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CLINICAL CASE STUDY: AN OVERVIEW ON LOW MOLECULAR WEIGHT HEPARINS (LMWH) IN PATIENTS

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ABSTRACT

Heparin is a sulphate polysaccharide of glycosaminoglycan that is made predominantly by mast cells of connective tissue. It is used in the management of thromboembolic problems in medicine. Heparin acts as a catalyst for anti-thrombin III, increasing its activity by thousand times. The larger heparin species catalyses the inactivation of activated factors II and X , in contrast LMWH inactivates the activated factor X. The final effect for both is systemic anti-coagulation. Heparin also produces platelet aggregating antibodies and causes coagulopathy in rare conditions. LMWH especially Enoxaparin (Inj Clexane) proved an effective treatment in patients with Covid -19 infection by preventing thromboembolism and pulmonary embolism thereby, helped in survival of the patients by reducing the risk of death due to coagulation and fibrosis. Hence, clinical trial reports and SOAP analysis of clinical case studies in random subjects and patients reported the over-view of advantages using LMWH heparins in disease management and emergency traumatic injuries produced a beneficial role of using LMWH over unfractioned heparins.

INTRODUCTION

Heparin, also known as unfractionated heparin (UFH), is a medication and naturally occurring glycosaminoglycan. Since heparins depend on the activity of antithrombin, they are considered anticoagulants. Specifically, it is also used in the treatment of heart attacks and unstable angina. It is given by injection into a vein or under the skin. Other uses include inside test tubes and kidney dialysis machines[1]

Low-molecular-weight heparin (**LMWH**) is a class of anticoagulant medications. They are used in the prevention of blood clots and treatment of venous thromboembolism (deep vein thrombosis and pulmonary embolism) and in the treatment of myocardial infarction. Heparin has been fractionated into LMW forms (MW 3000–7000) by different techniques. LMW heparins have a different anticoagulant profile; i.e., they selectively inhibit factor Xa with little effect on IIa. They act only by inducing conformational change in AT III and not by providing scaffolding for interaction of AT III with thrombin. Low molecular weight heparin (LMWH) is an anticoagulant injected subcutaneously or intravenously and acts via activation of antithrombin III which in turn inactivates thrombin and factor Xa to produce its effect.[11]

Classification of heparins:

1. Indirect thrombin inhibitors
   a) Heparins
      High molecular weight Heparins (HMWH)
      Low Molecular weight heparins(LMWH)
      Enoxaparin , Dalteparin
2. Direct thrombin inhibitors
   Hirudin, Lepirudin , Agatroban

Pharmacological action of Heparins: Both heparin and LMWH exert their anticoagulant activity by activating antithrombin (earlier called antithrombin III), which accelerates the inactivation of coagulation enzymes thrombin (factor IIA), factor Xa and factor IXA [2]

Mechanism of action [7] Coagulation cascade is a normal physiological process which aims at preventing significant blood loss or hemorrhage following vascular injury. Unfortunately, there are times when a blood clot (thrombus) will form when it is not needed. For instance, some high risk conditions such as prolonged immobilization, surgery, or cancer can increase the risk of developing a blood clot which can potentially lead to significant consequences.

Contraindications reported with heparins[6] NICE and the BNF suggest that contraindications to all heparins include trauma, epidural half-life, hemorrhagic disorders, peptic ulcer disease, recent cerebral hemorrhage, severe hypertension, and recent surgery to the eye or nervous system. In these cases, the risks of anticoagulation and bleeding outweigh the potential benefit from LMWH acting as a VTE prophylaxis or at treatment doses. As LMWHs are self-administered, it is important to consider dosing in cases of chronic kidney disease, where there is a risk of accumulation and, thus, higher chances of problematic bleeding.

Therapeutic uses: LMWH can be given subcutaneously and does not require APTT monitoring, LMWH permits outpatient treatment of conditions such as deep vein thrombosis or pulmonary embolism that previously mandated inpatient hospitalization for unfractionated heparin administration.[3]

Adverse effects [4] unacceptable pain at the injection site

- uncontrolled bleeding (most serious side effect)
- Injection site reactions such as redness, bruising and irritation.
- Swelling of legs
- Loss of bone strength
- Fever
- Elevated liver enzymes
- Heparin induced thrombocytopenia
- Insomnia
- Confusion, Anaemia
- Increased heart rate, Bloating

