COMPARISON OF SUCRALFATE AND HYDROCORTISONE ENEMAS IN TREATMENT OF ACTIVE ULCERATIVE PROCTITIS; A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Sucralfate enema has been proposed and investigated in treatment of ulcerative proctitis, but its efficacy is still a matter of debate. Hydrocortisone enema is still an established drug in treatment of ulcerative proctitis. This study was designed to compare the effect of sucralfate enema with hydrocortisone enema. Patients with active sigmoidoscopic and histologic features of ulcerative proctitis were included. All patients had clinical manifestations of proctitis for at least four weeks prior to the study and had negative parasitic stool culture. The total of 25 patients entered the study. They were randomly divided in two groups; group I (n =14) and group II (n = 11) who received sucralfate and hydrocortisone enemas respectively for 4 weeks. Both groups had a significant improvement in clinical features, histologic activity and sigmoidoscopic evaluation in comparison with the baseline. Furthermore there was no significant differences between the two groups concerning mean changes of clinical, sigmoidoscopic, and histologic grading, after treatment. Considering the low cost and minimal adverse effects of sucralfate, and almost equal efficacy in comparison with hydrocortisone enema, its usage can be recommended.

Key words: Sucralfate, Hydrocortisone, Ulcerative colitis, Proctitis, Enema

INTRODUCTION

Ulcerative proctitis, ulcerative colitis limited to rectum, is a disease without a well-known etiology and its treatment is an important clinical concern. Although several modalities of treatment are known and examined in different studies and trials, the issue seems to remain as a subject for further investigations.

Sucralfate enema has been proposed and investigated in the treatment of ulcerative proctitis (1-6). Sucralfate is frequently used in upper gastrointestinal tract ulcers and seems to be an effective treatment with several healing effects on inflammations and ulcers. Sucralfate can form a protective barrier to fecal toxins by adhesion to positively-charged proteins on ulcer bases (7,8). It reduces microvascular injury by stimulating angiogenesis (9) and binds efficiently to basic fibroblastic growth factor (bFGF), thereby enhancing epithelial regeneration (10). Sucralfate has also been shown to have a cytoprotective activity through stimulation of the prostaglandin secretion and binding to bile salts (11).

Sucralfate is an inexpensive and easily available drug in our country. This randomized double-blind study was designed to compare effects of sucralfate enema with the conventional treatment (hydrocortisone enema) for patients with distal ulcerative proctitis.

MATERIALS AND METHODS

Patients

The present study was designed as a double blind randomized controlled clinical trial performed in patients referred to Gastroenterology and Hepatology Clinic of Imam Khomeini Hospital between September 1, 2001 and November 1, 2002. Patients with active sigmoidoscopic and histologic features of ulcerative proctitis not extended more than 20cm from the anal margin were included in this study. All enrolled patients had clinical manifestations of proctitis for at least four weeks prior to the study and had negative parasitic stool culture. Patients excluded from the study if they were receiving systemic or topical corticosteroid, sulfasalazin more than

4 g/d, mesalamine more than 2.5 g/d and/or immunosuppressive agents. Also, if patients had known allergy to sucralfate, hydrocortisone, Hydroxypropylmethyl cellulose (HPMC) and/or Carboxyvinyl polymer (Carbapol®) were excluded from the study.

Patients were randomized into two groups; group I and group II received sucralfate enema and hydrocortisone enema respectively for 4 weeks.

Methods

Sucralfate was formulated as 6 g/60 ml and hydrocortisone as 100 mg/60 ml suspension. Suspensions were coded, and distributed by a clinical pharmacist under supervision of a faculty of pharmacy. Both treatments were packed in similar packages and labeled as *RCTex*. Patients were instructed to take the formulation as enema twice a day for two weeks followed by once a day for the remaining two weeks. The pharmacist monitored the usage of drug and the compliance of patients by making contact with them.

Each package had a specific code encoding the type of treatment. Both patients and physicians were blinded regarding the type of medications. Each patient received a package according to the assigned number at the time of randomization.

