Effect of N-acetylcysteine on remission maintenance in patients with ulcerative colitis: A Randomized controlled clinical trial

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Research

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Abstract

Background: The use of antioxidant agents is suggested as a complementary therapy in UC patients for prevention of flares. Considering the potent antioxidant activity of N-acetylcysteine (NAC), in the present study we aimed to assess the effect of this supplement on remission maintenance in patients with ulcerative colitis (UC).

Methods: In the present double-blind randomized controlled clinical trial, 168 volunteer UC patients who were on high dose corticosteroid for flare-up management, were recruited. The patients received 400 mg NAC or placebo twice daily for 16 weeks. Simultaneously, the prednisolone dose was tapered. The patients were followed up six more weeks post-intervention. The primary efficacy of the treatment was remaining in remission. The secondary outcomes were the endoscopic relapse, serum level of hs-CRP, hemoglobin, and fecal calprotectin level.

Results: During 22 weeks follow up, 25 patients experienced relapses, six of them were in the NAC group and 19 of them were in the placebo group. There was a significant difference between the NAC and placebo groups regarding the relapse-free period ($P=0.007$). Compared with the NAC group, significantly more patients in the placebo group had an endoscopic relapse ($p<0.001$). At the end of the intervention period (16 weeks) and 6 weeks post-intervention, the mean fecal calprotectin, serum erythrocyte sedimentation rate, and hs-CRP levels were significantly lower in the NAC group compared with the placebo group ($p<0.05$).

Conclusion: The findings indicated that NAC had a significantly more positive effect on the maintenance of remission compared with placebo in UC patients that were in the steroid-tapering phase of therapy.

Background:

Ulcerative colitis (UC) is a chronic disease characterized by superficial and diffuse inflammation of the colon and rectum [1]. The pattern of disease activity is characterized by periods of active inflammation alternating with periods of remission. Corticosteroids are highly effective in moderately to severely active UC, however, more than 25% of patients will relapse when corticosteroid treatment is discontinued [2]. The goal of UC treatment is to maintain remission for as long as possible while limiting the use of steroids to the minimum required [3].

Different factors including reactive oxygen species (ROS) and pro-inflammatory cytokines have a long-standing implication in both the etiology and the progression of UC [4]. It has been shown that the inflamed mucosa in patients with ulcerative colitis produce ROS. Considering the low antioxidant capacity of colonic mucosa, the imbalance between pro-oxidants and antioxidant capacity may exist [5]. Earlier studies pointed out that some treatment options such as 5-ASA and sulfasalazine have antioxidant and free-radical scavenging action and are associated with a lower number of flares. Thus, treatment with antioxidant agents is suggested as a complementary therapy in UC patients [5].

Accordingly, different antioxidant reagents such as ω -3 fatty acids [6], melatonin [7], and vitamin A [8] are studied for the prevention of relapse in ulcerative colitis. N-acetylcysteine (NAC) is also a potent antioxidant and its effect in the prevention of colonic damage and inflammatory response was studied in a few animal studies and its promising effect in rats has been shown [5, 9-12]. In the only human study, Guijarro et al showed the positive effect of mesalamine plus N-acetylcysteine in reducing disease activity and serum level of IL-8 in patients with mild and moderate ulcerative colitis [13]. However, the effect of NAC in the prevention of relapse in ulcerative colitis patients has not been studied. Considering the pathogenic effect of lipid peroxidation in UC [14] and also the potent antioxidant effect of NAC, we postulated that this supplement may have a positive effect on the prevention of relapse in patients with ulcerative colitis. So, in the present randomized clinical trial, we aimed to assess the effect of supplementation of NAC on remission maintenance in patients with UC.

Methods:

Patients:

In the present two-arm, parallel design, double-blind randomized controlled clinical trial, volunteer ulcerative colitis patients who referred to the inflammatory bowel disease (IBD) clinic of Imam Reza hospital, belongs to the Tabriz University of medical sciences were enrolled. The patients were diagnosed previously based on standard diagnostic criteria including characteristic endoscopic and histological appearances. The patients were included if they aged 18-75 years of age, have pancolitis and treated with a high dose of prednisolone (1 mg/kg), and achieved clinical remission. The pregnant and breastfeeding patients, the patients with heart, renal and pulmonary failure, and the ones who use anti-TNF- α agents were ineligible.