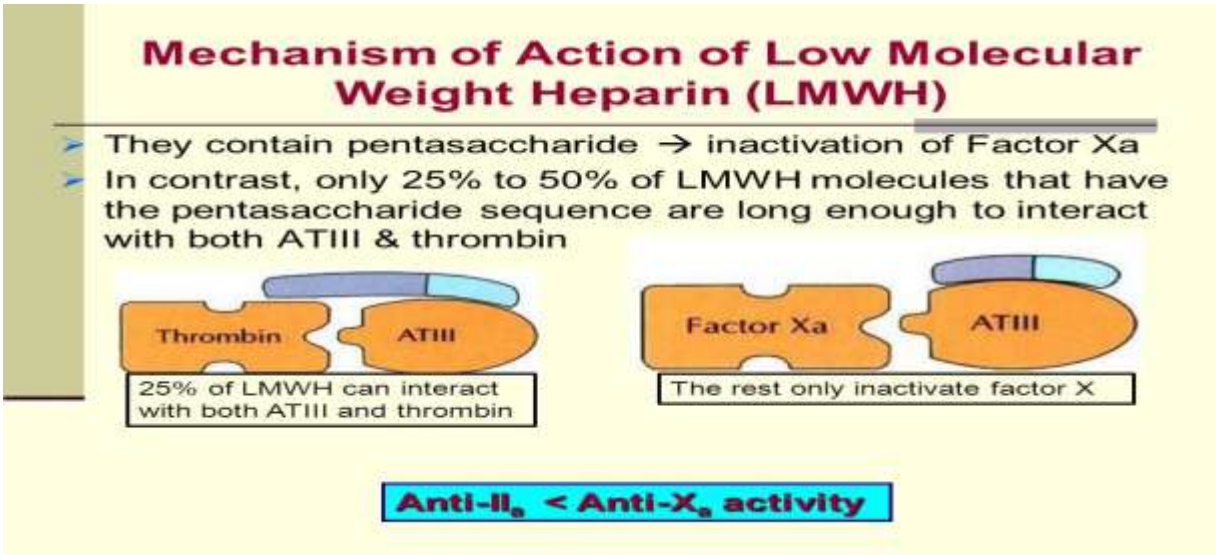
SOAP analysis of clinical case studies in patients treated with LMWH

Clinical trials using low molecular weight heparin in hospitals in advanced cancer subjects.

Objective: To prospectively assess whether low-molecular-weight heparin (LMWH) provides a survival benefit in patients with advanced cancer.

Patients and methods: Between December 1998 and June 2001, we performed a randomized controlled study of patients with advanced cancer. Initially, the study was double blinded and placebo controlled, with the patients receiving daily injections of 5000 U of LMWH or saline. However, because of low accrual midway through the study, the placebo injection arm was eliminated, and the study became open labeled, with patients receiving LMWH injections plus standard clinical care or standard clinical care alone. The primary study end point was overall survival.

Results: Of 141 patients randomized to this clinical trial, 3 dropped out, leaving 138 patients. The median survival time was 10.5 months (95% confidence interval, 7.6-12.2 months) for the combined standard care and placebo groups. The median survival time for the combined LMWH arms was 7.3 months (95% confidence interval, 4.8-12.2 months). These median survival times were not significantly different (log-rank P = .46). The median survival times for the blinded and unblinded LMWH groups were 6.2 months and 9.0 months, respectively.



DRUG NAME	DVT/PE PROPHYLAXIS	DVT/PE TREATMENT	UNSTABLE ANGINA/MI
ENOXAPARIN	30mg SQ BID or 40mg SQ daily	1mg /kg BID or 1.5 mg/kg once daily	1 mg/kg q 12 hrs
DALETPARIN	2500-5000 units QD	200 units/kg QD or 100 units /kg BID	120 units/kg (max 10,000) q 12 hrs
TINZAPARIN	2500-4500 anti-xa units	175 anti-xa units/kg once daily	---

Agent	Patients, n/total (%)	LMWH	Heparin	Relative risk reduction(95%)
Nadroparin (Fraxiparin)	20/361 (5.5)	32/355 (9.0)	40 (−5–66)	0.07
Tinzaparin (Logiparin)	6/213 (2.8)	15/219 (6.9)	59 (−1–83)	0.07
Enoxaparin (Clexane)	13/314 (4.1)	20/320 (6.3)	35 (−32–68)	0.23
Dalteparin (Fragmin)	16/322 (5.0)	8/339 (2.4)	-110(374-7)	O.07

The median survival times were 10.3 months for the blinded placebo arm and 10.5 months for the standard care arm. The rate of severe or life-threatening venous thromboembolism was 6% in the LMWH arms and 7% in the control arms. The rate of severe or life-threatening bleeding was 3% in the LMWH arms and 7% in the control arms.

2. The effect of low molecular weight heparin on survival in patients with advanced malignancy

Objective: Studies in cancer patients with venous thromboembolism suggested that low molecular weight heparin may prolong survival. In a double-blind study, we evaluated the effect of low molecular weight heparin on survival in patients with advanced malignancy without venous thromboembolism.

