Study the Efficacy of Budesonide Enema in Treating Collagenous Microscopic Colitis: An Egyptian Trial

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To cite this article:
doi: 10.11648/j.ajim.20150306.14

Abstract: Chronic diarrhea can have a substantial impact on the patient’s quality of life and overall health. Microscopic colitis (MC) is an inflammatory bowel disease, which is characterized by chronic watery diarrhea. Many drugs, including steroids, had emerged to treat MC. Our aim was testing the efficacy of Budesonide enema in improvement of patients with collagenous microscopic colitis both clinically and histopathologically. 22 patients with active microscopic colitis were enrolled in the present study, 15 women, and 7 men, with mean age of 60.9±8.5 years. Mean duration of symptoms was 2.6±0.8 years. Patients were given Budesonide enema 2mg/100ml twice daily for 2 weeks then, once daily for 4 weeks. They were evaluated both clinically and histopathologically after 6 weeks.18 patients (81.8%) showed high statistically significant decrease in the thickness of collagen layer, and degree of inflammation. The patients' frequency of stool decreased from 7.6±1.0 to 2.7±1.6 motions/day (p<0.001), and also consistency of stool improved (p<0.001). We concluded that Budesonide enema in a dose of 2 mg/100ml was well tolerated and effective in induction of remission in active collagenous colitis. Effects on both clinical symptoms and inflammatory infiltrate were seen. Recurrence rate after stopping treatment is moderate. Non-responders may need prolonged duration of treatment or omitting the drugs that may be responsible for colonic inflammation.

Keywords: Chronic Diarrhea, Collagenous Colitis, Budesonide Enema

1. Introduction

Microscopic colitis (MC) is an inflammatory bowel disease of unknown etiology, which is characterized by chronic watery diarrhea, no macroscopic signs of large bowel involvement in the presence of specific patho-morphological changes. There are two major forms of MC, which are similar in its clinical picture, yet, heterogeneous in histological criteria: collagenous colitis (CC) and lymphocytic colitis (LC) [1].

CC was described by Lindstrom and Freeman in 1976 in a report of a patient with chronic diarrhea whose colonic biopsy specimens revealed a thickened sub-epithelial collagen layer, similar to that observed in patients with collagenous sprue [2]. In 1980, Read described microscopic colitis [3], which is clinically indistinguishable from CC but is differentiated from it by colonic biopsy features. Later, the term lymphocytic colitis (LC) was proposed by Lazenby [4], to replace the term microscopic colitis and to distinguish it from infectious colitis and inflammatory bowel disease. Population-based studies have shown that the incidence rate of microscopic colitis varies between 1 and 12 per 100,000 persons per year [5]. The overall incidence of MC appears to have increased substantially in recent years [6]. The reasons for these apparent increase in disease incidence are not clear, but increased clinical awareness, more frequent performance of diagnostic colonic biopsies, and increased use of medications that cause MC have been proposed [7]. The increased incidence has stabilized over the past years, and the incidence is associated with female gender and increasing age [8]. MC can occur in patients of any age but typically presents in late middle age and elderly. The average age at diagnosis is approximately 65 years [9]. The reason for that is unknown, and also the higher rate among women are also unknown but might be related to the higher likelihood of autoimmune diseases, hormonal alterations and/or an...
ascertainment bias as women may be more likely to seek help for intermittent watery diarrhea [10].

Identifiable risk factors for MC include; increasing age [11], female sex [11], autoimmune diseases such as thyroid diseases [12], and coeliac disease, past or current diagnosis of malignancy [13], and solid organ transplant [14]. MC has been associated with the use of several medications including non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRIs), beta-blockers, statins, biphosphonates, ticlopidine, flutamide, and proton-pump inhibitors [15].

The exact cause of microscopic colitis is unknown. Some factors are implicated as etiological factors, Genetic contribution [16], autoimmune basis [17], bile acid malabsorption [18], and gastrointestinal infection [19, 20] as Yersinia, Clostridium difficile, and Campylobacter.

Patients with MC typically present with chronic watery, non-bloody diarrhea, although a minority of patients may present with an acute onset. The precise mechanism of this diarrhea is not well understood. Factors that may play a role include bile salt induced injury, active chloride excretion, decrease in net sodium absorption, creation of a diffusion barrier by collagen band and increased local inflammatory mediators such as nitric oxide, prostaglandins, and inflammatory cytokines [10]. Associated symptoms include nocturnal bowel motions, mild abdominal pain, fatigue, slight weight loss, arthralgias, and faecal incontinence. Symptoms are often attributed to an irritable bowel syndrome [10].