One hundred ninety-eight patients with active ulcerative colitis were treated with prednisolone 1 mg/kg and Mesalamine 4 g/day for four weeks. One hundred seventy-five volunteer patients with clinical responses at the end of week 4 consent to participate in the study. The patients were randomized using a computer-generated randomization chart. The patients in the intervention group (n=82) were supplemented with 400 mg NAC twice daily and the patients in the placebo group (n=86) were received the placebo for 16 weeks. Simultaneously, prednisolone dose was tapered by 5 mg/week to a daily dose of 20 mg/day, then slow the taper to 2.5 mg/week until prednisolone is discontinued (14 weeks).

NAC was purchased from Hexal, Germany. NAC and placebo were labeled as A and B administered by a researcher who was not part of the data collection or analysis. The appearance and characteristics of the NAC and placebo were identical. The patients and the outcome an assessor were blind to group assignment.

Full written consent was obtained from all subjects. The study had the approval of the Tabriz University of medical sciences Ethics Committee (Ethics code: IR.TBZMED.REC.1398.408). This trial was registered at the Iranian registry of clinical trials (irct.ir). Identifier NO. IRCT20190713044185N1.

The sample size was calculated based on the result of a previous study that revealed that the clinical response in the NAC group was higher (66%) than the placebo group (44%). By assuming a two-sided significance level of 1% and power of 80% with equal allocation to the two arms, we needed 80 patients in each arm of the trial. To allow for dropout, 87 patients recruited per arm.

Measurements:

The patients were visited every two weeks during the intervention (16 weeks) and followed up six more weeks post-intervention. In all visits, full blood count, fecal calprotectin, erythrocyte sedimentation rate (ESR), and high sensitive C-reactive protein (hs-CRP) levels were checked. Additionally, the relevant questionnaire for calculation of disease severity using partial mayo score was completed. The combined scores of rectal bleeding (0-3), stool frequency (0-3), and physician's global assessment (0-3) were used for calculation of partial mayo score (0-9). According to partial mayo score, the total score of <2 was considered as remission, 2-5 as a mild activity, 5-7 as moderate activity, and >7 as a severe activity. In addition, at last visit, the endoscopic Mayo score was also calculated by an expert gastroenterologist-endoscopist (0 to 3).

Assessment of compliance was a predefined analysis whereby patients taking >80% of their prescribed study medication were considered compliant. Compliance with study medication was calculated by pill count every two weeks.

Evaluation of the therapeutic efficacy

The primary efficacy of the treatment was remaining in remission. Clinical relapse was defined as exacerbation of symptoms with a partial Mayo score of ≥ 3 , or modification of treatment [dose escalation, the addition of steroids, tacrolimus, topical formulations, or biologics] accompanied by worsening of symptoms. The secondary outcomes were the endoscopic relapse (endoscopic score of >1), serum level of hs-CRP, hemoglobin, and fecal calprotectin level.

Assessment of safety

The hematological and biochemical studies including liver function tests (LFT), blood urea nitrogen (BUN), and creatinine were performed at regular intervals by the analytical laboratory services of the corresponding hospital. Moreover, a treating physician

who was blind to the patients' treatment assignments evaluated the adverse effects including nausea, vomiting, diarrhea, constipation, drowsiness, chest pain, and skin rash.

Statistical analysis:

SPSS version 21 was used for statistical analysis. The normality of data distribution was analyzed using the Kolmogorov-Smirnov test. The continuous data were presented as mean and standard deviations and the categorical data were present as number and frequency. The chi-square test (for nominal variable) and independent t-test (for continuous variable) were used for comparison of the baseline characteristics. One-way analysis of covariance (ANCOVA) was used for comparison of the follow-up characteristics with adjusting for age, sex, disease duration, and baseline values. Time to relapse was analyzed by Kaplan-Meier methodology and measured from the date of the first dose of study medication to the relapse date. Treatment differences were analyzed using a log-rank test. Intention-to-treat (ITT) analysis was done and p-value of less than 0.05 was considered as significant.

