

HEPARIN IN THE TREATMENT OF ULCERATIVE COLITIS, DOES IT HAVE ANY ROLE?

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Abstract : Ulcerative colitis is an idiopathic, chronic inflammatory condition with increased prevalence in the western countries as compared to India. At present a number of drugs are available for the treatment of ulcerative colitis but still 15-20% patients require colostomy. Recently extensive experimental studies showed efficacy of heparin in this condition, but clinical trials in humans showed variable response as such there is a need of large randomized controlled trial to establish its efficacy.

Key words: Heparin, ulcerative colitis, inflammation

INTRODUCTION

Ulcerative colitis is an inflammatory disease, primarily involving the colonic mucosa; the extent and severity of colon involvement are variable. The incidence of ulcerative colitis in western countries is 6-8 cases per 1,00,000 populations approximately. Ulcerative colitis seems to be rare among South Asians residing in the Indian subcontinent but is common amongst migrants to developed countries. The reported incidence of ulcerative colitis from north India is 6.02 per 100,000. Despite intensive research, pathogenesis remains unclear, but certain features of the disease have suggested several possible areas of aetiological importance. Most emphasis has been given to the inflammatory hypothesis, suggested by heavy mucosal infiltration by inflammatory cells, inflammatory cytokines and increased mucosal permeability.

Drugs like 5-aminosalicylic acid (sulfasalazine), different antibiotics, corticosteroid, immunomodulatory drugs, and IgG anti-TNF α antibody infliximab (restricted use) have shown variable effectiveness, none of these induce complete remission; 15% patients need colostomy as a consequence of failed medical therapy. Apart from the anticoagulant action/anti-inflammatory property of heparin has been proved in several studies. Heparin is a member of a family of polysaccharides known as glycosaminoglycans. It is synthesized exclusively in the most cells of lung, intestine and liver, the effects are mediated by its physicochemical properties of the compound rather than the specified pharmacological properties which depend upon the 3-D-sulfated group on glucosamine. Since this proteoglycan is present in varying structures and are capable of binding chemokines, various ligands, growth factor proteins, ECM, causing cell adhesion and can modulate a variety of biological events beyond simply serving as a non-thrombogenic surface. Leukocyte recruitment from the vasculature to the site of inflammation is one of the initial events in inflammation. Heparin has been shown to interfere with the key first step in leukocyte recruitment by inhibiting binding of P-selection and L-selection to rCAM-1 in vascular endothelial cells¹.

Heparin has been extensively studied in the experimental model. Russian scientists were the first to use unfractionated heparin in this drug as early as 1980 of unfractionated heparin in moderately severe non-specific ulcerative colitis; 8 mg produced rapid relief of rectal bleeding and colostomy rates decreased from 16% to 6%². Since then there have been several open uncontrolled studies employing both fractionated and unfractionated heparin^{3,4}. The study by Gaffney et al, showed positive clinical response in 9 of 10 patients with prolonged remission; steroids and/or sulfasalazine were continued. The only reported side effect was injection site haematoma in one patient and rectal bleeding increased in two patients in the first week of therapy. Similar protocol was followed in another open label study by Bazier et al. showed significant clinical improvement but one of them required surgery for major haemorrhagic complication LMWH has less effect on coagulation profile and bone mineralization compared to UFH and it is easy to use⁵.

The first randomized, multicentric, comparative trial was designed by Panes et al⁶. Comparison was made between intravenous methyl-prednisolone and heparin infusion in 25 patients. This study reported that monotherapy of heparin is not having any significant improvement over methyl prednisolone besides it increases bleeding complications. But the open label study by Bazier et al, had shown significant clinical improvement with UFH monotherapy though this study was conducted in small number of patients.

Vri et al⁶, enrolled active severe ulcerative colitis patients refractory to steroid

therapy daily. 20 out of 25 patients showed good improvement endoscopically and histologic features of inflammation improved but there was no significant reduction in the number of mucosal micro thrombi. No serious adverse events were noted and tolerability was excellent. The largest trial reported so far in 100 patients of mild to moderate ulcerative colitis who were treated with LMW heparin for six weeks showed no benefit of low molecular weight heparin over placebo in mild to moderately active ulcerative colitis⁸. (Table)

Table Clinical trials of heparin in ulcerative colitis patients

Authors	Study design	Patient Selection	Heparin and other treatment	Duration of Treatment	Result
1. Gaffney et al, 1995	Open label	10, poorly controlled UC	UFH, IV to SC along with sulfasalazine and prednisolone	6 months or more	Remission in 9 patients
2. Bazier et al, 1996	Open label	6, moderate to severe UC refractory to steroid	UFH, IV to SC. No other drugs allowed	4 weeks	Significant clinical improvement in 4 patients
3. Evans et al, 1997	Open label	16, active UC (relapse cases) unresponsive to high dose corticosteroid	UFH, IV to SC	12 weeks	Remission in 14 patients
4. Folwaczny et al, 1999	Open label	13, severely active UC, CD 4, CD 12, mild to moderately active UC, refractory to steroid	UFH, IV then SC	8 weeks	Remission in 7, Remission in none
5. Torkvist et al, 1999	Open label	17 of UC, 3 of CD	LMWH, SC	12 weeks	Complete remission in 6 Symptomatic improvement in 5 patients
6. Ang et al, 2000	Randomized Controlled trial	25, moderate to severe UC	Heparin IV & SC, hydrocortisone And oral prednisolone	5 weeks	Equal efficacy with steroid
7. Panes et al, 2000	Multicentric Randomized comparative trial with blinding	25, moderate to severe UC	LMWH, IV infusion Vs Placebo IV infusion in addition to methyl prednisolone infusion	8 weeks	No significant benefit
8. Botan et al, 2001	Open label	12, UC patients with flare ups	LMWH, SC weekly all patients were taking high dose mesalazine	12 weeks	Clinical remission in 8 patients
9. Vrij et al, 2001	Open label	25, moderate to severe active steroid refractory UC	LMWH, SC BD	8 weeks	Improved clinical symptoms in all Patients No benefit over placebo
10. Bloom S et al, 2004	Randomized trial	100 patients of UC	LMWH Vs placebo	6 weeks	No benefit over placebo

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