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ENOXAPARIN IN MANAGEMENT OF LICHEN PLANUS – A REVIEW.

Dental Science

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ABSTRACT

Lichen planus is a unique chronic, immunologically mediated mucocutaneous disease, of unknown etiology that was first described as a disease of the skin, however it can also affect mucosal surfaces, including those that line the oral cavity. The prevalence of Oral lichen planus(OLP) among general population is of 1-2%. Various treatment modalities have been used for Lichen planus but few recent advancements in the management have emerged to reduce the side effects. Low dose, low molecular weight heparin (enoxaparin) has been proven to be effective in various types of Lichen planus. Enoxaparin has been shown to inhibit the expression of heparanase enzyme that is produced by CD4 lymphocytes (this enzyme is crucial in T-cell migration to target tissue). This paper presents a review of enoxaparin as a treatment modality in lichen planus.

KEYWORDS

Oral Lichen Planus, Management, Enoxaparin.

INTRODUCTION

Mucocutaneous lesions are a group of diseases that affect the skin as well as the mucous membrane.[1] Lichen Planus (LP) is one among those mucocutaneous lesions. Lichen planus is a common papulosquamous skin disorder derived from the Greek word "*leichen*" means tree moss and Latin word "*planus*" means flat by the English physician Erasmus Wilson in 1866. Wickham, a French physician, in 1895 wrote a paper on a pathognomonic signs of "Wilson's lichen" as fine white grayish lines that could be seen on the skin papules of the disease (later known as Wickham's striae). [2] Lichen planus is a common inflammatory disorder that affects the skin, mucous membranes, nails, and hair .[3] Lichen planus (LP) is defined as a chronic inflammatory mucocutaneous disease of unknown etiology affecting mainly middle-aged women.[4] There are two clinical types of lichen planus: The Cutaneous and Mucosal variety.

It is characterized by itchy, purplish, polygonal, flat-topped papules with lacy white lines (Wickham's striae). Without therapy, the skin lesions usually resolve over 6–18 months, although in up to 20% of patients relapse occurs in the same area as the initial episode and Chronicity is more likely with oral lichen planus (OLP).

The etiology of Lichen Planus is yet to be fully understood, but an immunological abnormality is believed to play an important role, notably involving antigen-presenting cells.[5]

The nature of the antigen implicated in OLP is uncertain, however numerous predisposing factors are known to induce OLP are identified. These are systemic medications, dental materials, chronic liver disease and hepatitis C virus, stress, genetics, tobacco chewing, Graft versus Host disease. Systemic medications such as antimalarial drugs, non-steroidal anti-inflammatory drugs, antihypertensive agents, diuretics, oral hypoglycemic agents, beta blockers, penicillin's, sulfonamides, tetracycline's, heavy metals, thyroid preparations, antiretroviral medication have been reported to cause OLP. Association of OLP with several different autoimmune diseases such as alopecia areata, dermatitis herpetiformis, myasthenia gravis, *etc.* has been documented. Periods of psychological stress and anxiety are associated with aggravation of OLP in most of the studies. Genetic predisposition also play a role in OLP pathogenesis.[6]

Lichen planus is characterized by features of a cell mediated attack on the epidermis by activated T-lymphocytes. It has been suggested that an unknown antigen is processed by Langerhans cells, which activates T-lymphocytes that subsequently destroy the basal layer.[7]

Cell mediated immunity plays a major role in triggering the clinical expression of the disease. Both CD4 and CD8 T-cells are found in lesions of skin. The majority of lymphocytes in the infiltrate of LP are CD8 and CD45RO (memory) positive cells. These cells are considered responsible for the development of the most characteristic change observed in the lichenoid reaction namely, apoptosis (cell death).

T-cells may become activated via antigen presenting cells such as langerhans cells which recognize unknown foreign antigen (which could be virus, drug or contact sensitizer), then process and present this antigen to the T lymphocytes. Activated lymphocytes both helper subset (Th1 and Th2) and cytotoxic suppressor cells release soluble mediators (cytokines and chemokines) such as interleukins IL2, IL4, IL10, interferon-γ and TNF-α which stimulate the accumulation of more lymphocytes. The infiltrate is epidermotropic and attacks keratinocytes, this process leads to the destruction of the epidermis referred as the lichenoid tissue reaction.[8]

HEPARIN

Heparin is an anticoagulant that inhibits the development and progression of clot formation by acting on different phases of the coagulation pathway . These drugs neither lyse clots nor influence the fibrinolytic pathway.

Anticoagulants are class of oral and parenteral drugs in which heparins are rapidly acting parenteral anticoagulants .