The natural history of MC is variable. Many cases are self-limited, with symptoms lasting a few weeks or months. Others may be symptomatic for years in a relapsing or continuous pattern. Although a small number of case reports have suggested that MC may lead to development of ulcerative colitis, a small case series of patients with MC showed that none developed ulcerative colitis or Crohn's disease after a follow-up of at least 6 years [21]. MC also does not appear to affect colorectal cancer risk [22].

Diagnoses of microscopic colitis depends on (i) history of chronic, watery, non-bloody diarrhea, (ii) normal or near normal endoscopic and/or radiographic findings, and (iii) colonoscopy with random colonic biopsies sent for histopathological examination for findings consistent with MC to confirm the diagnosis.

Treatment recommendations for MC are based on case reports and uncontrolled studies, and give a suggested algorithm include; withdrawal of medications associated with MC, dietary changes (avoid caffeine, lactose), trial of anti-diarrheal [23], trial of budesonide, and if no improvement, diagnosis should be confirmed and other disorders should be ruled out. Prednisolone / azathioprine / mercaptopurine / methotrexate should be considered in severe MC.

Corticosteroids used in treatment of microscopic colitis decrease levels of inflammatory cytokines such as interleukin-1, Interleukin-6, and tumor necrosis factor through inhibition of protein synthesis and transcription [24]. Unfortunately, systemic steroids have numerous undesirable side effects as hypertension, osteoporosis, and diabetes mellitus. Budesonide is a synthetic steroid of the glucocorticoid family with a high topical anti-inflammatory activity and limited systemic availability, so many of the adverse events associated with systemic corticosteroids are diminished [25]. Budesonide is the drug which has been proved to be efficient by randomized, placebo-controlled trials, in treatment of moderate to severe microscopic colitis [9]. Budesonide therapy resulted in a significant improvement in both clinical symptoms and histological inflammatory changes, but the relapse frequency is about 61–80% [26], the relapse frequency is reduced by sustained treatment at low dosage [27].

Most studies investigated the efficacy of Budesonide tablets in treatment of CC, and LC [28, 29]. To our knowledge, no current study investigates the efficacy of Budesonide enema in treatment of microscopic colitis. On the other hand, a lot of studies showed the efficacy of Budesonide enema in treatment of Ulcerative colitis and proctitis [30].

We hypothesized that Budesonide enema may be effective in treatment of cases of microscopic colitis as well as its effectiveness in cases of ulcerative colitis. Our aim of this study was testing the efficacy of Budesonide enema in improvement of patients with collagenous microscopic colitis both clinically and histopathologically.

2. Materials and Methods

The current study was performed in Gastroenterology Department, Faculty of Medicine- Alexandria University. The study was approved by the ethics committee of the faculty of medicine- Alexandria University. All study participants were given a detailed description of the study; its purpose and benefits, and their written informed consent was obtained.

22 Patients of both genders (15 women and 7 men), aged 45 years and older diagnosed with active microscopic colitis were included in the present study. Diagnostic criteria were histological findings of thickening of a sub-epithelial collagen layer of more than 10 µm. Clinical activity was defined as a daily stool frequency of >4. Patients with other types of bowel disease, as infectious colitis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), or ischemic colitis, celiac disease , malignancy or any severe concomitant disease, partial colonic resection, intolerance to corticosteroids, as well as pregnancy and lactation all were excluded from the study. In addition, patients treated with steroids, aminosalicylates, antibiotics, and immune-suppressants during the past 4 weeks before the study also were excluded from the study.

At baseline, thorough medical history was taken for all patients. Stool frequency and consistency were recorded at baseline and after six weeks by asking the patient for the average number of stools per day within the past 7 days and for the dominant type of stool consistency.

Colonoscopy was performed at baseline before treatment with multiple biopsies taken from transverse, descending, and sigmoid colon as well as from the rectum for histologic
assessment. Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Sections (5-µm thick) were stained with hematoxylin and eosin (H&E), and in borderline cases, Masson trichrome stain was used. An expert pathologist assessed the thickness of collagen layer at 10 points at a magnification of 600 on a monitor screen. The inflammation in the lamina propria was assessed and graded from 0 to 3; 0 = no inflammation; 1 = mild (inflammatory infiltrate confined to the upper part of the lamina propria); 2 = moderate (inflammatory infiltrate extending beyond the base of the crypts); and 3 = severe (heavy inflammatory infiltrate occupying the lamina propria and infiltrating the lamina muscularis mucosa).

