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Effects of oral N-acetyl cysteine on pain and plasma biochemical parameters in fibrocystic breast disorder: A randomized controlled trial

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ABSTRACT

Background: Fibrocystic change is the most common benign lesion in breasts of a woman in her reproductive age. It is an outcome of estrogen excess due to sex hormone imbalance. Cyclical pain as the most common symptom worsens life quality, compels patient to seek health care support continuously, and imposes large amounts of expense to both patient and health system. Current study aims to evaluate effects of N-acetyl cysteine on decreasing pain and changes in plasma biochemistry.

Method: A total of 64 eligible women participated in this double-blinded randomized controlled trial. They were between 18 and 40 years. Participants were randomly allocated into oral N-acetyl cysteine and placebo receivers. Intervention and follow-up lasted for, respectively, a 12-week drugs-on and 12-month drugs-off period. Visual analog scaling was applied to measure severity of pain. Peripheral venous plasma was extracted and compared for inflammatory parameters including high-sensitivity C-reactive protein, total antioxidant capacity, malondialdehyde, total plasma glutathione, lipid profile, and fasting blood sugar.

Results: Oral N-acetyl cysteine significantly decreased feeling of cyclical mastalgia ($P < .01$) after 12 weeks of consumption. In addition to lowering of plasma level of high-sensitivity C-reactive protein ($P = .008$), total plasma glutathione significantly increased ($P = .02$) among N-acetyl cysteine receivers. No change in lipid profile and insulin sensitivity was seen.

Conclusion: N-Acetyl cysteine could mitigate cyclical mastalgia. Inflammation as a considered reason for cyclical mastalgia also was halted by N-acetyl cysteine consumption.

INTRODUCTION

Fibrocystic change (FCC) is the most common lesion of breast and manifests usually with pain. Although most etiologies for FCC are benign, some studies have reported malignancies similar to the FCC. Therefore, comprehensive workup for such lesion is mandated in selected patients [1,2]. FCC is limited to the female gender and specifically seen in reproductive ages. According to presented epidemiologic reports, the incidence of FCC is globally high, predominant in the third decade of life, and differs from 20% to 57% [3,4]. Cyclical mastalgia lowers quality of life by mitigating patient's function in sexual, physical, social, occupational, and educational activities [1,5]. Additionally, progressive doubt and fear for breast cancer gradually develop into psychiatric disorders [6]. Pathologically, excessive estrogen and imbalance in estrogen to progesterone ratio following sex hormone releasing cycles are paramount points for FCC development. Diagnosis of FCC is confirmed by history taking, physical examination, and breast imaging [7]. Benign characteristic in physical examination including palpable, nontender, mobile, and round-shaped lesion is highly suggestive for FCC, although evidence of firmness, pain, and tenderness does not absolutely exclude FCC [8]. Ultrasound study in FCC shows an oval well-defined mass with microlobulated borders and posterior acoustic enhancement [6,8]. However, if any doubt remains for presence of malignancy, then taking biopsy for following histopathologic study is absolutely indicated [6,8]. Whenever FCC diagnosis is established, the treatment of choice is breast lumpectomy, although it is not primarily selected in clinics. Regarding benign nature of FCC in association with

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its slow growth, close observation of the lesion beside therapy of symptoms is considered as the first line of treatment. To date, various herbal and synthetic medications like evening primrose oil; vitagnus; vitamins including D, E, and B; probiotics; metformin; and antioxidant agents have been introduced for prevention of symptoms in FCC, although there is no general consensus on any [1,6,9–12].

N-acetyl cysteine (NAC), a mucolytic antioxidant, acts through the opening of disulfide bonds and is primarily exerted in urine. It is located in B category for pregnant women, which means that it may be acceptable to use if needed. Previous reviews on NAC have manifested that consumption of NAC is associated with decrease in plasma levels of tumor necrosis factor alpha (TNF-α), lipid peroxidation derivatives, malondialdehyde (MDA), interleukin 6, high-sensitivity C-reactive protein (hs-CRP), insulin resistance, fasting blood sugar, low-density lipid cholesterol (LDL-chol), and liver enzymes [13–19].

