Journal of Crohn's and Colitis (2014) 8, 208–214

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# Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis — A randomized, placebo-controlled, pilot study

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Received 24 July 2013; received in revised form 3 August 2013; accepted 12 August 2013

**KEYWORDS**
Ulcerative colitis;
NCB-02;
Curcumin

**Abstract**

*Background and aims:* Curcumin, an active ingredient of turmeric with anti-inflammatory properties, has been demonstrated to be useful in experimental models of ulcerative colitis (UC). It's efficacy in humans needs to be investigated.
*Methods:* A randomized, double-blind, single-centre pilot trial was conducted in patients with distal UC (<25 cm involvement) and mild-to-moderate disease activity. Forty-five patients were randomized to either NCB-02 (standardized curcumin preparation) enema plus oral 5-ASA or placebo enema plus oral 5-ASA. Primary end point was disease response, defined as reduction in Ulcerative Colitis Diseases Activity Index by 3 points at 8 weeks, and secondary end points were improvement in endoscopic activity and disease remission at 8 weeks.
*Results:* Response to treatment was observed in 56.5% in NCB-02 group compared to 36.4% (p = 0.175) in placebo group. At week 8, clinical remission was observed in 43.4% of patients in NCB-02 group compared to 22.7% in placebo group (p = 0.14) and improvement on endoscopy in 52.2% of patients in NCB-02 group compared to 36.4% of patients in placebo group (p = 0.29). Per protocol analysis revealed significantly better outcomes in NCB-02 group, in terms of clinical response (92.9% vs. 50%, p = 0.01), clinical remission (71.4% vs. 31.3%, p = 0.03), and improvement on endoscopy (85.7% vs. 50%, p = 0.04).

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1873-9946/$ - see front matter 
http://dx.doi.org/10.1016/j.crohns.2013.08.006

*Conclusion:* In this pilot study we found some evidence that use of NCB-02 enema may tend to result in greater improvements in disease activity compared to placebo in patients with mild-to-moderate distal UC. The role of NCB-02 as a novel therapy for UC should be investigated further.


## 1. Introduction

Inappropriate and persistent immune response against commensal intestinal bacterial flora plays a central role in the pathogenesis of ulcerative colitis (UC).[1] There is an enhanced T-cell response to the bowel luminal contents accompanied by excessive neutrophil influx in colonic tissue, leading to persistent colonic inflammation and tissue destruction. The role of proinflammatory cytokines Interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, IL-12, and interferon (IFN)-γ in initiating and sustaining the mucosal inflammation has been established in animal models as well as in human studies.[2,3] Nuclear Factor kappa B (NF-κB) is the main up-regulator of expression of these cytokines, and is strongly activated in UC and Crohn's disease (CD) suggesting an important role in their pathogenesis.[4] 5-aminosalicylates (5-ASA) and corticosteroids, which are the mainstay of treatment of UC, have been shown to inhibit activation of NF-κB.[5,6] However, 20% to 30% of patients fail to respond to the drugs given for induction of remission.[7] Corticosteroids are also associated with significant side effects especially in the long term. Hence, new alternatives for the treatment of UC constantly are being sought.

Recently, curcumin, an active ingredient of turmeric (*Curcuma longa*), an Indian herb, which has been used in Indian Ayurvedic system for the treatment for inflammatory conditions, has generated great attention because of its significant anti-inflammatory properties. In experimental models, curcumin has been shown to prevent trinitrobenzene sulfonic acid (TNBS)[8] and dextran sodium sulphate (DSS) induced colitis.[9,10] Inhibition of NF-κB was postulated to be the key mechanism responsible for the anti-inflammatory action of curcumin.[11,12] The mechanistic action of curcumin involves inhibition of IKK (IκB kinase) which leads to inhibition of both cytokine mediated phosphorylation and degradation of IκB, which is an inhibitor of NF-κB.[13] Suppression of NF-κB activation in the colonic mucosa along with favourable expression of Th1 and Th2 cytokines has been demonstrated in curcumin pretreated mice with TNBS-induced colitis.[12] Other proposed mechanisms are, reduced COX-2 and iNOS production through inhibition of p38 MAPK (mitogen activated protein kinase) signalling,[14] and modulation of neutrophil chemotaxis.[15] With a multitude of effects as described, curcumin leads to a reduction of various pro-inflammatory cytokines such as IFN-γ, IL-17[16], IL-1β[17] as well as myeloperoxidase activity in the colon[16,17] which is a marker of neutrophilic infiltration.