Results:

From a total of 168 ulcerative colitis patients who included in the study, two patients in the NAC group and four patients in the placebo group were loss to follow up. The data were reported for 168 patients (86 in the supplementation group and 82 in the placebo group) (Fig. 1).

The mean (standard deviation) age of the participants was 39.33 (12.62) years and 47% of them were male. At baseline, there were no significant differences between the two groups in the case of demographics, disease, and biochemical features (Table 1).

During 22 weeks follow up, 25 patients experienced relapse, 22 during the intervention phase, and three during the post-intervention phase. Six of the relapsed patients were in the intervention group and 19 of them were in the placebo group. As can be seen in figure 2, according to the Kaplan-Meire analysis, the median (95% confidence interval) duration of the relapse-free period was 21.12 (20.44-21.79) weeks in the intervention group and 19.55 (18.56, 20.55) weeks in the placebo group. There was a significant difference between the two groups regarding the relapse-free period ($P=0.007$). All patients in both groups were relapse-free in the first two months of study. However, in the third month (when the prednisolone dose reduced to less than 10 mg/day), 7% of patients in the intervention group and 19% of patients in the placebo group were relapsed. After discontinuation of NAC and steroids, 93% of the patients in the NAC group and 78% of patients in the placebo group were relapse-free.

The secondary outcomes of the study were endoscopic relapse and changes in biochemical parameters. As depicted in figure 3, compared with NAC group, significantly more patients in the placebo group had an endoscopic relapse ($p\text{-value}<0.001$)

There were no significant differences between the two groups regarding the biochemical analysis at baseline. At the end of the intervention period (16 weeks) and 6 weeks post-intervention, the mean fecal calprotectin and serum ESR and hs-CRP levels were significantly lower in the NAC group compared with the placebo group. Moreover, the mean hemoglobin level was significantly higher in the NAC group (table 2).

There were no significant changes in clinical laboratory parameters in either treatment group. Significantly more patients reported nausea in the NAC group (19.51%) compared with the placebo (3.48%) group ($p=0.001$). But no patient left the study due to nausea.

Discussion:

Remission maintenance is an essential issue in managing IBD [15] and different approaches including 5-ASA, steroids, and biological agents are used for this purpose. However, partial effectiveness, high price, and serious side-effects demanded the investigation of new strategies to maintain remission in UC patients. Considering the antioxidant and anti-inflammatory potential of N-acetylcysteine, different animal studies aimed at investigating its effect in ulcerative colitis and showed that NAC

effectively improved the mucosal damage, antioxidant and anti-inflammatory status [5, 9, 10, 12, 13]. To the best of our knowledge, there is only one human study that assessed the effect of NAC in patients with ulcerative colitis [13]. Guijarro et al in a short-term pilot study investigated the effect of 4-week supplementation of NAC with Mesalamine on the induction of remission in UC patients and showed that compared with baseline, the disease activity score and serum level of inflammatory factors were significantly lower in NAC group but not in the placebo group. However, there were no significant differences between the two groups regarding achieving clinical remission [13]. In the present study, for the first time, we investigated the effect of N-acetylcysteine in the prevention of relapse in patients with ulcerative colitis during the tapering phase of corticosteroids. We showed that the median relapse-free duration in the NAC group was significantly longer than the placebo group. Besides, at the end of the supplementation period, 93% of the patients in the NAC group were relapse-free, however, in the placebo group, 81% of patients were relapse-free. In the post-intervention phase, the percent of relapse-free patients was reached to 78% in the placebo group. In addition, we showed the positive effect of NAC on endoscopic remission and fecal calprotectin compared with placebo. Studies indicated that fecal calprotectin is a reliable predictor of mucosal healing in ulcerative colitis patients. So, it could be inferred that the lower level of calprotectin in the NAC group was due to mucosal healing in these patients.

