Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial

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BASED ON ARTICLE

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ABSTRACT

Background: The incidence of thromboembolism in children is much lesser as compared to adults. Most of the treatment options for pediatric thromboembolism are extrapolated from studies in adults with little direct documentation of its efficacy and safety in children. So far mainly parenteral heparin and vitamin K antagonists (VKA) are used in children as anticoagulants. This study was carried out in children with venous thromboembolism (VTE) to assess safety and efficacy of newer oral anticoagulant-Rivaroxaban compared to standard anticoagulants in children.

Methods: The study was conducted in 107 hospitals across 28 countries (Australia, Israel, Japan, and China, and countries in Europe, South America, and North America). Children from birth (> 37 weeks gestation and >2.6 kg birth weight) to 17 years of age with documented acute venous thromboembolism and who were initiated on heparin were enrolled. Children were assigned in 2:1 ratio to receive rivaroxaban or standard anticoagulants. It was an open label study, with randomisation stratified as per the age groups, site of venous thromboembolism and catheter-related venous thrombosis. Rivaroxaban was used either as a suspension or immediate release film coated tablets. The main treatment period was 3 months. Reassessment by imaging was done at the end of treatment period. The primary efficacy outcome studied included recurrence of venous thromboembolism, safety and side effects like bleeding were independently assessed.

Results: Over a period of 4 years, 520 children were screened and 500 of them were enrolled from Pediatric hospitals. 117 (23%) cases were Cerebral vein or sinus thrombosis (non-catheter related), 127 (25%) cases were catheter-related venous thromboembolism, and 256 (51%) cases were other non-catheter-related venous thromboembolism. The incidence of symptomatic recurrent venous thromboembolism was 1% in rivoraxaban group and 3% in standard anticoagulation group. 3% of children had bleeding, all in form of minor bleeds in Rivaroxaban group whereas 2% of children in standard group has bleeding including major bleeds in 2 children. Absolute and relative efficacy and safety estimates of rivaroxaban versus standard anticoagulation estimates were similar to those in rivaroxaban studies in adults. Imaging to evaluate efficacy showed an improved effect of rivaroxaban on thrombotic burden as compared to standard anticoagulants There were no treatment-related mortality.

Conclusions: Treatment with Rivaroxaban compared to standard therapy in children with acute venous thromboembolism resulted in a similarly low recurrence risk and reduced thrombotic burden without increased bleeding.

Commentary: The VTE in children is common in infants and adolescents thus representing bimodal peak. Over the last many years, incidence of thrombosis has been increasing in pediatric patients. It can be attributed to improved survival in preterms, increased use of central venous access devices, early detection and better survival of cancer patients and cancer therapies. Currently Unfractionated Heparin, Low molecular weight Heparin and VKA are used for the treatment for VTE in pediatrics. These are not optimal as Heparin is only available in parenteral form and VKA use requires frequent monitoring of PT/aPTT. The newer Direct Oral Aanticoagulant drugs (DOAC) like Rivaroxaban and Dabigataran are recently approved for use in paediatrics. They have the advantage of being able to be given orally and minimum need for monitoring.

The incidence of thrombosis in children is much lesser as compared to adults and most of the thrombosis treatment strategies are extrapolated from adult data.

Two trials -EINSTEIN Junior and DIVERSITY evaluated Rivaroxaban and Dabigatran for use in paediatric patients. These trials did not include neonates less than 37 weeks and body weight less than 2.6 kg. The trials used these DOAC after 5-21 days of parenteral anticoagulation. Both the trials had similar results in terms of thrombus resolution, prevention of recurrent VTE and no increase in bleeding events.

Apixaban and Edoxaban are other direct Xa inhibitors. There are ongoing Pediatric clinical trials to evaluate them.

Children with renal and liver dysfunction were excluded from both DIVERSITY and EINSTEIN Junior trial. So, at present there is no data on safety for use of DOAC in children with renal or liver function derangements.

Risk of abnormal uterine bleeding is noted in adult women on rivaroxaban. It needs to be studied in menstruating adolescent females with VTE.

Drug interaction-CYP3A4 is important for metabolism of Rivaroxaban. Drugs which may interact therefore are Rifampicin, Carbamezapine, Clarithromycin, Phenobarbitone, Fluconazole, Phenytoin and cyclosporin.

Interactions with DOAC are much less common in DOAC compared to VKA.

Rivaroxaban tablets can be crushed and mixed with applesauce but Dabigatrin capsule must be swallowed intact.

Studies have shown that the risk of bleeding with DOACs is low but targeted agents for reversal of DOAC are not available. Dialysis or hemo-filtration can be used to clear Dabigatrin but not for Rivaroxaban.

Andexanet alfa use is approved in adults for reversal of life threatening bleeds with rivaroxaban.

DOACs have several advantages over standard anti coagulation. Limitations for their use are unavailability of reversal agents, inadequate knowledge of drug interactions and no data of use in newborns < 37 weeks of gestation.

There are many trials ongoing which may provide additional data and guidelines to use other DOACs. Additional research is needed regarding reversal agents for DOAC and their pharmacokinetics, dose management during procedures.

Availability and approval of oral anti coagulants for paediatric patients will prove to be very effective over coming years for patients and their parents as they can be easily administered and require less monitoring.

Abbreviations:

VTE Venous thromboembolism

VKA-Vitamin K analogues

DOAC-Direct oral anticoagulants