The clinical experience with curcumin in UC is limited.[18,19] The good safety profile of curcumin places it as a promising therapeutic agent in the treatment of UC, and requires further evaluation. The present study is designed to assess the efficacy and safety of topical curcumin preparation as remission inducing agent in patients with active ulcerative colitis with distal involvement.

## 2. Patients and methods

### 2.1. Design

This single centre, double-blind, randomized, placebo-controlled, pilot study was conducted at the All India Institute of Medical Sciences, New Delhi between August 2008 and July 2009.

### 2.2. Participants

Adult patients (>18 y) who had mild-to-moderately active ulcerative proctitis and proctosigmoiditis (Ulcerative Colitis Disease Activity Index [UCDAI] score,[20] 3–9), with endoscopic disease extent up to 25 cm from the anal verge were included in this study. Patients receiving oral mesalamine were included if the dose was stable for more than 8 weeks. Patients were excluded if they were receiving rectal mesalamine or steroids in the preceding 4 weeks or had disease extending proximal to 25 cm, evidence of severe disease (UCDAI score ≥10), steroid initiation/dose escalation within the past 2 weeks, azathioprine initiation in the past 6 months or change in dose of azathioprine in the last 3 months. Patients were also excluded if they were started on oral 5-ASA in the preceding 8 weeks. Patients requiring hospitalization and imminent need for surgery, lactating and pregnant women, and those who received any investigational medicines within 3 months were excluded. Patients with significant hepatic, renal, endocrine, respiratory, neurologic, or cardiovascular diseases also were excluded.

### 2.3. Randomization

#### 2.3.1. Sequence generation

The random numbers were generated by computerized random number. The randomization list and numbered packing of the intervention were prepared by a person not involved in the study.

#### 2.3.2. Randomization-allocation concealment

All the randomization numbers were concealed in separate envelopes and marked by patient number on the outer envelope.

#### 2.3.3. Randomization implementation

The randomization was performed by staff not involved with the study. Patients were assigned in the next serial number (corresponding to the randomization code) of the intervention.

#### 2.3.4. Blinding

The individual sealed envelope method was used to maintain blinding of the investigators and study participants.

#### 2.3.5. Activity of ulcerative colitis

The activity of UC was assessed using the UCDAI scoring. The UCDAI score was calculated by a single investigator (Vikas Singla) by adding the individual scores of the 4 parameters: bowel frequency, rectal bleeding, endoscopic score, and physician's rating of severity.[20] Rectal bleeding and stool frequency score were assessed by asking the patient about his/her symptoms over the past 7 days.

#### 2.3.6. Interventions

NCB-02 is a standardized extract of *Curcuma longa* with a composition of 72% curcumin, 18.08% demethoxy curcumin and 9.42% bis-demethoxy curcumin. Eligible patients were assigned randomly, in a 1:1 ratio, to receive either NCB-02 (curcumin) enema or placebo enema once daily for 8 weeks. For the purpose of study, NCB-02 enema and identical appearing placebo enema were manufactured and supplied by Himalaya Drug Company, Bangalore. Each NCB-02 enema contained 140 mg of NCB-02 (curcumin) preparation dissolved in 20 ml of water. Patients were advised to take the enema preparation in the night prior to sleep. In addition to the trial medications, all the patients received oral mesalamine in a dosage of 800 mg twice daily.

