
Enoxaparin	24 (53.3)
Thrombus Resolution Achieved	
Yes	15 (65.2)
No	4 (17.3)
Partial	3 (13.0)
Switched to another anticoagulation	1 (4.3)
Imaging Modality used for diagnosis	
MRA/MRV/MRI	9 (24.3)
CT	9 (24.3)
Doppler	17 (45.9)
Echo	2 (5.4)
Imaging Modality used to assess VTE recurrence	
MRA/MRV/MRI	5 (19.2)
CT	7 (26.9)
Doppler	13 (50.0)
Echo	1 (3.8)
Location of VTE	
Upper extremity	9 (20.0)
Lower extremity	9 (20.0)
CNS/Head and Neck	10 (22.2)
Internal Jugular Vein	3
Heart	2 (4.4)
Lungs	2 (4.4)
Subclavian	2 (4.4)
Portal vein	1 (2.2)
Subclavian vein	2 (4.4)
None	8 (17.8)

*Others included immunodeficiencies, heart defects and unidentified diagnosis; PICC: Peripherally inserted central catheter, VTE: Venous thromboembolism, MRA: Magnetic resonance angiography, MRI: Magnetic resonance imaging, MRV: Magnetic resonance venography, CT: Computerised tomography, CNS: Central nervous system.

was given rivaroxaban. In 11(33.3%) cases, the thrombus status could not be confirmed.

Serial imaging was performed in 24(53.3%) patients (Table), and the median duration for reassessment of developing VTE was 5 weeks (IQR: 4-6 weeks). There were 4(8.9%) patients who were reassessed within 4 weeks, while 3(6.7%) were reassessed between 12 and 18 weeks. Recurrence of VTE occurred in 2(4.4%) patients around 6 months after the discontinuation of rivaroxaban.

Adverse effects included gingival bleeding in 1(2.2%) and bleeding from the tracheostomy site in 1(2.2%). There were 13(28.9%) deaths in the cohort. Of those, 6(13.3%) were due to their primary oncological disorder. Other causes included sepsis, intractable seizures, immunodeficiency, and cardiomyopathy. There was 1(2.2%) mortality due to the progression of a pulmonary embolism (PE) in an adolescent, but compliance with rivaroxaban at home in this case could not be verified.

The cost of rivaroxaban for a child weighing 20kg using 10mg/day for 90 days was <$20 (PKR4,459) compared to enoxaparin $750 (PKR167,218).

Discussion

The primary findings of the current study included complete resolution of VTE in a significant proportion of the cases (45.5%) based on serial imaging, while no change in thrombus status was seen in 4 patients.

Our data also supports the favourable safety profile of rivaroxaban reported in literature.[22-24] The recurrence rate of VTE after the discontinuation of the drug was also low (6%). Out of 13 deaths, one could be attributed to the progression of VTE. The study could identify directly observed bleeding events in 2 patients, one with intermittent episodes of gingival bleeding, and one with an episode of bleeding from the tracheostomy site, which resolved on the discontinuation of rivaroxaban. It is noteworthy that standard anticoagulation was used prior to rivaroxaban administration in 31 patients. However, when rivaroxaban was used as the primary anticoagulant, there were no reported bleeding events.

Additionally, the current study found that rivaroxaban was more cost-effective than standard anti-coagulation medications. Medication noncompliance can be heavily attributed to the burden of the cost of medications worldwide, but especially in LMICs.[25-28] The cost to treat a child weighing 20kg for 90 days was almost $750 when using LMWH. This excluded the additional cost of $17 for consumables, like needles, syringes and alcohol swabs, required for the administration of LMWH. Moreover, the fear of needles and the trauma of injections twice daily experienced by the paediatric population is another downside of using LMWH. The same regimen was found to cost <$20 when a DOAC was given. With this disparity in cost, it is likely that adopting DOACS to treat thrombotic states will lead to a huge cost reduction in Pakistan, a country where the annual GDP per capita is between $1500-1600.[25,29,30]

The current study has limitations owing to its retrospective design and the short duration of follow-up, which is a challenge often faced in LMICs where treatment abandonment is common. The data were based entirely on medical records, and there was a lack of observable compliance with medications at home. The strength of the current study is the descriptive cost-effectiveness analysis. Besides, the AKUH is a large referral centre for all complex paediatric cases, which strengthens the generalisability of the findings.

Conclusion

Rivaroxaban was administered appropriately and safely in the management of paediatric VTE, with no major bleeding complications observed. Given its ease of administration, the absence of the need for therapeutic level monitoring, and cost-effectiveness, DOACs may emerge as the preferred agents for paediatric VTE treatment.

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Author Contribution:

AM: Data analysis, methodology, formal analysis and writing – original draft.

BM, ZF, AB & NM: Data analysis, writing, review and editing.

SA: Data analysis, Concept, methodology, writing, review, editing and supervision.