Patients with MC received budesonide enema (enemacort®) at a dose (2 mg/100mL) twice daily for two weeks then once daily in the evening for 4 weeks. Clinic visits were scheduled and patients were re-evaluated after 6 weeks both clinically and histologically.

Patients were monitored for the occurrence of adverse events throughout the study. Compliance with study medication was checked by counting the medication returned at the follow-up visit.

The efficacy end point was clinical remission defined as a reduction in stool frequency less than 4/day. Patients were also evaluated for the change in stool consistency.

The histologic results were examined at 6 weeks after baseline and classified as remission (reduction in thickness of collagen layer less than 10 µm, plus a reduction in lamina propria inflammation), or no-response (no change in thickness of collagen layer, plus no change in lamina propria inflammation).

All patients who achieved clinical remission followed clinically for 6 weeks for recurrence of symptoms (stool frequency and consistency). According to the inclusion criteria of the clinical trial, a clinical relapse was defined as >4 watery or loose stools/day on average per week.

3. Results

22 patients diagnosed with active microscopic colitis were enrolled in the present study, 15 women (68.2%) and 7 men (31.8%). The range of patients’ age was 46-75 years, with a mean of 60.9±8.5 years. The duration of symptoms ranged from 1.5 – 4 years, with a mean of 2.6±0.8 years. At baseline, the stool frequency of the patients ranged from 0 to 3 motions/day, with a mean of 7.6±1.0 motions/day. 17 patients (77.3%) had watery diarrhea, and 5 patients (22.7%) had soft stools/day.

Patients received Budesonide enema (enemacort®) at a dose of 2 mg/100mL twice daily for two weeks then once daily at night for 4 weeks. The patients were reviewed after 6 weeks for clinical improvement and prepared for colonoscopies to check histological response. 18 patients (81.8%) showed clinical improvement as determined by decrease in stool frequency less than 4 times/day and also improvement of stool consistency. Table 1 represents the Clinical and histological findings of the patients at baseline and after 6 weeks of treatment with Budesonide enema.

<table>
<thead>
<tr>
<th>Stool frequency</th>
<th>At baseline</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>6-9</td>
<td>1-6</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>7±6±1.0</td>
<td>2.7±1.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stool consistency</th>
<th>At baseline</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery</td>
<td>17</td>
<td>0</td>
<td>0.001*</td>
</tr>
<tr>
<td>Soft</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Well formed</td>
<td>0</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thickness of collagen layer (µm)</th>
<th>At baseline</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>7-20</td>
<td>3-12</td>
<td>0.002*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.3±2.7</td>
<td>6.1±2.2</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1.0±0.7</td>
<td>0.2±0.4</td>
<td>0.023*</td>
</tr>
<tr>
<td>Range</td>
<td>12.3±2.9</td>
<td>5.8±2.5</td>
<td>0.0041*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>23.4±3.9</td>
<td>8.4±2.2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>12-30</td>
<td>6-15</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>19.9±4.6</td>
<td>8.1±2.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degree of inflammation</th>
<th>At baseline</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>1-3</td>
<td>0-2</td>
<td>0.0023*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2.3±0.8</td>
<td>0.9±0.6</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0-3</td>
<td>0-1</td>
<td>0.023*</td>
</tr>
<tr>
<td>Range</td>
<td>1.0±0.7</td>
<td>0.2±0.4</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2.8±0.4</td>
<td>0.8±0.8</td>
<td>0.0041*</td>
</tr>
<tr>
<td>Range</td>
<td>0-3</td>
<td>0-1</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.3±0.9</td>
<td>0.3±0.5</td>
<td>0.0054*</td>
</tr>
</tbody>
</table>

Table 2 represents the correlation between clinical symptoms and its duration, the thickness of the collagen layer, and the degree of inflammation. Stool frequency and consistency were highly positively correlated with the duration of the symptoms, the thickness of the collagen layer, and the degree of inflammation.

Table 2. The Correlation between clinical symptoms and other parameters.

<table>
<thead>
<tr>
<th>Stool frequency and consistency</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>0.465</td>
<td>0.001*</td>
</tr>
<tr>
<td>Degree of inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>0.412</td>
<td>0.003*</td>
</tr>
<tr>
<td>D</td>
<td>0.395</td>
<td>0.014*</td>
</tr>
<tr>
<td>S</td>
<td>0.411</td>
<td>0.001*</td>
</tr>
<tr>
<td>R</td>
<td>0.398</td>
<td>0.006*</td>
</tr>
<tr>
<td>Thickness of collagen layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>0.416</td>
<td>0.001*</td>
</tr>
<tr>
<td>D</td>
<td>0.369</td>
<td>0.0165*</td>
</tr>
<tr>
<td>S</td>
<td>0.406</td>
<td>0.003*</td>
</tr>
<tr>
<td>R</td>
<td>0.368</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

P is significant ≤ 0.005.
4. Discussion

Chronic diarrhea can have a substantial impact on the patient’s quality of life and overall health. A wide range of problems can cause chronic diarrhea. Up to 10% - 20% of patients with chronic diarrhea are diagnosed with microscopic colitis (MC) [11].