#### 2.3.7. Assessment

At entry to the study (screening visit), each patient's demographic characteristics, medical history, and current medications were recorded. At this point, baseline clinical laboratory tests were conducted. All the laboratory tests were performed at the local laboratories. Individual disease activity was assessed at the baseline visit and after 4 and 8 weeks. At each visit, a detailed clinical assessment was performed. All the patients underwent sigmoidoscopic examination at the baseline and 8th week. All adverse events were documented. Participants' compliance in taking the study medications was assessed by the investigators, who counted the used and the unused enema preparations that the patients were required to bring with them on follow-up visits (weeks 4 and 8). If the condition of the patients deteriorated clinically (as defined by an increase in UCDAI score $\geq 3$), they were classified as treatment failure, and were withdrawn from the study and put on standard medical treatment.

### 2.4. Outcome measures

#### 2.4.1. Primary outcome measure

The primary outcome measure was improvement in disease activity. This was defined as a decrease in the UCDAI score at the end of 8 weeks, by equal or more than 3 from baseline score.

#### 2.4.2. Secondary outcome measures

Secondary outcome measures were proportion of patients achieving remission and improvement in endoscopic disease activity. Remission was defined as decrease in UCDAI to less than 3 at week 8. Improvement in endoscopic disease activity was defined as decrease in mucosal appearance score by at least one at 8 weeks compared to the baseline score.

### 2.5. Trial registration, ethics committee approval and patient consent

The trial has been registered under Clinical Trials Registry — India (CTRI) at Indian Council of Medical Research (number — CTRI/2011/04/001695). The protocol was approved by the investigational review at our centre. Written informed consent was obtained from all the participants. Patients were allowed to withdraw at any time point during the study, either because of lack of efficacy or for any other reasons.

#### 2.5.1. Safety assessment

Safety assessment was performed on the following protocol: eliciting of a detailed medical history; conduct of a detailed physical examination and biochemistry and hemogram at each visit, and documentation of any adverse events that occurred during the study period.

#### 2.5.2. Statistical analysis

Data were presented in terms of mean ± standard deviation or median with interquartile range for quantitative variables, and proportion and percentage in case of categorical variables. Comparisons between study groups for continuous variables were performed by using the unpaired *t* tests. In cases in which the data did not follow normal distribution, the comparison was performed by using a nonparametric Mann–Whitney test. The comparison for different categorical variables between 2 groups was performed by the chi-square test/Fisher exact test (in case of expected cell counts less than 5). The analysis was subjected to intention-to-treat analysis as well as per-protocol analysis for all the primary and secondary end points. SPSS version 11.5 version (Chicago, IL, USA) was used for analysis of results. Significance level was chosen at 0.05 for all the efficacy measures.

## 3. Results

### 3.1. Participant flow (Fig. 1)

Of the 48 patients screened for inclusion in the study, 3 could not be included because of refusal to give consent. A total of 45 patients were randomized; 23 received NCB-02 enema and 22 received placebo enema. 14 patients in the NCB-02 group and 16 patients in the placebo group completed the entire study. Among the 9 patients who could not complete 8 week treatment in the NCB-02 arm, 5 had worsening of symptoms and 4 were lost to follow-up evaluation. In the placebo group, 2 were lost to follow-up evaluation and 4 patients had worsening of symptoms and discontinued therapy.

### 3.2. Demographic and clinical characteristics

The demographic and clinical characteristics such as age, sex, and extent of disease in both groups were comparable (Table 1). The mean baseline UCDAI scores in the NCB-02 and placebo groups were 6.13 ± 2.13 and 6.09 ± 2.06, respectively. Although the proportion of patients receiving oral mesalamine was comparable in both the groups (18 [78.3%] in NCB-02 group vs. 16 [72.7%] in placebo