Cyclical mastalgia is a monthly painful period disturbing patient's quality of life and can cause deep stress disorders if it remains untreated. Feeling painful attacks periodically, seeking health care support continuously, performing serial paraclinic studies, paying large amounts of time and expense, and sense of being diseased would alter patient's psychiatric stability and compel her to experience inappropriate analgesics or unapproved drugs. Therefore, identifying suitable medication with sufficient potency to control such pain could be interesting and helpful to recover patients. Based on previous studies that have demonstrated NAC could act as sulfhydryl group donor, restore glutathione, scavenge free radical, and also regulate production of sex hormones including estrogen and progesterone, we hypothesized that NAC could positively change oxidative stress reactions leading to inflammation and following FCC formation [8–12]. According to this hypothesis, this study aims to investigate possible effects of NAC on pain and biochemical parameters related to FCC.

MATERIALS AND METHOD

After ethical committee approved study design by reference code IR.KAUMS.MEDNT.REC.1398.124, study was registered in the national research center with registration number IRCT20170513033941N69, which is available at www.irct.ir. This double-blinded controlled trial recruited women with cyclical mastalgia who referred to our clinic from summer 2019 to spring of 2020. Eighteen- to 40-year-old women who met inclusion criteria were enrolled. Participation criteria included feeling moderate to severe cyclical mastalgia in the recent 6 months due to confirmed FCC, absence of concurrent or history of malignancy, and negative history of using any synthetic or herbal medication to suppress pain. Pregnancy, breastfeeding, fever, history of chronic inflammatory or infectious disease, history of previous breast or thoracic surgery, taking concurrent antibiotics, supplement (vitamins or minerals), hormonal (oral contraceptives, tamoxifen, danazol, bromocriptine or etc) or anti-inflammatory (steroids or NSAIDs) medications, and any suspicion of breast cancer were exclusion criteria. Written consent form was obtained from all entrants following verbal explanation of all study steps. Participants promised to take study drugs regularly and make no other innovation in their lifestyle.

Based on data of another similar study [17], first ($\alpha = 0.05$) and second errors ($\beta = 0.2$) were calculated. Regarding 80% power of test in addition to possible 10% flush, 74 participants were needed. Figure 1 shows flow diagram of the study. In clinic, a surgical intern gave a number to each eligible patient for allocation at first visit. Subjects were allocated to 2 groups through a stratified 4-block randomization based on body mass index (BMI) and age: NAC and placebo receivers, with 37 members in each group. Both authors and participants were unaware of group allocation. A surgical resident selected blocks for group allocation and gave members appropriate medications. According to data of previous study [14], we also intervened for a total period of 12 weeks.

Diagnosis of FCC was confirmed for all by physical examination and imaging studies. Demographic data including of age, weight, height, and BMI were all recorded at first and last visit (after 12 weeks), respectively. Visual Analog Scale (VAS) instrument was applied to score severity of pain. Participant selected a number between 0 and 10 on her first day of menstruation cycle. Scores 1–3, 4–6, and 7–10, respectively, were interpreted as mild, moderate, and severe pain [6].

Plasma biochemical changes were followed by studying 10 mL of peripheral venous blood sample prior and after all medications were used.