Methods: Patients with metastasized or locally advanced solid tumors were randomly assigned to receive a 6-week course of subcutaneous nadroparin or placebo. The primary efficacy analysis was based on time from random assignment to death. The primary safety outcome was major bleeding.

Results: In total, 148 patients were allocated to nadroparin and 154 patients were allocated

to placebo. Mean follow-up was 1 year. In the intention-to-treat analysis the overall hazard ratio of mortality was 0.75 (95% CI, 0.59 to 0.96) with a median survival of 8.0 months in the nadroparin recipients versus 6.6 months in the placebo group. After adjustment for potential confounders, the treatment effect remained statistically significant. Major bleeding occurred in five (3%) of nadroparin-treated patients and in one (1%) of the placebo recipients (P = .12). In the a priori specified subgroup of patients with a life expectancy of 6 months or more at enrollment, the hazard ratio was 0.64 (95% CI, 0.45 to 0.90) with a median survival of 15.4 and 9.4 months, respectively. For patients with a shorter life expectancy, the hazard ratio was 0.88 (95% CI, 0.62 to 1.25)

3. A Randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer

Objective: Small cell lung cancer (SCLC) is a chemotherapy-responsive tumor type but most patients ultimately experience disease progression. SCLC is associated with alterations in the coagulation system. The present randomized clinical trial (RCT) was designed to determine whether addition of low-molecular-weight heparin (LMWH) to combination chemotherapy (CT) would improve SCLC outcome compared with CT alone.

Methods: Combination CT consisted of cyclophosphamide, epirubicine and vincristine (CEV) given at 3-weekly intervals for six cycles. Eighty-four patients were randomized to receive either CT alone (n = 42) or CT plus LMWH (n = 42). LMWH consisted of dalteparin given at a dose of 5000 U once daily during the 18 weeks of CT. Results Overall tumor response rates were 42.5% with CT alone and 69.2% with CT plus LMWH (P = 0.07). Median progression-free survival was 6.0 months with CT alone and 10.0 months with CT plus LMWH (P = 0.01). Median overall survival was 8.0 months with CT alone and 13.0 months with CT plus LMWH (P = 0.01). Similar improvement in survival with LMWH treatment occurred in patients with both limited and extensive disease stages. The risk of death in the CT + LMWH group relative to that in the CT group was 0.56 (95% confidence interval 0.30, 0.86) (P = 0.012 by log rank test). Toxicity from the experimental treatment was minimal and there were no treatment-related deaths.

4.The clinical case study of LMWH in a patient with traumatic head injury

Objective : A clinical case study reported to have a beneficial role of Heparins in traumatic head injury of a patient who had alleged to have a head injury due to fall from the steps and had right shoulder and clavicle dislocation. Had an episode of seizure for one minute. After the diagnosis a CT scan of brain and USG of chest and abdomen reported injuries and internal bleeding. The treatment is done using LMWH.

Assessment : The patient maintained stable respiration and got recovered post treatment with Inj Enoxaparin 20% /100ml along with Inj Eptoin 100mg.

5. Clinical case study of a patient with coagulopathy using heparins

Objective: We report a case of a 56-year-old woman with a history of idiopathic thrombocytopenic purpura (ITP) following splenectomy on mycophenolate mofetil (MMF), who developed moderate bleeding after stopping MMF. Her laboratory testing suggested the presence of an abnormal circulating heparin-like anticoagulant with demonstrable anti-Xa activity. She was initially treated with antifibrinolytic therapy and was subsequently started on MMF alongside intravenous immunoglobulin, which significantly improved her bleeding symptoms. The presence of abnormal circulating heparin-like anticoagulants is a rare cause of coagulopathy. Few cases exist in the literature, with nearly all occurring in the setting of hematologic or solid-organ malignancy. The mechanism by which these endogenous anticoagulants develop is unclear. Clinical manifestations range from mild bleeding and bruising to life-threatening hemorrhage refractory to conventional therapy. Diagnosis of a heparin-like anticoagulant is based on coagulation testing as well as exclusion of other exogenous anticoagulants, acquired inhibitors, and/or factor deficiencies.

CONCLUSION:

A brief course of subcutaneous low molecular weight heparin favorably influences the survival in patients with advanced malignancy and deserves additional clinical evaluation. These results support the concept that anticoagulants, and particularly LMWH, may improve clinical outcomes. LMWH have gained an advantage over high molecular weight heparins and direct heparins due to coagulopathy in some cases of patients during conventional therapy. Further clinical trials of this relatively non-toxic treatment approach are indicated.

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