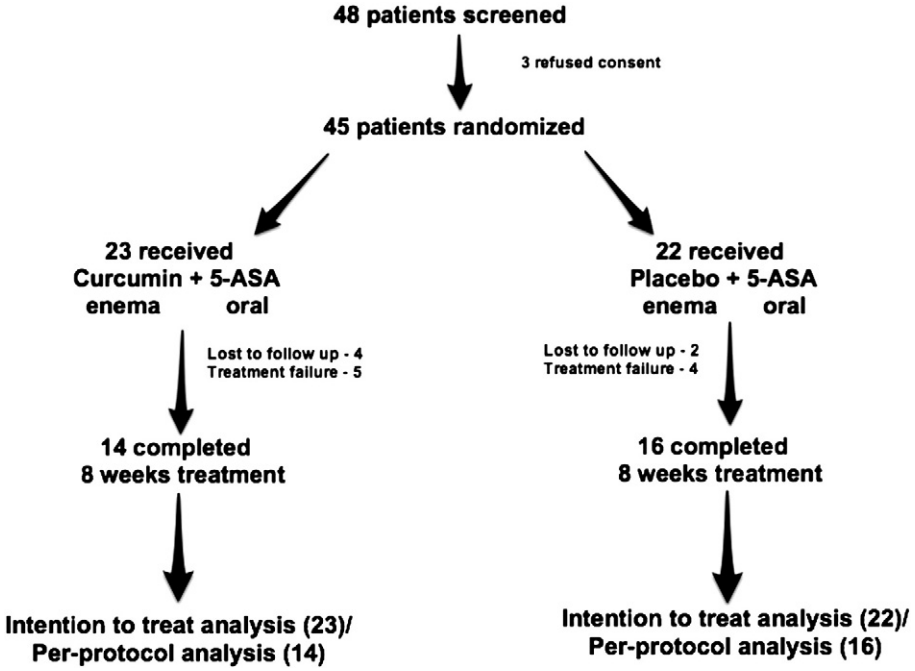


**Figure 1** CONSORT flow chart.

group, p = 0.18), significantly higher proportion of patients had history of steroid usage in the NCB-02 group (12 [52.2%] in NCB-02 group vs. 1 [4.5%] in placebo group, p < 0.001). Also the duration of disease was significantly higher in the NCB-02 group compared to the placebo group (median [interquartile range], 60 [36–96] vs. 33 [12–72], p = 0.046).

### 3.3. Intention to treat analysis (listed in Table 2)

At the end of 8 weeks, the proportion of patients who had response to treatment was higher in the NCB-02 arm, but the difference was not statistically significant (13/23 [56.5%] in NCB-02 group vs. 8/22 [36.4%] in placebo group, p = 0.18). Higher proportion of patients in NCB-02 group were in remission at the end of 8 weeks, but the difference was not statistically significant (10/23 [43.5%] in NCB-02 group vs. 5/22 [22.7%] in placebo group, p = 0.14). Higher number of patients in NCB-02 group achieved improvement in endoscopic disease activity, however the difference was not statistically significant (12/23 [52.2%] in NCB-02 group vs. 8/22 [36.4%] in placebo group, p = 0.29).

### 3.4. Per protocol analysis (listed in Table 2)

Patients who completed 8 weeks of treatment were subjected to per protocol analysis. Significantly higher proportion of patients in NCB-02 group had response to treatment (13/14 [92.9%] in NCB-02 group vs. 8/16 [50%] in placebo group, p = 0.01) and were in remission (10/14 [71.4%] in NCB-02 group vs. 5/16 [31.3%] in placebo group, p = 0.03) after 8 weeks of treatment. Improvement in endoscopic disease activity was also significantly higher among the patients in the NCB-02 group (12/14 [85.7%] in NCB-02 group vs. 8/16 [50%] in placebo group, p = 0.04).

**Table 1** Patient characteristics.

| Variables | | NCB-02 (curcumin) group n = 23 | Placebo group n = 22 | p value |
|---|---|---|---|---|
| Mean age in years — mean ± SD | | 32.7 ± 8.9 | 35.5 ± 13.8 | 0.39 |
| Male sex n (%) | | 12 (52.2) | 11 (50) | 0.88 |
| Extent of disease | Proctosigmoiditis — n (%) | 12 (52.2) | 14 (63.6) | 0.55 |
| | Proctitis — n (%) | 11 (47.8) | 8 (36.4) | |
| Duration of disease in months — median (interquartile range) | | 60 (36–96) | 33 (12–72) | 0.046 |
| Drugs used in past | ASA — n (%) | 18 (78.3%) | 16 (72.7%) | 0.18 |
| | Steroids — n (%) | 12 (52.2%) | 1 (4.5%) | <0.001 |
| | AZA — n (%) | 2 (8.7%) | 1 (4.5%) | |
| Baseline score — mean ± SD | | 6.13 ± 2.13 | 6.09 ± 2.06 | 0.950 |