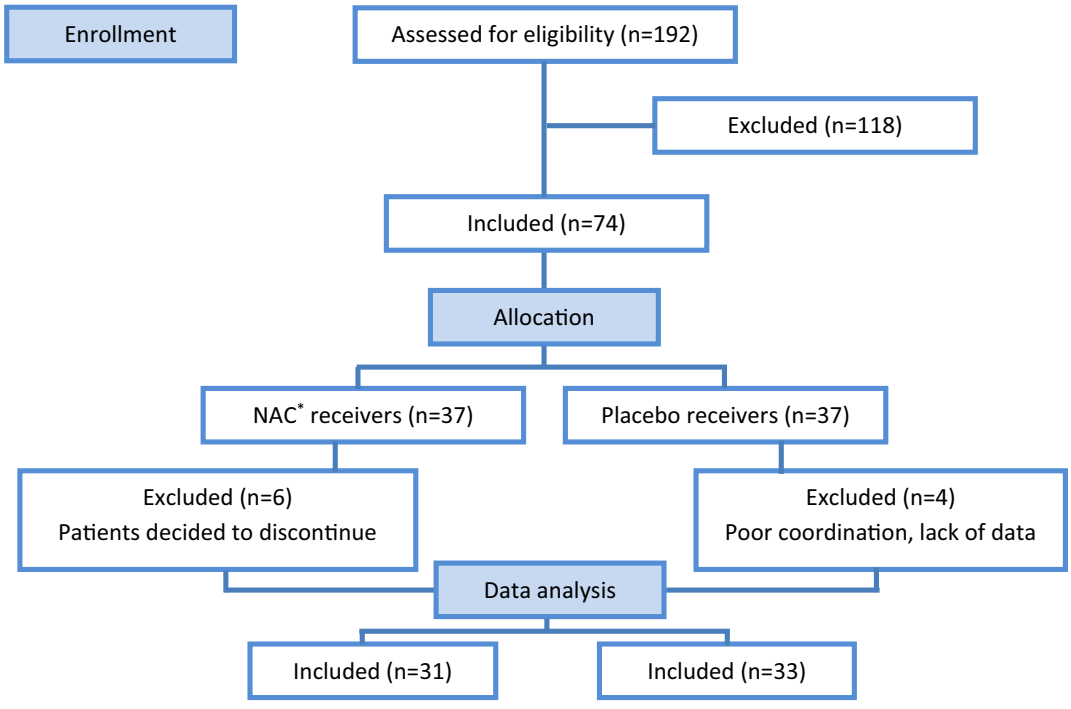

Fig 1. Flowchart of the study *N-acetyl cysteine.

Blood aspiration was performed in the morning of the once middle 3 days of menstruation cycle following 12 hours of overnight fasting. All blood-filled tubes were centrifuged at 2,000 cycles for 5 minutes and stored at −80 °C. Biochemical parameters including TAC (mmol/L), MDA (μmol/L), and total plasma glutathione (TPG) (μmol/L) were evaluated by ELISA method (Crystal day lab kit, China). High-sensitivity CRP (ng/mL) was measured through the latex-enhanced technique (Crystal day lab kit, China). Fasting blood sugar (FBS) and lipid panel including triglyceride (TG) and high- (HDL) and low-density lipoprotein (LDL) were measured via spectrophotometry (mmol/L) (Crystal day lab kit, China).

At first visit, 84 tablets were given to every patient for daily consumption of a tablet in next 12 weeks. In NAC group, each tablet contained 600 mg N-acetyl cysteine (Osvah Pharmaceutical Co., Iran). Placebo tablets contained starch; were made by the same company; and were fully identical in size, shape, and color to virtual NAC drug. Follow-up visit was done at the end of the study, after 12 weeks, and any complication of drug or placebo consumption was recorded. We have also planned to review patients' clinical condition after a 6- and 12-month drugs-off period following the study, which was completed by a direct visit or using other connections.

Statistical data analysis was calculated by the SPSS version 21 computer software. The Kolmogorov–Smirnov test was used to define the normality of the data. Nonparametric data were introduced by numbers and percent. The independent *t* test and the ANOVA were applied to compare means. Difference between parametric variables was calculated by χ^2 or Fisher exact examinations. This report was finally collected in compatible with the CONSORT criteria [20].

RESULTS

Data of a total of 64 eligible women between 18 and 40 years of age finally underwent analysis. Of all, 31 patients remained in intervention group and the rest (33) were placebo receivers. At the end of the study, nearly 90% of all prepared tablets were eaten that showed a good coordination. There was no difference between groups for demographic and anthropometric variables. Table 1 illustrates findings of the latter.

