CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Long-term Low-Molecular-Weight Heparin and the Post-Thrombotic Syndrome: A Systematic Review

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ABSTRACT

OBJECTIVE: Post-thrombotic syndrome causes considerable morbidity. The Home-LITE study showed a lower incidence of post-thrombotic syndrome and venous ulcers after 3 months of treating deep vein thrombosis with the low-molecular-weight heparin tinzaparin versus oral anticoagulation. This systematic review examined whether long-term treatment of deep vein thrombosis using low-molecular-weight heparin, rather than oral anticoagulation, reduces development of post-thrombotic syndrome.

METHODS: We identified 9 articles comparing treatment of deep vein thrombosis using long-term low-molecular-weight heparin with any comparator, which reported outcomes relevant to the post-thrombotic syndrome assessed ≥ 3 months post-deep vein thrombosis.

RESULTS: Pooled analysis of 2 studies yielded an 87% risk reduction with low-molecular-weight heparin in the incidence of venous ulcers at ≥ 3 months ($P = .019$). One study showed an overall odds ratio of 0.77 ($P = .001$) favoring low-molecular-weight heparin for the presence of 8 patient-reported post-thrombotic syndrome signs and symptoms. Pooled analysis of 5 studies showed a risk ratio for low-molecular-weight heparin versus oral anticoagulation of 0.66 ($P < .0001$) for complete recanalization of thrombosed veins.

CONCLUSION: These results support the lower incidence of post-thrombotic syndrome and venous ulcers observed in Home-LITE. Long-term treatment with low-molecular-weight heparin rather than oral anticoagulation after a deep vein thrombosis may reduce or prevent development of signs and symptoms associated with post-thrombotic syndrome. Post-thrombotic syndrome and associated acute ulcers may develop more rapidly after deep vein thrombosis than previously recognized.

 • *The American Journal of Medicine (2011) 124, 756-765*

KEYWORDS: Deep vein thrombosis; Low-molecular-weight heparin; Post-thrombotic syndrome; Recanalization; Venous ulcer

Post-thrombotic syndrome is a common sequela of deep vein thrombosis, occurring in 20% to 50% of patients within 2 years after a deep vein thrombosis.[1,2] Current knowledge of post-thrombotic syndrome has been reviewed recently.[3] The pathophysiology of post-thrombotic syndrome is incompletely understood, but its development post-deep vein thrombosis is believed to be related to the presence of persistent venous obstruction and reflux, as well as calf muscle pump dysfunction[4] and inflammation.[3,5,6] Although standard anticoagulant treatment of deep vein thrombosis prevents thrombus extension and embolization to the pulmonary arteries, it does not directly lyse the acute thrombus, which may be only partially cleared. It is thought that the thrombus itself may not only obstruct venous flow but also

Funding: LEO Pharma supported this study financially.

Conflict of Interest: R. Hull has received grants/research support from Bayer Pharmaceuticals Corp, LEO Pharma Inc, and Sanofi-Aventis; been a consultant for Bayer Pharmaceuticals Corp, LEO Pharma, Inc, Pfizer Inc, GlaxoSmithKline, and Wyeth Pharmaceuticals; and sat on advisory boards for Bayer Pharmaceuticals Corp, Pfizer Inc, and Sanofi-Aventis. J. Liang has no conflicts of interest to declare. G. Townshend is an employee of Watermeadow Medical, which received payment from LEO Pharma for work on this manuscript. Editorial assistance was provided by Watermeadow Medical.

Authorship: R. Hull had the original idea for the study, provided guidance and input into all drafts, and is the guarantor of the study. G. Townshend performed the literature searches, made the study selection, and wrote the first draft. J. Liang performed the statistical analyses.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2011.02.033

lead to damage of the delicate valves of the deep veins, probably in association with mediators of inflammation. Together, these processes result in venous hypertension and venous valvular reflux, which are considered to be the main pathophysiologic processes that lead to the clinical manifestations of post-thrombotic syndrome.[1,4,7] Patients at highest risk for post-thrombotic syndrome seem to be female, obese, and older, and have extensive or more proximal deep vein thrombosis, previous deep vein thrombosis (especially if ipsilateral), and signs of post-thrombotic syndrome at 1 month.[2]

The most common symptoms of post-thrombotic syndrome are persistent or intermittent pain, heaviness, swelling, itching, and tingling or cramping in the limb, which are typically aggravated by standing or walking. Typical clinical signs of post-thrombotic syndrome include edema, venous ectasia, hyperpigmentation, eczema, varicose collateral veins, and, in severe cases, lipodermatosclerosis and venous ulceration (the most severe complication of post-thrombotic syndrome).[7,8] These symptoms are often chronic and lifestyle-limiting and present with different severities over time.