Types of heparin

- Unfractionated heparin
- Low-molecular-weight heparin
  - Enoxaparin
  - Tinzaparin
  - Dalteparin
  - Certoparin
  - Bemiparin
  - Reviparin
- Heparinoids
  - Danaparoid

Unfractionated heparin has been previously used for many years but now it has been replaced by low molecular weight heparins as they are effective and safer and there is no need to routinely monitor their efficacy.[9]

TABLE 1: MECHANISMS OF ACTION AND MONITORING GUIDELINES FOR HEPARINS [9].

Anticoagulants	Mechanism of action	Monitoring Guideline	Clinical relevance and side effect
Coumarins (Vitamin K antagonists)	Inhibition of vitamin K epoxy reductase that converts vitamin K to active vitamin KH2, which is required by clotting factors II, VII, IX and X for γ-carboxylation	Prothrombin time INR to be maintained between 2 and 3	Monitoring is essential due to the narrow therapeutic index and unpredictable response. Bleeding is the major adverse effect, especially in patients with higher INRs, chronic liver and kidney failure and those on antiplatelet drugs and NSAIDs
Direct thrombin inhibitors	Antithrombotic effect by direct and reversible binding to the active site of thrombin leading to inhibition of fibrin formation, platelets, and factors V, VIII, XIII, protein C activation Dabigatran binds both to free and clot-bound thrombin and also promotes fibrinolysis indirectly by increasing tissue plasminogen activator (tPA) levels and inhibition of thrombin-activable fibrinolysis inhibitor (TAFI)	6th hourly aPTT measurement until sustainable therapeutic levels (with a goal of 1.5-3 times the baseline for argatroban and 1.5-2.5 times the baseline for bivalirudin) are reached; desirudin does not routinely need monitoring	Among the parenterally administered direct thrombin inhibitors, bivalirudin has the shortest half-life and is apt for perioperative prophylaxis. Oral direct thrombin inhibitors have rapid onset and more predictable anticoagulant response, avoiding the need for monitoring
Factor Xa inhibitors	Same as heparin	Monitoring for fondaparinux is not routinely essential	Fondaparinux is avoided in severe renal failure as it is exclusively excreted through the kidney

ENOXAPARIN

LMWHs are produced by depolymerization of unfractionated heparin. Their average molecular weight is below 8000 Da. LMWHs are commonly used in clinical practice to prevent and treat venous thromboembolism. Enoxaparin is the first low-molecular-weight heparin (LMWH) which is approved by the Food and Drug Administration. Advantage of using enoxprin is because it has longer half-life, more predictable anticoagulant response, easier dosage adjustment, no requirement for monitoring except special circumstances, and less bleeding risk.

. Enoxaparin is obtained by controlled chemical eliminative cleavage of the benzyl ester of heparin with alkaline treatment. This process results in the formation of LMW chains, of which typically 15–25% contain a 1,6-anhydroglucosamine at the reducing end.[10]

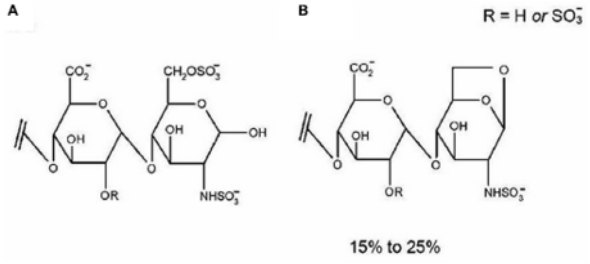


Fig.1. (a) The disaccharide contains two residues of uronic acid and d-glucosamine linked by a 14 glycosidic linkage. Approximately 15–25% of enoxaparin oligosaccharides contain 1,6-anhydro groups at their reducing end (b) as a result of chemical b-eliminative cleavage of unfractionated heparin.[10]

It shows less ability to prolong the activated partial thromboplastin time and less microvascular bleeding than unfractioned heparin.[13] They exert antithrombotic effect by inhibiting activated factor X (Xa). The ratio of their anti-Xa to anti-IIa activity is greater than 1.[12,13]

Low molecular weight heparin in low doses has lymphoid antiproliferative and immunomodulatory properties. At a dose of 3 mg weekly, heparin injections have been reported to significantly improve the symptoms of pruritus and activity of the disease. Four to six injections of heparin induced complete regression of lesions within 4 to 10 weeks.[7,11]

ENOXAPARIN IN LICHEN PLANUS

Various studies have been reported that LMWHs have some actions beyond mere anticoagulation such as regulation of cell proliferation and inflammation, inhibition of neutrophil chemotaxis, and accumulation of eosinophils. LMWHs have been tried on treatment of only a few dermatological disorders to date, and the majority of these studies have been conducted on lichen planus.[13]