Upon entry into the trial, patients were evaluated based on clinical, sigmoidoscopic, and histologilc examinations. Also paraclinical tests including complete blood count, erythrocyte sedimentation rate (ESR), and serum biochemistry were performed. Patients were assessed clinically two weeks after entering into the study. Furthermore all the initial assessments and evaluations including sigmoidoscopic, histologic and paraclinical examination were done four weeks after admission to the study. All sigmoidoscopies were performed by the same gastroenterologist and all biopsy specimens were studied by the same experienced pathologist.

Clinical activity of the disease was determined according to the criteria of Truelove & Edward (12), the macroscopic appearance of the rectum at sigmoidoscopy was graded using Truelove & Witts' criteria (13) and histologic activity was expressed according to the criteria of Truelove & Richards (14).

Clinical response was classified as: I, "clinical remission", defined as having all the features of one or two non-bloody stools a day, no fever and no tachycardia, normal or returning to normal hemoglobin and normal ESR and gaining weight: II, "no change", this category consisted of patients in whom no changes in the above criteria were observed: III, "clinical improvement" was defined as an intermediate condition between the first and second categories.

Three categories for sigmoidoscopic response were: I, "sigmoidoscopic remission", normal appearance of rectosigmoid at the end of treatment: II, "no response", similar or aggrevated endoscopic finding at the end of treatment: III, "sigmoidoscopic improvement", reduction of at least one grade of activity.

Histological response was categorized as: I, "histological remission", normalization of histologic findings: II, "no response", without change or with increase in histologic grading: III, "histological improvement", a reduction in histologic grade, but not normalization.

This study was approved by the ethical committee of Vice Chancellor for Research, Tehran University of Medical Sciences. Consent forms according to the rules of Iranian Ministry of Health and Helsinki Declaration was taken from all patients and their data were considered completely confidential.

Statistical Analysis

All data were entered to a database and analyzed by the use of software of SPSS for windows (version 10.0.5, USA).

For comparison between two groups, Mann-Whitney U-test and chi-square test were used. Wilcoxon signed ranks test were utilized to evaluate the efficacy of treatment within each group. P value less than 0.05 was considered significant.

RESULTS

Fourteen patients were randomized into the first group to get sucralfate enema, and 12 patients were randomized into the second group to receive hydrocortisone enema. One of the patients in group II, who was primarily diagnosed with ulcerative proctitis, showed aggrevation of symptom upon beginning of the treatment and in the secondary colonoscopic evaluation, was diagnosed with Crohn's disease and as a result was excluded from the study.

There was no significant statistical differences between two groups considering age, sex, socio-economic status, duration of disease and also clinical, sigmoidoscopical, and histological activity of disease prior to the treatment. The data concerning these variables are summarized in table 1.

Table 1- Demographic, clinical, and paraclinical characteristics of patients at the admission

		Group I (N=14)	Group II (N=11)	*P* value
Age (year) [1]		25 (18-58)	29 (16-50)	0.72 [2]
Sex (M/F ratio)		9/5	8/3	0.20 [3]
Socio- economic Status	Good Moderate	0 14	3 8	0.07 [3]
Smoking		1	2	0.40 [3]
Duration of Disease (year) [1]		1.5 (0-7.3)	1.5 (0-8.5)	0.81 [2]
Clinical activity	Mild Moderate	10 4	8 3	0.94 [3]
Sigmoidoscopic Activity	Mild Moderate Severe	2 9 3	1 6 4	0.69 [3]
Histological Activity	Mild Moderate Severe	3 8 3	2 8 1	0.65 [3]

1 Median (Range)

2 Mann – whitney u test

3 Chi – square test

Group I: 6g/BID (sucralfate enema) for two weeks followed by 6g/day for the next two weeks

Group II: 100mg/BID (hydrocortisone enema) for two weeks followed by 100mg/day for the next two weeks

Four patients from group I (28.6%) and 3 patients in group II (27.3%) had the history of the treatment with either 5-aminosalicylic acid (5-ASA) or corticosteroids for their disease.

