Safety and efficacy of low molecular weight heparins in children: a systematic review of the literature and meta-analysis of single-arm studies


CRD summary
This review concluded that the primary prophylaxis, and treatment of venous and arterial thrombosis, with low molecular weight heparins was safe and effective in children aged 18 years and under. The unknown quality of the included studies and methodological flaws means the authors conclusions may not be reliable and are not entirely consistent with the results.

Authors' objectives
To evaluate the use of low-molecular weight heparins as primary prophylaxis in children at risk of venous thromboembolic events and as secondary prophylaxis in children suffering from symptomatic venous thromboembolic events.

Searching
PubMed, EMBASE, Web of Science and The Cochrane Library were searched from 1980 to 2010 without language restrictions; search terms were reported. The reference lists of identified studies were checked to identify additional studies.

Study selection
Published single-arm studies of low-molecular weight heparins for the treatment and secondary prophylaxis of symptomatic venous thromboembolic events were eligible for inclusion. Efficacy and safety data had to be reported. Participants were children aged 18 years and under. Case reports were excluded.

The included studies were conducted in 12 different countries. The patients ranged from neonates to adolescents up to 18 years old. The low-molecular weight heparins treatments used were enoxaparin, dalteparin, nadroprarin, tinzaparin and reviparin, given at a range of doses. The duration of the studies, where stated, ranged from seven days to three months.

Two reviewers performed the study selection; any disagreements over selection were resolved through discussion.

Assessment of study quality
The reviewers did not state they assessed methodological quality.

Data extraction
Data were extracted to calculate incidence rates and 95% confidence intervals for the outcomes of recurrent venous thromboembolic events or major bleeding episodes.

Two reviewers extracted data. In the event of missing information, the reviewers contacted the study authors for the data.

Methods of synthesis
Pooled incidence rates and 95% confidence intervals were calculated using the Laird and Mosteller method. Statistical heterogeneity was evaluated using $I^2$; in the event of significant statistical heterogeneity, a random-effects model was used. Meta-regression analyses were performed to ascertain the effect of study period, patient age and study country on the results.

Results of the review
Thirty-five studies (2,251 children) were included in the review; two randomised controlled trials, 16 prospective cohort studies, 12 retrospective cohort studies, two pharmacokinetic studies and three studies where study design was not stated.
The pooled incidence rates for efficacy for primary prophylaxis in children at risk of venous thromboembolic events was 0.047 (95% CI 0.023 to 0.091; five studies) and treatment with low-molecular weight heparins for secondary prophylaxis was 0.052 (95% CI 0.037 to 0.073; ten studies). The incidence rate of a major bleeding event on low-molecular weight heparins treatment was significantly higher at 0.050 (95% CI 0.031 to 0.078; 15 studies). Moderate heterogeneity was observed for safety outcomes ($I^2=44\%$), but statistical heterogeneity for efficacy outcomes was not substantial ($I^2=12\%$).

The results of the meta-regression analyses showed there were no statistically significant effects on the efficacy results related to age at first venous thromboembolic events, publication year or study country. However, the country of study was shown to have an effect on bleeding events; countries in which twice daily low-molecular weight heparins treatment was administered with a peak target range of 0.5 and 1.0IU/mL anti-factor Xa levels showed significantly higher bleeding rates than countries in which low-molecular weight heparins was administered once daily.

**Authors' conclusions**
The use of low-weight molecular heparins as primary prophylaxis, and in the treatment of venous and arterial thrombosis was safe and effective in children.

**CRD commentary**
The review addressed a clear question and criteria for the inclusion of studies in the review were defined. Appropriate databases were searched for relevant studies without language restrictions. There were minimal attempts to identify unpublished studies which meant there was some risk of publication bias. Steps were taken to minimise errors and bias for the performance of study selection and data extraction. There was no assessment of methodological quality, which meant the reliability of the results was unknown.

The results of observational studies were associated with several potential biases which meant the authors' decision to combine the results from differing study designs in a meta-analysis may not have been appropriate. In addition, the authors concluded that low molecular weight heparins were safe for use in children despite the statistically significant increase in bleeding episodes observed in the results.

In general, the lack of information on study quality and the possible inappropriate combination of results means that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further randomised trials were required to determine the optimal frequency, intensity and duration of treatment. In addition, further studies on intravenous administration of low-molecular weight heparins in children were required, as were studies to achieve patency when arteriovenous fistulas were in place in critically ill children.

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