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Review

Low molecular weight heparin versus unfractionated heparin in the management of cerebral venous thrombosis: A systematic review and meta-analysis

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HIGHLIGHTS

- 3 studies were included for meta-analysis comparing LMWH and UH in the immediate management of CVT, a total of 179 and 372 patients in the LMWH and UH group respectively.
- LMWH showed trends towards improved mortality and functional outcome.
- Low number of clinical trials impeded analysis.
- A high power randomized controlled trial is required to conclusively answer the question.

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ABSTRACT

Introduction: There are two main choices of anti-coagulation in cerebral venous thrombosis: Unfractionated heparin versus low molecular weight heparin. A consensus is yet to be reached regarding which agent is optimal. Therefore the aim of this systematic review and meta-analysis was to identify which agent is most effective in treating CVT.

Methods: Databases Pubmed (MEDLINE), Google Scholar and hand-picked references from papers of interest were reviewed. Studies comparing the use of low molecular weight heparin and unfractionated heparin in adult patients with a confirmed diagnosis of cerebral vein thrombosis were selected. Data was recorded for patient mortality, functional outcome and haemorrhagic complications of therapy.

Results: A total of 2761 papers were identified, 74 abstracts were screened, with 5 papers being read in full text and three studies suitable for final inclusion. A total of 179 patients were in the LMWH group and 352 patients were in the UH group. Mortality and functional outcome trended towards favouring LMWH with OR [95% CI] of 0.51 [0.23, 1.10], $p = 0.09$ and 0.79 [0.49, 1.26] $p = 0.32$ respectively. There was no difference in extra-cranial haemorrhage rates between either agent with a OR [95% CI] of 1.00 [0.29, 3.52] $p = 0.99$.

Conclusion: Trends towards improved mortality and improved functional outcomes were seen in patients treated with LMWH. No result reached statistical significance due to low numbers of studies available for inclusion. There is a need for further large scale randomized trials to definitively investigate the potential benefits of LMWH in the treatment of CVT.

Contents

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1. Introduction

Cerebral venous thrombosis (CVT) is a rare but potentially devastating condition. CVT has an estimated incidence of 3–4 people per 1 million of the population and a pre-disposition to affect young females [1]. The main stay of treatment for CVT surrounds early recognition, and more recently trials have shown anti-coagulation with heparin either in unfractionated or low molecular weight forms can improve outcome in CVT despite the risk of haemorrhagic transformation [2].

A number of trials compared UH and LMWH in the setting of deep vein thrombosis (DVT) of the legs during the nineties [3], leading to the conclusion that LMWH is a suitable and safer alternative to UH in this cohort of patients. LMWH is now the established gold standard treatment in most units in the United Kingdom for DVT. A similar approach has been emerging in the treatment of CVT; examining LMWH and UH, however no clear consensus appears to have been reached. There are two main issues in terms of identifying if UH or LMWH is superior in the treatment of CVT: 1) the disease is relatively rare making randomised trials with sufficient power difficult 2) the risk of haemorrhagic transformation in CVT have made the use of anti-coagulation controversial in the past [4]. In 2012 a Cochrane review by Coutinho et al. demonstrated that anti-coagulation is safe in CVT, however there remains limited evidence as to which form of anti-coagulation is optimal [5].

LWMH has a number of benefits over UH. LMWH can be given in once or twice daily regimes without the need for activated partial thromboplastin time ratio (APTR) titration or a continuous intravenous infusion that is needed with UH. In addition to this they appear to have a better safety profile reducing the risks of heparin induced thrombocytopenia and bleeding theoretically having the potential to reduce the risk of haemorrhagic transformation [6]. However, LMWH does not provide the rapid onset of action and easy reversibility that is possible with UH.

Therefore we aim to report the results of the first combined systematic review and meta-analysis examining the use of LMWH versus UH in CVT. It is hoped that by compiling a number of trial results that it is possible to suggest which therapy is superior and safer in the treatment of CVT to guide further research and evidence.

2. Methods

This systematic review was conducted in accordance with the PRISMA statement. Pubmed and Google Scholar were searched for the terms “cerebral vein thrombosis” and “heparin” on the 23rd June 2016. References were hand-picked from papers which were read in full text. Inclusion criteria included papers comparing low molecular weight heparin with unfractionated in patients over 18 with CVT diagnosed by MR venography. Prospective studies were permitted to increase the power of the study. Papers not available in full text in English were excluded. Paper identification was undertaken by two independent reviewers AP and AQ and any disagreements were resolved by discussion until agreement was reached.

Outcomes for mortality, functional outcome and both intracranial and extra-cranial haemorrhage were analysed. All papers were evaluated for bias. All statistical analysis was undertaken using the Revman© software. If heterogeneity is low a fixed effects analysis will be used, if the results are varied a random effects analysis will be deemed more appropriate. Statistical significance is set at $p = 0.05$.

3. Results

A total of 2761 non-duplicate papers were retrieved from our initial search. 74 abstracts were screened, with 5 papers were read in full text. Three papers were suitable for analysis published between 2010 and 2015 [7–9]; 1 prospective cohort study and two randomized controlled trials *(see* Fig. 1 *for the search strategy protocol)*. In total 179 patients were treated with LMWH and 352 patients were treated in UH group *(see* Table 1 *for the study characteristics)*. Two papers favoured the use of LMWH and one was equivalent.

3.1. Mortality

All three studies were included for mortality analysis. Mortality was higher in the UH group in two of the studies and equivalent in the other. Meta-analysis of the data showed an OR [95% CI] of 0.51 [0.23, 1.10], $p = 0.09$ favouring LMWH *(*Fig. 2*)*.

3.2. Functional outcome

Afshari et al., were excluded for this part of the analysis as the data given was the average Modified Rankin Score (MRS) with standard deviations. The number of patients who did not make a complete functional recovery (demonstrated by and Barthel Index of 20/20 or a MRS of 0 was evaluated in both papers. Both studies demonstrate fewer incomplete recoveries in the LMWH however again this did not reach significance with a OR [95% CI] of 0.79 [0.49, 1.26] $p = 0.32$.