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

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Summary

Background Treatment of venous thromboembolism in children is based on data obtained in adults with little direct documentation of its efficacy and safety in children. The aim of our study was to compare the efficacy and safety of rivaroxaban versus standard anticoagulants in children with venous thromboembolism.

Methods In a multicentre, parallel-group, open-label, randomised study, children (aged 0–17 years) attending 107 paediatric hospitals in 28 countries with documented acute venous thromboembolism who had started heparinisation were assigned (2:1) to bodyweight-adjusted rivaroxaban (tablets or suspension) in a 20-mg equivalent dose or standard anticoagulants (heparin or switched to vitamin K antagonist). Randomisation was stratified by age and venous thromboembolism site. The main treatment period was 3 months (1 month in children <2 years of age with catheter-related venous thromboembolism). The primary efficacy outcome, symptomatic recurrent venous thromboembolism (assessed by intention-to-treat), and the principal safety outcome, major or clinically relevant non-major bleeding (assessed in participants who received ≥1 dose), were centrally assessed by investigators who were unaware of treatment assignment. Repeat imaging was obtained at the end of the main treatment period and compared with baseline imaging tests. This trial is registered with ClinicalTrials.gov, number NCT02234843 and has been completed.

Findings From Nov 14, 2014, to Sept 28, 2018, 500 (96%) of the 520 children screened for eligibility were enrolled. After a median follow-up of 91 days (IQR 87–95) in children who had a study treatment period of 3 months (n=463) and 31 days (IQR 29–35) in children who had a study treatment period of 1 month (n=37), symptomatic recurrent venous thromboembolism occurred in four (1%) of 335 children receiving rivaroxaban and five (3%) of 165 receiving standard anticoagulants (hazard ratio [HR] 0·40, 95% CI 0·11–1·41). Repeat imaging showed an improved effect of rivaroxaban on thrombotic burden as compared with standard anticoagulants (p=0·012). Major or clinically relevant non-major bleeding in participants who received ≥1 dose occurred in ten (3%) of 329 children (all non-major) receiving rivaroxaban and in three (2%) of 162 children (two major and one non-major) receiving standard anticoagulants (HR 1·58, 95% CI 0·51–6·27). Absolute and relative efficacy and safety estimates of rivaroxaban versus standard anticoagulation estimates were similar to those in rivaroxaban studies in adults. There were no treatment-related deaths.

Interpretation In children with acute venous thromboembolism, treatment with rivaroxaban resulted in a similarly low recurrence risk and reduced thrombotic burden without increased bleeding, as compared with standard anticoagulants.

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Introduction

As a result of improved treatment and survival of children with life-threatening or chronic medical conditions and increased awareness among paediatricians, venous thromboembolism is being identified more often in childhood.[1,2] The incidence of venous thromboembolism in children has been estimated at 0·01–0·05 per 1000 children per year,[3–5] which is 20–100 times lower than in adults.[6] Children with venous thromboembolism constitute a challenge to paediatricians because, with only a single small randomised trial available,[7] there is a paucity of data about the effectiveness and harms of anticoagulants in this group.[8] Furthermore, the pathophysiology of thrombosis, its anatomical distribution, and pharmacological responses to anticoagulants differ between children and adults.[1,8]