The observed positive effect of NAC in the prevention of relapse in UC patients may be attributed to its antioxidant and anti-inflammatory effects. NAC is a scavenger of ROS [16] and it is a precursor of cysteine [17]. So, it has an important role in glutathione synthesis which is the primary endogenous antioxidant [18]. Considering that the higher level of oxidative stress in UC patients indicates the disease activation, NAC with its antioxidant activity could have beneficial effects in preventing relapse in UC patients. Besides, it has been shown that the antioxidant activity of NAC could also induce anti-inflammatory properties. NAC could inhibit the activation of NF- κ B [19-21]. NF- κ B is activated in response to oxidative stress [22, 23], and induces transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, MMPs, Cox-2, and inducible nitric oxide. These pro-inflammatory factors, in turn, will affect the epithelial cells and promote a leaky barrier. So, NAC through its antioxidant properties could prevent activation of NF- κ B and inflammatory responses [24]. Previous animal studies showed the anti-inflammatory effect of NAC in murine models of colitis. [5, 12, 25]. In the present study, we also showed the positive effect of NAC on hs-CRP, the marker of systemic inflammation. Studies showed the association between serum hs-CRP and disease severity in ulcerative colitis patients [26]. However, in a previous study in ulcerative colitis patients, there were no significant differences between NAC and placebo groups regarding the hs-CRP level [13]. The observed differences between the result of the present study and a previous human study may be due to the differences in the treatment pattern (mesalamin+NAC Vs. steroid+NAC), duration of treatment with NAC (four weeks vs. 16 weeks) and the severity of symptoms.

The findings of the present study should be interpreted considering the limitations of the study. We did not evaluate the histopathological remission. We also did not assess the degree of mucosal healing by endoscopy before randomization, but we assessed the fecal calprotectin level that was a reliable indicator of disease activity in UC patients. Besides, the follow-up of patients after discontinuation of NAC was relatively short (6 weeks), so, no firm conclusion about the relapse-free time after discontinuation of NAC should be made.

Conclusion:

In conclusion, to the best of our knowledge, this is the first study that assessed the effect of NAC on the maintenance of remission in ulcerative colitis patients. The findings indicated that NAC in combination with a standardized steroid taper had a significantly more positive effect on the maintenance of remission compared with placebo in UC patients. However, due to the short duration of follow-up for assessing steroid-free response, more studies with longer duration of follow up are needed.

Declarations:

Ethics approval and consent to participate: This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.REC.1398.408). Written informed consent was obtained from all participants

Consent for publication: None required.

Availability of data and materials: The datasets supporting the conclusions of this research are included within the article.

Competing interests: the authors declare no conflict of interest

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References:

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F: **Ulcerative colitis.***The Lancet* 2017, **389**:1756-1770.
2. Truelove SC, Witts L: **Cortisone in ulcerative colitis.***Br Med J* 1955, **2**:1041.
3. Okayasu M, Ogata H, Yoshiyama Y: **Use of corticosteroids for remission induction therapy in patients with new-onset ulcerative colitis in real-world settings.***J Mark Access Health Policy* 2019, **7**:1565889.
4. Seril DN, Liao J, Yang G-Y, Yang CS: **Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models.***Carcinogenesis* 2003, **24**:353-362.
5. Nosál'ová V, Černá S, Bauer V: **Effect of N-acetylcysteine on colitis induced by acetic acid in rats.***General Pharmacology: The Vascular System* 2000, **35**:77-81.
6. Barbosa DS, Cecchini R, El Kadri MZ, Rodríguez MAM, Burini RC, Dichi I: **Decreased oxidative stress in patients with ulcerative colitis supplemented with fish oil ω -3 fatty acids.***Nutrition* 2003, **19**:837-842.
7. Chojnacki C, Wisniewska-Jarosinska M, Walecka-Kapica E, Klupinska G, Jaworek J, Chojnacki J: **Evaluation of melatonin effectiveness in the adjuvant treatment of ulcerative colitis.***J Physiol Pharmacol* 2011, **62**:327.
8. Shirazi KM, Nikniaz Z, Shirazi AM, Rohani M: **Vitamin A supplementation decreases disease activity index in patients with ulcerative colitis: A randomized controlled clinical trial.***Complement Ther Med* 2018, **41**:215-219.
9. Tohoku Journal of Experimental MedicineAkgun E, Caliskan C, Celik H, Ozutemiz A, Tuncyurek M, Aydin H: **Effects of N-acetylcysteine treatment on oxidative stress in acetic acid-induced experimental colitis in rats.***J Int Med Res* 2005, **33**:196-206.
10. Amrouche-Mekkioui I, Djerdjouri B: **N-acetylcysteine improves redox status, mitochondrial dysfunction, mucin-depleted crypts and epithelial hyperplasia in dextran sulfate sodium-induced oxidative colitis in mice.***Eur J Pharmacol* 2012, **691**:209-217.
11. Siddiqui A, Ancha H, Tedesco D, Lightfoot S, Stewart CA, Harty RF: **Antioxidant therapy with N-acetylcysteine plus mesalamine accelerates mucosal healing in a rodent model of colitis.***Dig Dis Sci* 2006, **51**:698-705.
12. You Y, Fu J-J, Meng J, Huang G-D, Liu Y-H: **Effect of N-acetylcysteine on the murine model of colitis induced by dextran sodium sulfate through up-regulating PON1 activity.***Dig Dis Sci* 2009, **54**:1643-1650.
13. Guijarro LG, Mate J, Gisbert JP, Perez-Calle JL, Marin-Jimenez I, Arriaza E, Olleros T, Delgado M, Castillejo MS, Prieto-Merino D, et al: **N-acetyl-L-cysteine combined with mesalamine in the treatment of ulcerative colitis: randomized, placebo-controlled pilot study.***World J Gastroenterol* 2008, **14**:2851-2857.
14. Balmus IM, Ciobica A, Trifan A, Stanciu C: **The implications of oxidative stress and antioxidant therapies in inflammatory bowel disease: clinical aspects and animal models.***Saudi J Gastroenterol* 2016, **22**:3.

