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Full Length Article

Comparison of the efficacy of fixed-dose enoxaparin and adjusted-dose unfractionated heparin in patients with cerebral venous thrombosis

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ABSTRACT

Objective: Anticoagulants are the standard treatment for cerebral venous thrombosis (CVT). Although low-molecular-weight heparin (LMWH) is recommended in CVT, the specific type and dosage regimen of LMWH have never been specifically suggested. This study compared the clinical outcomes and adverse events in patients who received adjusted-dose unfractionated heparin (AD-UFH) versus fixed-dose enoxaparin (FD-E).

Methods: A retrospective cohort study was conducted at a university hospital in Thailand. Patients included in the study were those treated for CVT initially with either AD-UFH or FD-E followed by oral warfarin for 1 year between January 2002 and December 2015. Electronic medical records were reviewed by the investigators. The baseline clinical characteristics, anticoagulant regimens, complications and outcomes at hospital discharge and 1-year follow-up were analyzed. Clinical outcomes (independency defined by modified Rankin score (mRS) 0–2 at hospital discharge and 1-year follow-up) and adverse events (gastrointestinal bleeding and intracranial hemorrhage) were compared between patients who received AD-UFH or FD-E.

Results: Seventy-five patients met the inclusion criteria. Thirty-nine patients received AD-UFH and 36 patients received FD-E. The baseline demographic and clinical characteristics between the two groups were comparable. Independency at hospital discharge accounted for 51.28% in the AD-UFH group and 61.11% in the FD-E group ($p = 0.392$). There were no significant differences in the incidence of expansion of preexisting intracerebral hematoma (14.29% vs 18.18%; $p = 0.773$) or new symptomatic intracranial hemorrhage (7.69% vs 8.33%; $p = 0.855$). Independency at 1-year follow-up was also comparable between the two groups (71.78% vs 77.78%; $p = 0.552$).

Conclusion: This current study suggested a comparable efficacy and safety of FD-E and AD-UFH in patients with CVT.

1. Introduction

Cerebral venous thrombosis (CVT) is a potentially fatal disease [1]. The incidence of CVT in Europe and America was estimated to be 3–4 patients per million population while the incidence in the Asian population was not well documented [2]. Although there are various precipitating factors that contribute to CVT, different genetic backgrounds lead to a lower incidence of thrombophilia-related CVT in the Asian population than in the Western population [3].

The mainstay treatment of CVT is anticoagulants. The benefit of anticoagulants over a placebo has been confirmed for decades [4,5]. Both unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) are recommended in the standard guidelines [6,7]. However, the evidence supporting the use of LMWH in CVT is limited to nadroparin and dalteparin which are not available in many countries [5,8]. Most of the evidence showed only short term outcomes ranging from status at hospital discharge to 3 months follow-up.

In Thailand, despite scarce evidence, enoxaparin has been used in treating various venous thromboses including CVT. The regimens prescribed for CVT treatment are either fixed or weight-adjusted. The current study was conducted to compare the efficacy and adverse effects of adjusted-dose unfractionated heparin (AD-UFH) versus fixed-dose enoxaparin (FD-E) at hospital discharge and at 1-year follow-up.

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2. Materials and methods

2.1. Samples

This is a retrospective cohort study conducted at a tertiary care university hospital in southern Thailand. The study protocol was approved by the institution's Ethics Committee. The electronic medical records of patients diagnosed with CVT by International Classification of Diseases, the Tenth Revision (ICD-10) under the codes of I636 (cerebral infarction due to CVT), I676 (nonpyogenic thrombosis of intracranial venous system), O225 (CVT in pregnancy) and G08 (intracranial and intraspinal phlebitis and thrombophlebitis) who were treated with either AD-UFH or FD-E from January 2002 to December 2015 were selected for review.

The sample size estimation was based on the findings derived from a study by Misra et al. [8] in patients with cerebral venous sinus thrombosis that compared the efficacy and safety of UFH and LMWH on death during hospitalization, which is one of the clinical outcome variables in this current study. To detect a difference of proportion of death during hospitalization between the UFH and LMPH groups (0.18 and 0, respectively), a net number of 39 patients per group was needed to achieve a power of 80% at an alpha of 0.05 [9].

2.2. Inclusion and exclusion criteria

Patients were selected if they met the following inclusion criteria: (1) aged 15 years or older; (2) diagnosis of CVT as confirmed by positive findings by the following means: i) magnetic resonance imaging, ii) magnetic resonance venography or iii) cerebral angiography; (3) treated primarily with subcutaneous enoxaparin 60 mg every 12 h or intravenous adjusted-dose UFH (loading dose 80 units/kg followed by 18 units/kg/hr) to keep activated partial-thromboplastin time (aPTT) at 60–85 s and (4) continually treated with oral warfarin to keep the international normalized ratio (INR) at 2–3 for at least 1 year. Enoxaparin is contraindicated in patients with a low creatinine clearance (< 30 mL/min/1.73 m2), but UFH is not contraindicated in these patients. Therefore, patients with a low creatinine clearance were excluded from the study to avoid allocation bias which helped make the groups more comparable.