**Table 2** Results.

| Intention to treat analysis | | | |
|---|---|---|---|
| | NCB-02 (curcumin) group n = 23 | Placebo group n = 22 | p value |
| Response — n (%) | 13 (56.5%) | 8 (36.4%) | 0.18 |
| Remission — n (%) | 10 (43.5%) | 5 (22.7%) | 0.14 |
| Mucosal healing — n (%) | 12 (52.2%) | 8 (36.4%) | 0.29 |
| **Per protocol analysis** | | | |
| | NCB-02 (curcumin) group n = 14 | Placebo group n = 16 | p value |
| Response — n (%) | 13 (92.9%) | 8 (50%) | 0.01 |
| Remission — n (%) | 10 (71.4%) | 5 (31.3) | 0.03 |
| Mucosal healing — n (%) | 12 (85.7%) | 8 (50%) | 0.04 |

### 3.5. Predictors of response

On univariate analysis (shown in Table 3), response to treatment was not associated with sex, extent, randomized group, or previous therapy.

### 3.6. Treatment failure

5 patients in NCB-02 arm and 4 patients in placebo arm had aggravation of disease (p value not significant). Trial medication was stopped and all these patients were treated with oral/topical steroids. Treatment failure in all these 9 patients occurred during the first month of treatment in the trial.

### 3.7. Side effects

No serious side effects were observed in any patient. 5 patients in the NCB-02 group, and 4 patients in the placebo arm had aggravation of symptoms, and the difference was not significant.

## 4. Discussion

This is the first randomized controlled study evaluating the efficacy of NCB-02 (curcumin) enema as a remission inducing agent. We chose the topical preparation of curcumin, as curcumin has high first pass metabolism and hence may not reach the colonocytes in active form. Also GI side effects such as dyspepsia are well known with oral curcumin which may result in poor compliance to the medical therapy.[19] We did not report any GI related side effects, which would ensure better compliance with the topical curcumin.

An important observation in the present study is that curcumin enema is safely tolerated. Though the outcome difference was not statistically significant on intention-to-treat analysis, there was a trend towards better outcomes in the NCB-02 group. If we can hypothetically estimate the power of the study, for an efficacy of 20% power of the study with the sample size of 45 is 0.3. This suggests that for a true difference of 20%, with a sample size of 45, 70% true values will be overlooked. Per protocol analysis revealed statistical significant improvement in both subjective and objective parameters. There could be a few factors contributing to the finding that there is no statistically significant difference in the outcomes in the intention-to-treat analysis — a) the number of patients in the study is small, there is a likely chance that a possible positive outcome after therapy with NCB-02 enema is overlooked in the intention-to-treat analysis, and b) there is a significant proportion of patients (nearly 40% in the NCB-02 arm and 28% in the placebo arm) who had not completed the study period which could have further also contributed to the same.

An interesting observation to note is that more patients in NCB-02 arm had received steroids in the past which had occurred despite the randomization protocol followed. However, the efficacy of NCB-02 enema was found to be equivalent to placebo in the intention-to-treat analysis and better than placebo in the per-protocol analysis.

Curcumin is a major component of turmeric, a spice which is widely used in India and China, and possesses many anti-inflammatory activities. Curcumin was used in animal models of colitis, and was found to be beneficial in prevention as well as treatment of experimental colitis.[8–10] Sugimoto et al. demonstrated that curcumin can suppress colonic inflammation induced by TNBS in a mice model of colitis, and documented the decrease in concentration of NF-κB in colonocytes of treated mice.[8] Recently curcumin was found to be effective in prevention of DSS induced colitis, and the explained mechanism was regulation of oxidant/anti-oxidant balance and modulation of the release of inflammatory cytokines TNF-alpha and nitric oxide (NO).[9,10] Beneficial effects in UC as documented in animal models, are likely due to inhibition of NF-κB in the intestinal cells, a chief co-ordinator of the inflammation in these cells.[11,12] In addition curcumin may act on other inflammatory pathways also.[14,15] Mesalamine is also known to act through NF-κB pathway,[21] the same mechanism targeted by curcumin. Yet in the present study, the combination of curcumin and