Feeling of pain after 12 weeks of daily NAC tablet consumption obviously is mitigated ($P < .001$). Neither NAC nor placebo has impact on weight ($P = .1$) or BMI ($P = .4$). Measurements of biochemical parameters are shown in Table 2.

Table 2 implies that NAC can decrease the level of hs-CRP ($P = .008$) concurrent to increasing TPG ($P = .02$) and HDL cholesterol ($P = .02$). However, it has no influence on other biochemical indexes including MDA, TAC, TC, TG, LDL, and FBS. Namely, there is no obvious delivery from insulin resistance, hypertriglyceridemia, and LDL hypercholesterolemia following NAC consumption. Follow-up findings in the 6- and 12-month drugs-off period after the study was completed showed remaining of significant difference between groups of the study regarding the relief from cyclical mastalgia symptoms ($P < .01$). However, numbers of respondents were not favorable. From 31 and 33 members of NAC and placebo receivers, 14 (45.2%) and 12 (36.4%), respectively, were visited or responded to our calls ($P = .2$). Twelve (85.7%) and 9 (64.3%) of NAC receivers, respectively, remained satisfied after a 6- and 12-month drugs-off period ($P = .08$). In contrast, we found 5 (41.7%) and 2 (16.7%) of placebo receivers, respectively, free of cyclical mastalgia after a 6- and 12-month drugs-off period ($P = .4$). Therefore, analysis showed NAC could place patients in a painless margin for at least 12 months after drug cessation. There was also no remarkable side effect to report.

Table 1
Demographic and anthropometric data of study participants.

Variable	*Unit*	*Study week*	*NAC receivers (n = 31)*	*Placebo receivers (n = 33)*	P *value*
Age	y	1	29.7 ± 6.2*	31.9 ± 5.6	.1
Height	cm		158.4 ± 10.0	162.4 ± 8.5	.09
Weight	kg	1	73.6 ± 13.6	78.3 ± 10.9	.1
		12	73.8 ± 13.8	78.6 ± 10.6	
BMI	kg/m^2	1	29.1 ± 1.3	29.7 ± 3.5	.4
		12	29.2 ± 3.3	29.8 ± 3.5	
Feeling pain	VAS	1	5.6 ± 1.5	5.7 ± 1.5	<.001
	score	12	2.9 ± 1.7	5.7 ± 1.8	

*Mean ± SD.

DISCUSSION

Cyclical mastalgia is the commonest disturbing symptom of FCC. Despite broad variety of introduced medications to control symptoms of FCC, results have not been satisfying. There are many examples for statement about synthetic and herbal medications like evening primrose oil, vitagnus, vitamins, and metformin, although there is no general consensus on any. Based on our knowledge, there was no identical study in the literature with similar purpose and it was the first in this regard. Current study measured possible impacts of NAC on reducing mastalgia due to FCC. Final outcomes implied that pain reduces after using 600 mg oral NAC tablet for at least a 12-week period. Pharmacologically, NAC impacts both the production and release of progesterone from ovarian granulosa cells [21]. The latter may be considered to confront estrogen excess and rebalance estrogen to progesterone ratio, which finally ends in preventing FCC formation.

NAC also mitigates inflammation and regulates hs-CRP, TPG, and HDL cholesterol, although it has no influence on other biochemical parameters like MDA, TAC, TC, TG, LDL, and FBS. Namely, NAC could not recover dyslipidemia and insulin resistance in case of sex hormone imbalance.

In 2009, an American double-blinded crossover study with 24 subjects revealed that daily consumption of 1800 mg NAC decreases plasma level of hs-CRP after 4 weeks. Other advocates showed similar finding among cirrhotic patients after injecting intravenous NAC in 2017 [15,17]. Other pilot studies with total of nearly 60 patients in 2020 claimed that using 600–1200 mg of NAC among patients with metabolic syndrome or dependent on regular hemodialysis can result in reduction of both lipid peroxidation derivatives and inflammatory biomarkers like hs-CRP [16,19]. Biochemical studies revealed that NAC prevents inflammation by inhibiting the expression of NF-kappa B gene in cell nucleus [22,23].