15. Kamat N, Kedia S, Ghoshal UC, Nehra A, Makharia G, Sood A, Midha V, Gupta V, Choudhuri G, Ahuja V: **Effectiveness and safety of adalimumab biosimilar in inflammatory bowel disease: a multicenter study.***Indian J Gastroenterol* 2019, **38**:44-54.
16. Buanne P, Di Carlo E, Caputi L, Brandolini L, Mosca M, Cattani F, Pellegrini L, Biordi L, Coletti G, Sorrentino C: **Crucial pathophysiological role of CXCR2 in experimental ulcerative colitis in mice.***J Leukoc Biol* 2007, **82**:1239-1246.
17. Dilger RN, Baker D: **Oral N-acetyl-L-cysteine is a safe and effective precursor of cysteine.***J Anim Sci* 2007, **85**:1712-1718.
18. Cetinkaya A, Bulbuloglu E, Kurutas EB, Ciralik H, Kantarceken B, Buyukbese MA: **Beneficial effects of N-acetylcysteine on acetic acid-induced colitis in rats.***Tohoku J Exp Med* 2005, **206**:131-139.
19. Kim H, Seo JY, Roh KH, Lim JW, Kim KH: **Suppression of NF-κB activation and cytokine production by N-acetylcysteine in pancreatic acinar cells.***Free Radic Biol Med* 2000, **29**:674-683.
20. Verhasselt V, Berghe WV, Vanderheyde N, Willems F, Haegeman G, Goldman M: **N-acetyl-L-cysteine inhibits primary human T cell responses at the dendritic cell level: association with NF-κB inhibition.***J Immunol* 1999, **162**:2569-2574.
21. Zhang Z, Xiong T, Zheng R, Huang J, Guo L: **N-acetyl cysteine protects HUVECs against lipopolysaccharide-mediated inflammatory reaction by blocking the NF-κB signaling pathway.***Mol Med Rep* 2019, **20**:4349-4357.
22. Anrather J, Racchumi G, Iadecola C: **NF-κB regulates phagocytic NADPH oxidase by inducing the expression of gp91phox.***J Biol Chem* 2006, **281**:5657-5667.
23. Moreno MaU, San José G, Orbe J, Páramo JA, Beloqui O, Díez J, Zalba G: **Preliminary characterisation of the promoter of the human p22phox gene: identification of a new polymorphism associated with hypertension.***FEBS Lett* 2003, **542**:27-31.
24. Pinkus R, Bergelson S, Daniel V: **Phenobarbital induction of AP-1 binding activity mediates activation of glutathione S-transferase and quinone reductase gene expression.***Biochem J* 1993, **290**:637-640.
25. Ancha HR, Kurella RR, McKimmey CC, Lightfoot S, Harty RF: **Effects of N-acetylcysteine plus mesalamine on prostaglandin synthesis and nitric oxide generation in TNBS-induced colitis in rats.***Dig Dis Sci* 2009, **54**:758-766.
26. Chang S, Malter L, Hudesman D: **Disease monitoring in inflammatory bowel disease.***World J Gastroenterol* 2015, **21**:11246.