**Table 3** Predictors of response to treatment.

| Variables | Responders n = 21 | Non responders n = 24 | p value |
|---|---|---|---|
| NCB-02 (Curcumin) enema vs. placebo — n (%) | 13 (61.9%) | 10 (41.7%) | 0.18 |
| Male Sex — n (%) | 9 (42.9%) | 14 (58.3%) | 0.3 |
| Extent: Proctosigmoiditid/proctitis — n (%) | 12 (57.1%) | 14 (58.3%) | 0.94 |
| Previous treatment with steroids — n (%) | 5 (23.8%) | 8 (33.3%) | 0.48 |
| Previous treatment with oral 5-ASA — n (%) | 16 (76.2%) | 18 (75%) | 0.99 |
| Previous treatment with azathioprine — n (%) | 0 | 3 (12.5%) | 0.09 |

mesalamine had shown trends towards beneficial effect over mesalamine alone which may be either due to synergistic action of curcumin with mesalamine or effect of curcumin on other inflammatory pathways.

Previously Holt et al. reported the beneficial effect in five patients of ulcerative proctitis treated with oral curcumin.[18] Hanai et al. have investigated the efficacy of oral curcumin as maintenance therapy in patients with UC in a randomized, double-blind placebo controlled trial.[19] Curcumin was used orally, in the dosage of 2 g/day for 6 months in this study in which 89 patients were randomized. Though there was a trend towards lower rates of clinical relapse at 6 months and 12 months and there was a trend towards improvement with regards to endoscopic activity, none of these outcomes reached statistical significance. The most common side effects were GI related in this study. The major limitation of this study is the small sample size and thenceforth the limited power of the study. A recent cochrane systematic review of the efficacy of curcumin in UC also reiterated these findings.[22]

Curcumin has been reported to have chemopreventive activity in animal models of colon cancer.[23,24] The chemopreventive activity of curcumin has been suggested to be related to inhibition of cyclo-oxygenase-2 expression. One of the most important clinical issues in the management of patients with long-standing inflammatory bowel disease (IBD) is an increased risk for development of dysplasia and neoplasia. Long term treatment with curcumin may not only improve colitis but also may inhibit the development of colorectal cancer in patients with IBD, which needs to be studied further.

The current therapy for UC is restricted by the limited efficacy and potential side effects of the commonly used therapeutic options. In the present study, we documented the efficacy of curcumin in per-protocol analysis in the patients who were already on standard therapy, which can be a potential and safe therapy for the management of patients with UC. In conclusion, this double blinded, randomized pilot study demonstrated a possible beneficial outcome as shown in per-protocol analysis with curcumin in patients with ulcerative colitis with distal involvement and mild-to-moderate disease activity without any significant side effects. Further work with larger sample size, should be carried out for the evaluation of effect of topical curcumin.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Contributorship statement

Vikas Singla: Data acquisition, data analysis, data interpretation, drafting of the manuscript, and final approval of the manuscript

Venigalla Pratap Mouli: Data interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of manuscript

Sushil Kumar Garg: Data analysis, critical revision of the manuscript for important intellectual content, and final approval of manuscript

Tarun Rai: Data acquisition, and final approval of manuscript

Bikash Narayan Choudhury: Data acquisition, and final approval of manuscript

Prashant Verma: Data acquisition, and final approval of manuscript

Rachana Deb: Data acquisition, and final approval of manuscript

Veena Tiwari: Data acquisition, and final approval of manuscript

Sarika Rohatgi: Data acquisition, and final approval of manuscript

Rajan Dhingra: Data acquisition, and final approval of manuscript

Saurabh Kedia: Data acquisition, and final approval of manuscript

Piyush Kumar Sharma: Data acquisition, and final approval of manuscript

Govind Makharia: Critical revision of the manuscript for important intellectual content, and final approval of manuscript

Vineet Ahuja: Concept and study design, data acquisition, data interpretation, critical revision of the article for important intellectual content, and final approval of the article.

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