The current study involved 22 patients diagnosed as active microscopic colitis, with a mean age of 60.9±8.5 years. Gentile et al. [31], proposed that the increased incidence of MC with increasing age could represent a normal aging process. Another explanation for increased incidence of MC with age was given by Drossman and his colleagues [32], as young patients presented with abdominal pain or chronic diarrhea are usually diagnosed as irritable bowel syndrome and colonoscopy is avoided while in elderly patients colonoscopy is often prescribed to exclude malignancy. Thus younger people are less frequently examined by colonoscopy than older patients, which may miss the diagnosis in young adults and gives apparently increase incidence in elderly population. Also, the barrier function of the gut epithelium may be diminished in the course of a lifetime, thus by advancing age the barrier function becomes more impaired that may explain increase incidence of MC in elderly.

In our study, more than half of patients (68.2%) were females. Estrogens and progesterone have been shown to exhibit anti-inflammatory and epithelial barrier-enhancing properties in experimentally induced colitis in rats [33]. At menopause, the fall in estrogen level may theoretically explain increase incidence of MC in middle-aged and elderly females [34].

In our study, 8 patients (36.4%) were on regular, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPI). 2 patients (9.1%) were on Eltroxin for hypothyroidism, 3 patients (13.6%) on oral hypoglycemic drugs, and another 2 patients (9.1%) were on beta-blockers for hypertension. Many researchers found similar connections between the previously mentioned medications and MC [9, 15, 35]. Arthralgia and various autoimmune conditions as thyroid dysfunction, rheumatoid arthritis, and psoriasis often occur in patients with microscopic colitis [11, 23, 26]. In our study, 8 patients (36.4%) had chronic arthralgia and osteoarthritis with high ESR, 2 patients (9.1%) had hypothyroidism, and another 3 patients (13.6%) were diabetics on oral hypoglycemic medications. Roth et al. [37], stated that the concomitant existence of many, severe diseases and the intake of several drugs may have a synergistic, harmful effect on the colonic mucosa.

Inflammatory bowel diseases (IBDs) are inflammatory conditions characterized by chronic, uncontrolled inflammation of the gastrointestinal tract [38]. Crohn’s disease and ulcerative colitis are the two primary types of IBD [39], while unclassified colitis (IBDU) is a form of colitis with clinical and pathological characteristics that do not meet the criteria for classification as either ulcerative colitis or Crohn’s disease [40]. Collagenous and lymphocytic MC are lying under the classification; unclassified colitis [41]. Glucocorticosteroids are the standard treatment for IBDs as they result in rapid remission of disease activity [42]. New formulations of glucocorticosteroids have been developed with the aim of limiting systemic activity and reducing glucocorticosteroid adverse events. The pharmacokinetic profiles of the second-generation topical oral or rectal preparations are such that the agents have high local efficacy in the gut, but minimal systemic bioavailability due to highly efficient first-pass hepatic inactivation, thus minimizing any adverse systemic effects [43]. Most studies investigated the efficacy of budesonide tablets in induction of remission of cases of active microscopic colitis [9, 28, 29]. In contrast to pH-modified capsules a more rapid absorption of budesonide was observed after rectal administration of budesonide enemas. The enema reaches its maximum spread within 15 minutes after administration, while budesonide peak serum concentration was not reached except after 1.5 hours after dosing. Thus the enema spreads rapidly compared to the rate of absorption of oral budesonide. According to the viscosity of the enema the distance of spread can reach up to the proximal colon. Also budesonide is absorbed without time delay after enema administration. Extensive studies investigated the efficacy of budesonide enema in management of inflammatory bowel diseases namely ulcerative colitis [44, 45]. To our knowledge, no studies investigated the efficacy of budesonide enema in microscopic colitis. Using data from enema treatment in ulcerative colitis, it was an obvious consequence to use budesonide enema in microscopic colitis patients.

In our study, multiple random measurements in well oriented biopsies were done by an experienced pathologist. Thickness of collagen layer more than 10 µm, and degree of inflammation of lamina propria were more pronounced in biopsies obtained from sigmoid colon, and rectum, and less pronounced in transverse and descending colon biopsies. In accordance with our findings, other studies [46], found that microscopic colitis can be diagnosed from rectal or sigmoid colon biopsies in more than 90% of cases. While, Bonderup OK, et al. [47], detected inflammatory infiltrates were more prominent in proximal part of sigmoid colon than the rectum in more than half of their patients.