Lichen Planus represent a type IV (delayed type) hypersensitivity reaction to an antigenic stimulus residing within the epithelium. It has been shown that LMWHs inhibit T-cell migration and delayed-type hypersensitivity response at a very low dose through competitively inhibiting the activity of heparinase in T lymphocytes. Heparinase is released from activated T lymphocytes at the site of inflammation and related to the ability of activated T lymphocytes to penetrate the extracellular matrix and migrate to the target tissue. Beside this, heparin may inhibit the production of tumor necrosis factor alpha (TNF α)which has a key role in inflammation.It was shown that heparin also exhibits antiproliferative effects through interaction with keratinocyte generated, heparin-binding autocrine growth factors.[13]

Enoxaparin is the only derivative of heparin that has been so far evaluated for its clinical efficacy in LP. The studies have reported mixed but encouraging clinical outcomes. Ingber et al. (1994) demonstrated that low subcutaneous doses of enoxaparin inhibited the elicitation of allergic contact dermatitis. This preliminary finding led to the investigation of enoxaparin in 11 patients with histopathologically proven LP (Hodak et al., 1998). Subcutaneous injection of 3 mg of enoxaparin once-weekly for either 4 or 6 weeks resulted in complete regression of the eruption, with residual post-inflammatory hyperpigmentation in more than 70% of patients (8 out of 11). On the basis of these encouraging early findings, the potential role of enoxaparin in LP was further explored by researchers internationally.[5]

Stefanidou et al. (1999) evaluated the efficacy of enoxaparin in 18 patients with various types of LP and reported complete remission in 61% of patients and marked improvement in a further 11%. Similarly, Pacheco and Kerdel (2001) reported marked improvement in 5 out of 7 patients with LP when treated with enoxaparin. In another study, patients with LP were treated with enoxaparin for 4–14 weeks and 21 of 24 patients achieved complete remission (Akdeniz et al., 2005). Similarly, once-weekly use of enoxaparin over a period of 20 weeks resulted in a dramatic improvement in visual analog scale assessments of pain and itch in 13 out of 15 patients unresponsive to topical or oral corticosteroid therapy.

A study was conducted by Akdeniz et.al. to evaluate the efficiency of lowdose, low-molecular-weight heparin (enoxaparin) in the treatment of lichen planus (LP). Twenty-four patients clinically and histopathologically diagnosed as LP with intense pruritus were treated with 3 mg of enoxaparin (Clexane), subcutaneously once a week for 4–14 weeks.

Complete remission was observed in 20 of 24 patients (83%) who had widespread cutaneous involvement, but no or minimal effect was observed in four of 24 patients, three of whom had chronic hypertrophic LP. Low-dose enoxaparin was observed to be effective in the treatment of LP without any side-effects and he concluded that Enoxaparin may be an effective and simple alternative therapy for LP.[15]

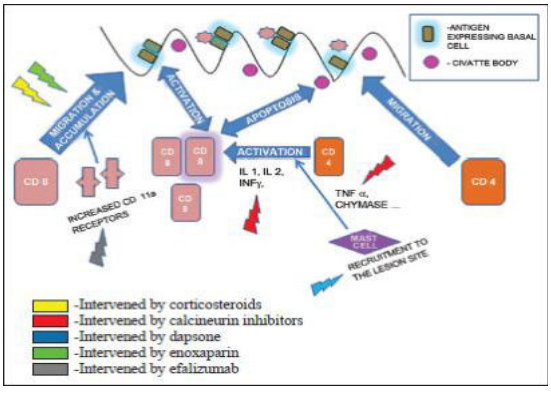
Lunge et.al conducted a comparative study on the efficacy and safety of methotrexate and low molecular weight heparin in generalized lichen planus patients along with 6 months follow up. In this study 40 patients with generalized lichen planus were enrolled after basic

evaluation 20 patients(11 males, 9 females) were started on low dose methotrexate & 20 patients(11 males, 9 females) on low molecular weight heparin. The response rate were appraised after once a week for 16 to 24 weeks for both methotrexate & low molecular weight heparin. Six month follow up was done for evaluating the recurrence rate. 5 mg of subcutaneous enoxaparin administered once weekly for 16–24 weeks produced remission of skin lesions in 13 out of 20 patients, 35% of patients showed relapse after discontinuation of enoxaparin. The authors concluded that methotrexate was not only more effective in terms of causing complete remission of the disease, but also better tolerated and associated with a lower recurrence rate than enoxaparin.[16]

TABLE 2 : Studies investigating the clinical efficacy of subcutaneous enoxaparin in patients with lichen planus (LP) [5].