CLINICAL SIGNIFICANCE

- Long-term treatment of deep vein thrombosis with low-molecular-weight heparin rather than oral anticoagulation may improve recanalization of thrombosed veins and reduce or prevent development of signs and symptoms of post-thrombotic syndrome, including venous ulcers.
- Post-thrombotic syndrome and associated acute ulcers may develop more rapidly after a deep vein thrombosis than previously recognized.
- Patients who experience early symptoms and signs that could indicate deep vein thrombosis, recurrent deep vein thrombosis, or post-thrombotic syndrome should be treated with long-term low-molecular-weight heparin rather than oral anticoagulation.

In light of the negative impact of post-thrombotic syndrome, it is surprising that preventative and therapeutic options remain limited. Elastic compression stockings are recommended to prevent post-thrombotic syndrome in at-risk patients or to treat post-thrombotic syndrome without venous leg ulcers[8,9] but may be challenging to use in real life. Intermittent pneumatic compression can be used for treatment if ulcers are present.[8] No sound evidence as yet exists to recommend thrombolysis for post-thrombotic syndrome prevention,[5,7] and waiting until post-thrombotic syndrome is well established may not be in the best interest of patient morbidity. On the basis of the pathophysiology described, providing adequate anticoagulation after a deep vein thrombosis may reduce the development of post-thrombotic syndrome[6,9,10] by preventing or reducing damage to the valves and microcirculation, and reducing inflammatory processes.

The Home-LITE study[11] reported that in patients treated with tinzaparin for 3 months after a deep vein thrombosis, the occurrence of patient-reported leg ulcers and symptoms of post-thrombotic syndrome at 3 months was significantly lower than in patients treated with long-term warfarin. This observation has potential implications for clinical care. We performed a systematic review to determine whether similar findings have been reported. Our review was framed to answer the following question: Does long-term treatment of deep vein thrombosis using a low-molecular-weight heparin, rather than usual care, reduce the development of post-thrombotic syndrome or improve recanalization of thrombosed veins?

MATERIALS AND METHODS

We attempted to identify all trials published up to August 2009 that compared prospective, randomized treatment of deep vein thrombosis using long-term (≥3-month) treatment with low-molecular-weight heparin versus any comparator group, and that reported outcomes relevant to post-thrombotic syndrome, recanalization of veins, or regression of thrombus size measured at least 3 months after the initial deep vein thrombosis. The methods are described in Supplementary Table 1.

RESULTS

We identified 9 studies that form the basis of this review (Table 1) (see Supplementary Table 1 online for details of study identification and selection).

This article reports only findings relevant to post-thrombotic syndrome and recanalization, thrombus lysis, or reflux. Results concerning incidence of recurrent deep vein thrombosis, death, and bleeding have been reviewed in other publications.[8,12-16]

Characteristics of Identified Studies

The studies differed with respect to their inclusion criteria (Table 1). In all studies except 2,[17,18] the diagnosis of deep vein thrombosis was objectively confirmed. Two studies excluded recurrent deep vein thrombosis.[18,19] One study[18] included deep vein thrombosis of the upper extremity (4% of cases).

Low-molecular-weight heparin treatment was with dalteparin (one study), enoxaparin (2 studies), nadroparin (2 studies), bemiparin (one study), or tinzaparin (3 studies) for 3 to 6 months. The comparator group in 7 studies consisted of initial unfractionated heparin or low-molecular-weight heparin, during which time oral anticoagulation was commenced, followed by international normalized ratio–adjusted oral anticoagulation only with warfarin or acenocoumarol for the duration of therapy. One study used a different low-molecular-weight heparin, parna-