We found a positive correlation between symptoms, and the degree of inflammation as well as the thickness of collagen layer; Lee and colleagues [48], analyzed a mixed material of collagenous colitis and lymphocytic colitis and found that the intensity of clinical symptoms was unrelated to the thickness of the collagen band but a correlation between daily stool weight and inflammation in the lamina propria was found. While, in study of Bonderup OK et al. [46], the correlation between symptoms and grade of inflammation was higher, and they suggest that clinical symptoms may be more closely related to colonic inflammation than to sub-epithelial collagen deposition.

In our study, 18 patients (81.8%) showed both clinical and histological improvement after 6 weeks of treatment. Histologically, the mean thickness of collagen layer of
colonic biopsies of transverse colon decreased from 12.3±2.7µm to 6.1±2.2 µm (p=0.002); in descending colon decreased from 12.2±2.9µm to 5.8±2.5µm (p<0.001), in sigmoid colon decreased from 23.4±3.9µm to 8.4±2.2µm (p<0.001), and in the rectum decreased from 19.9±4.6µm to 8.1±2.4µm (p<0.001). While in the non-responders, the mean thickness of collagen layer in transverse colon decreased from 13.5±5.44µm to 11.75±3.09µm (p=0.596), in descending colon decreased from 21.75±7.13µm to 19.25±3.20µm (p=0.5460), in sigmoid colon decreased from 22.75±3.09µm to 20.75±0.96 µm (p=0.263), and in the rectum decreased from 12.75±1.26µm to 11.5± 0.82 µm (p=0.151). Improvement was more evident in the sigmoid colon and rectum.

Also, improvement of the degree of inflammation was noted in responders; with a decrease from 2.3±0.8 to 0.9±0.6 in transverse colon (p=0.002), from 0.9±0.7 to 0.2±0.4 in descending colon (p=0.023), from 2.8±0.4 to 0.8±0.8 in sigmoid colon (p=0.004), and from 1.3±0.9 to 0.3±0.5 in the rectum (p=0.005). While, in the non-responders, the degree of inflammation decreased from 1±0.82 to 0.5±0.58 (p=0.358) in transverse colon, from 2.5±1.0 to 1.75±0.5 (p=0.228) in descending colon, from 2.75±0.5 to 2.25±0.5 (p=0.207), and from 1.75±0.5 to 1.25±0.5 (p=0.207).

The patients’ frequency of stool decreased from 7.6±1.0 to 2.7±1.6 motions/day (p<0.001), and also consistency of stool improved; as 18 patients had well-formed stool (p<0.001).

4 patients (18.2%) (non-responders), did not show improvement after 6 weeks of treatment neither histologically nor clinically although some improvement of stool consistency was noted. At baseline, the histological lesions of the non-responders were observed mainly in the transverse colon, and upper part of descending colon, and this may explain why those patients did not respond to treatment, as these lesions may be inaccessible by the enema. Another explanation; those patients were chronic users of NSAIDs, and they continue to use these drugs during the study, which may prevent improvement of underlying inflammation.

In a study by Stephen B et al. [49], budesonide enemas at 2.0 and 8.0 mg/100 mL were both clinically and statistically significantly superior to placebo in the treatment of active distal ulcerative colitis/proctitis. On the basis of this information, it seems that 2.0 mg/100 mL budesonide is the optimal dose for efficacy.

In our study, Follow up of patients for 6 weeks later, about 31.8% of patients had recurrence of symptoms; that their stool frequency is more than 4 times daily, plus passage of watery diarrhea according the our definition of clinical activity. Researchers showed that the remission rates of 139 patients with active ulcerative colitis at 4 weeks were 33%, 51% at 8 weeks of budesonide enema usage. They concluded that Budesonide enema 2 mg o.d. appears to be the optimal dosage in active distal UC but they could not show that budesonide enema twice weekly is sufficient to maintain remission [49].

5. Conclusion

We concluded that Budesonide enema in a dose of 2 mg/100ml was well tolerated and effective in induction of remission in cases of active collagenous colitis. Effects on both clinical symptoms and inflammatory infiltrate were seen. Recurrence rate after stopping treatment is moderate. Non-responders may need prolonged duration of treatment or omitting the drugs that may be responsible for colonic inflammation.

References


Inflamm Bowel Dis 1999; 5: 40–3.