Both groups showed significant improvement in clinical, histological and sigmoidoscopical evaluation compared with their admissions (P value <0.05). However there was no statistically significant differences in the treatment outcomes between two groups concerning clinical (P value=0.70), sigmoidoscopic (P value =0.24), and histologic grading (P value =0.29). These data are shown in table 2.

DISCUSSION

Sucralfate is a basic aluminium salt of sucrose octasulfate which is poorly absorbed from human gastrointestinal tract. Although oral sucralfate has been approved and extensively used in the treatment of peptic ulcer, reflux esophagitis, and erosive gastritis (15-17), the efficacy of sucralfate enema in patients with ulcerative proctitis is a matter of debate. It had been postulated that sucralfate is only active in acidic medium (18). It has been reported that the protective effect of sucralfate against mucosal injury was not dependent on an acidic medium (19). The efficacy of sucralfate suspenssion enema in prevention of post-polypectomy bleeding has been demonstrated (20).

Several studies have been performed on the possible effect of sucralfate enema in the treatment of distal ulcerative colitis (1-6). In 1986, Carling et al (2) studied the effectiveness of sucralfate enema (10 g twice a day) in 15

Table 2. Clinical, endoscopic, and histological response of patients at the end of 4 week

		Group I (N=14)	Group II (N=11)	*P* Value *
Clinical change	Remission [1]	10	7	0.70
	No change [2]	3	2	
	Improvement [3]	1	2	
Endoscopic change	Remission [4]	6	8	0.24
	No change [5]	5	1	
	Improvement [6]	3	2	
Histologic change	Remission [7]	4	5	0.29
	No change [8]	5	1	
	Improvement [9]	5	5	

Group I: sucralfate enema, Group II:hydrocortisone enema

* Chi –square test

1 defined as having all the features of one or two non-bloody stools a day, no fever and no tachycardia, normal or returning to normal hemoglobin and normal ESR and gaining weight

2 patients with no changes in above criteria

3 defined as an intermediate condition between first and second categories.

4 normal appearance of rectosigmoid at the end of treatment

5 similar or aggrevated endoscopic finding at the end of treatment

6 reduction of at least one grade of activity.

7 normalization of histologic findings

8 without change or with increase in histologic grading

9 a reduction in histologic grade, but not normalization.

patients with distal ulcerative colitis. Riley et al (3), compared sucralfate enema (4g/day) with prednisolone enema (20 mg/day) and concluded that although sucralfate enema was useful in improvement of disease, it was less effective than prednisolone. Ardizzone et al (1), reached to the similar results by comparing a higher dose of sucralfate enema (10 g twice a day) with hydrocortisone enema. In another study (4), the effect of sucralfate enema (20 g twice a day) was equal to that of prednisolone enema. These inconsistencies may be due to several factors including small number of patients enrolled in different studies, variations in the dose of sucralfate, evaluation of the disease activity, the formulation of the suspension, and variations in design of studies (control group, randomization, and blindness).

Sucralfate enema has also been compared with 5-ASA. In one study (5) sucralfate enema had an equal effect in comparison with 5-ASA and in the other while 5-ASA was effective in improvement of disease, both sucralfate enema and placebo were ineffective (6).

Our study was a double blind randomized controlled trial comparing sucralfate enema (6 g twice a day for the first two weeks and 6 g/day for the next two weeks) with hydrocortisone enema (100 mg twice a day for the first two weeks and 100 mg/day for the next two weeks). It is shown that patients receiving sucralfate enema achieved significant improvement and this is in accordance with most studies (1-5). It was also found that this improvement is comparable to that resulted from hydrocortisone enema which is in agreement with Riley et al's study (3).

We emphasize that sucralfate enema is an inexpensive and safer drug in comparison with widely used drugs like hydrocortisone, prednisolon, or 5-ASA enemas, and its usage can be recommended. The present study is an interim from a cohort in progress.

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