Author	Year	Study design	Patients	No. of patients	Enoxaparin dose/duration	Previous treatment	Clinical effect	Side effects
Neville et al.	2007	Case study	Patient with ulcerative LP and hepatitis C	1	30 mg biweekly for the first 2 weeks and then 3 mg biweekly for the next 4 weeks	Topical corticosteroid and topical immunosuppressant	Complete remission of the lesions and the patient was in remission for 18 months. A slight flare of LP on the palm was developed later on which was controlled with topical treatment of corticosteroid and immunosuppressant	No side effects were observed
Ameen and Alfadhly	2011	Open-label	Patients with recalcitrant LP	15	3 mg once a week for a period of 20 weeks	Topical and systemic corticosteroids	2 of 15 patients with mild form of LP had complete remission of the lesions. 13 of 15 patients with moderate or severe LP did not achieve complete remission. 13 of 15 patients reported significant reduction in itching	No side effects were observed
Yasar et al.	2011	Case series	Palmoplantar hyperkeratotic variant of LP	2	3 mg once a week for 12 weeks	Not specified	Skin lesions were healed in both the patients but oral mucosal lesions remained stable	No side effects were observed
Ucmak et al.	2012	Open-label	LP - Type of LP not specified	21	3 mg once a week for 12 weeks	Systemic or local treatment - pharmacological agent not specified	15 of 21 patients showed perfect recovery and 4 out of 21 patients showed distinct recovery; The terms "perfect recovery" and "distinct recovery" were not defined by the authors	No side effects were observed
Khan et al.	2014	Open-label	Cutaneous LP	37	3 mg once a week for 6 weeks	Not specified	Improvement in papular eruption, scaly lesions and pigmentation; Complete remission was not observed in any of the enoxaparin-treated patients	8 of 37 patients suffered from local bruises and headache
Iraji et al.	2013	Multicentre randomized clinical study	Disseminated LP	25	5 mg once a week until complete remission or a maximum of 8 weeks	Not specified	8 (32%) patients had complete remission, 10 (40%) patients had partial improvement and 7 patients (28%) had no improvement	No side effects were observed in 24 patients and one patient suffered from a rash of new lesions at the injection site
Lunge et al.	2016	Non-randomized controlled clinical study	Generalized LP	20	5 mg once a week for 16 to 24 weeks	Topical corticosteroid, antihistamines or emollients	13 patients had complete remission of skin lesions. However, 7 patients showed relapse after discontinuation of enoxaparin	No side effects were observed

PROPOSED SITES OF ACTION BASED ON PROPERTY OF DRUGS IN ORAL LICHEN PLANUS[17]



Adverse effects of LMWH

Although LMWHs are generally well-tolerated drugs and have minor side effects, they occasionally can lead to severe reactions. Before the commencement of the treatment, patients should be checked for platelet counts and creatinine clearance. Owing to the relatively long half-life of elimination of LMWHs and the lack of a specific antidote, it is difficult to reverse its anticoagulant action. The cutaneous side effects of LMWHs are various but most of the time not life threatening. In systematic reviews about LMWH induced skin necrosis, researchers-explained necrosis is usually benign and uncommon, rarely surgical treatment may be necessary. Skin necrosis may be caused by vasculitis (type III Arthus reaction) or heparin-induced thrombocytopenia. Although it has been shown that LMWHs inhibit delayed-type hypersensitivity reaction, there are some studies regarding delayed-type hypersensitivity reactions may be caused by LMWHs as well.[13]

Table 3. Adverse effects of LMWH

Cutaneous side effects	Other systemic side effects
Acral edema	Anaphylactic reactions
Acute generalized exanthematous pustulosis	Bleeding
Allergic reactions	Heparin induced thrombocytopenia
Alopecia	Hyperkalemia
Angioedema	Hypoaldosteronism
Bullous hemorrhagic dermatosis	Osteoporosis
Delayed-type hypersensitivity	
DRESS syndrome	
Ecchymosis	
Erythema	
Erythematous maculopapular rash	
Fat necrosis	
Nail discoloration	
Pruritus	
Purpura	
Pyoderma gangrenosum-like skin changes	
Skin necrosis	
Urticarial rash	

CONCLUSION

Despite the adverse effect of LMWH Enoxaparin is effective, simple and good alternative therapy for acute and chronic recalcitrant lichen planus, especially those who use prolonged courses of steroid therapy without any benefits.

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