2.3. Clinical data

Five distinctive neurological presentations were specifically defined: (1) focal neurologic deficit; (2) isolated increased intracranial pressure (the combination of progressive headache, vomiting, and papilledema with or without bilateral abducens nerves palsy, but no other focal neurologic abnormality, and elevated opening pressure of lumbar puncture more than 20 cm H_2O); (3) cavernous sinus syndrome (painful ophthalmoplegia, chemosis, proptosis, and a combination of at least 2 cranial neuropathies: i) oculomotor; ii) trochlear or iii) the first division of trigeminal or abducens neuropathy); (4) isolated headache (headache without abnormal neurologic signs) and (5) seizure. Level of consciousness was assessed by the Glasgow Coma Scale (GCS) score.

Patient demographics, clinical data and laboratory results were obtained by reviewing the electronic medical records. Patients diagnosed with CVT were treated with either AD-UFH or FD-E in combination with warfarin. When the INR of 2–3 was achieved, AD-UFH or FD-E was stopped and only warfarin was continued for at least 1 year. At hospital discharge, follow-up visits were scheduled based on the patient's performance status and the need to adjust the dosage of warfarin. All patients completed the clinical evaluation at 1 year to determine whether they should continue warfarin or not.

2.4. Outcome measurements

The clinical outcomes were evaluated by the modified Rankin Scale (mRS) classified into 2 groups: independency (mRS 0–2) and dependency or death (mRS 3–6). The primary outcome was independency (mRS 0–2) at hospital discharge. The secondary outcomes were independency at 1-year follow-up and adverse events at hospital discharge.

Adverse events were classified into 2 categories including (1) worsening functional outcome defined as an increment of mRS at hospital discharge at least 1 point from the baseline mRS at admission which did not contribute to death and (2) treatment-related complications including expansion of preexisting intracerebral hematoma (ICH), new symptomatic intracranial hemorrhage, gastrointestinal bleeding and other bleeding organs.

2.5. Data analysis

Demographic data, baseline characteristics, clinical outcomes and adverse events were compared between the AD-UFH and FD-E groups. Categorical variables were compared by the $\chi 2$ test. Independent *t*-test or Mann-Whitney *U* test for independent samples was applied for continuous variables. There were no missing data. All data analyses were based on two-sided test (alpha = 0.05). The statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic data

Seventy-five CVT patients were selected for this study. Thirty-nine and 36 patients were treated with AD-UFH and FD-E, respectively. All patients completed the 1-year clinical follow-up. The mean age ± SD of the AD-UFH group (37.72 ± 14.89, range 15–70) and the FD-E group (36.33 ± 17.72, range 15–72) were not significantly different ($t = 0.405$; $p = 0.687$). There were no statistically significant differences in baseline consciousness, dependency at admission, number of CVT sites or exposure to concurrent hormonal therapy between the two groups except one. It was noticed that the prevalence of preexisting ICH was significantly higher in the AD-UFH group than in the enoxaparin group (53.85% vs 30.56%; $p = 0.042$) (Table 1).

3.2. Causes of cerebral venous thrombosis

Various precipitating causes of CVT were identified in this study. Among the 75 patients, female-specific risk factors such as concurrent hormonal therapy, pregnancy and puerperium were found in only 14 cases (18.67%). Thrombophilia was scarcely found: only 4 cases in the UFH group (2 protein C deficiency and 2 protein S deficiency) and 5 cases in the enoxaparin group (4 antiphospholipid syndrome and 1 protein S deficiency). Paracranial and central nervous system infections were found in 8 cases (2 cryptococcal meningitis, 3 periorbital cellulitis with bacterial sinusitis, 1 aspergillosis sinusitis, 1 bacterial meningitis and 1 viral encephalitis). There were no statistically significant differences regarding the precipitating factors between the AD-UFH and FD-E groups.

3.3. Clinical outcomes

The primary endpoint of independency (mRS 0–2) at hospital discharge was observed in 51.28% in the AD-UFH group and 61.11% in the FD-E group ($p = 0.392$). Subgroup analysis in the CVT patients with preexisting ICH also showed no significant difference in the rate of independency between the AD-UFH and FD-E groups at discharge (38.10% vs 11.29%; $p = 0.540$). In-hospital death was found in 3 cases in the AD-UFH group (1 CVT-related death from brain herniation as a result of massive brain edema, 1 advanced adenocarcinoma of the lung and 1 *Acinetobacter baumannii* pneumonia with septic shock) and 1 case in the FD-E group (CVT related death from expanding intracerebral