Tables

Table 1: Baseline characteristics of ulcerative colitis patients

Variables	NAC group (n=82)	Placebo group (n=86)	p-value *
Age (years)	38.84±12.42	39.79±12.87	0.62
Sex n (%) male/female	42 (51.22)/40 (48.78)	37 (43)/49 (57)	0.28
Disease duration (months)	35.23±20.46	38.82±66.79	0.64
Calprotectin (µg/g)	33.45±16.09	33.78±15.74	0.89
ESR (mm/hr)	28.04±8.72	28.26±9.50	0.87
hs-CRP (mg/l)	1.13±0.90	1.23±1.01	0.48
Partial Mayo score	3.57±1.17	3.43±1.13	0.42
Hemoglobin (g/100ml)	12.01±1.49	12.03±1.55	0.92

NAC: N-acetylcysteine; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitive-C reactive protein; *independent t-test

Table 2: Effect of interventions on clinical characteristics in ulcerative colitis patients

Variable	Groups	Beginning	First month	Second month	Third month	Fourth month	Six weeks post-intervention
Calprotectin (µg/g)	NAC (n=82)	33.45±16.09	37.89±13.86	32.50±14.61	68.83±16.12	66.71±16.65	72.71±18.51
	Placebo (n=86)	33.78±15.74	37.56±13.47	33.64±15.54	138.28±24.41	167.91±27.80	171.42±28.56
	p-value *	0.89	0.87	0.62	0.01	0.002	0.005
ESR (mm/hr)	NAC (n=82)	28.04±8.72	29.01±10.06	27.17±9.45	30.88±13.42	28.36±13.39	30.23±1.57
	Placebo (n=86)	28.26±9.50	28.93±9.33	27.57±10.15	34.71±19.92	36.98±21.71	39.34±2.29
	p-value *	0.87	0.95	0.79	0.14	0.003	0.001
hs-CRP (mg/l)	NAC (n=82)	1.13±0.90	1.27±1.08	0.99±0.11	1.46±1.51	1.13±1.37	1.34±0.16
	Placebo (n=86)	1.23±1.01	1.26±1.12	1.08±0.12	1.75±1.93	1.69±2.12	2.22±0.22
	p-value *	0.48	0.94	0.58	0.28	0.04	0.002
Partial Mayo score	NAC (n=82)	3.57±1.17	2.87±0.97	2.83±1.10	2.90±1.81	2.82±1.74	2.80±0.25
	Placebo (n=86)	3.43±1.13	2.84±0.98	3.03±1.21	3.71±2.61	4.14±2.84	4.09±0.31
	p-value *	0.42	0.85	0.25	0.02	<0.001	0.007
Hemoglobin (g/100ml)	NAC (n=82)	12.01±1.49	12.73±1.15	13.58±0.77	13.87±0.76	14.11±0.83	14.37±0.84
	Placebo (n=86)	12.03±1.55	12.55±1.39	13.50±0.94	13.56±1.07	13.73±1.32	13.79±0.46
	p-value *	0.92	0.37	0.54	0.03	0.009	0.002

NAC: N-acetylcysteine; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitive-C reactive protein; *ANCOVA: between group comparison adjusted for age, sex and baseline values

Figures

Figure 1

the frequency of endoscopic relapse in NAC and placebo groups

Figure 2

Time of disease relapse for patients randomized to NAC (N-acetylcysteine) or placebo groups.

Figure 3

Flow chart for patient enrollment, randomization, and retention ITT: intention-to-treat