Current study showed NAC increases plasma level of HDL-cholesterol with no further effect on other lipid profile including LDL-cholesterol, TG, and TC. We again found no supporting evidence for using NAC and breaking insulin resistance. A pilot article in 2020 manifested among 35 patients that there is a direct contribution between using 1200 mg of NAC and decrease in FBS, TG, LDL-cholesterol, and insulin resistance and increase in HDL-cholesterol concurrently [19]. Another randomized controlled trial with 60 subjects showed that daily use of 1200 mg NAC in patients with nonalcoholic hepatic steatosis is associated with positive changes in plasma level of HDL-cholesterol, FBS, and also insulin sensitivity [17]. In contrast, some authors revealed consumption of 1,800 mg daily NAC breaks insulin resistance even more effectively than metformin in patients with polycystic ovary syndrome. Further, they did not report increase in in HDL-cholesterol following NAC consumption [14,18]. The possible reason for improvement of lipid profile and insulin sensitivity was introduced previously based on the fact that the NAC increases expression of PPAR-γ gene and production of cell surface glucose transferase-4 will be heightened followingly [24,25]. Differences between results may be due to different methodology, NAC dosage and length of consumption, sample characteristics, and reason for NAC prescription.

Overall, it seems NAC improves painful breasts, although it is not potent enough to prevent basic pathologic reason of FCC. Therefore, more histopathologic studies are recommended to identify local interactions

Table 2
Laboratory results of measuring biochemical parameters of all study subjects

Parameter	*Unit*	*NAC receivers (n = 31)*		*Placebo receivers (n = 33)*		P *value*
Time (wk)		*1*	*12*	*1*	*12*	
hs-CRP	ng/mL	5.2 ± 2.8*	3.2 ± 2.1	4.0 ± 2.6	4.3 ± 3.4	.008
MDA	μmol/L	2.9 ± 0.4	2.9 ± 0.3	3.2 ± 0.7	3.1 ± 0.7	.9
TPG	μmol/L	516.7 ± 113.0	607.9 ± 138.9	606.3 ± 169.1	587.1 ± 159.7	.02
TAC	mmol/L	658.3 ± 119.4	739.1 ± 90.8	712.2 ± 165.4	703.5 ± 214.2	.09
TC	mmol/L	161.0 ± 34.3	166.7 ± 31.2	150.4 ± 30.0	155.2 ± 28.3	.3
TG	mmol/L	172.1 ± 37.1	158.9 ± 29.1	142.5 ± 35.6	166.6 ± 40.8	.1
LDL	mmol/L	84.9 ± 37.0	88.7 ± 35.1	80.1 ± 30.1	79.0 ± 26.2	.2
HDL	mmol/L	41.1 ± 7.7	45.1 ± 8.1	41.7 ± 5.3	42.8 ± 6.3	.02
FBS	mmol/L	98.1 ± 13.2	98.6 ± 11.6	96.51 ± 11.1	98.1 ± 11.9	.8

*Mean ± SD.
TC, total cholesterol.

between cells, hormones, and drugs to discover specific characteristics of the disorder more exactly. Finally, having the knowledge that the NAC can relatively recover patients from pain in FCC helps following studies to focus on more details and also makes comparison of medication available in future meta-analysis.

Limitation

The small number of enrolled patients, relative short intervention time, lack of image-based evaluation of breast lesions at the end of the study, no measurement of progesterone and estrogen during the survey, data extraction from a single health center, and lack of similar study with identical topic which deprived us to have direct comparison are the limiting points of the current article.

In conclusion, N-acetyl cysteine even after a relatively short time of consumption could improve painful breasts in FCC. Additionally, it could regulate some associated inflammatory parameters. NAC had no positive impact on improvement of lipid profile or breaking insulin resistance when diagnosis of the FCC is in the background.

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Author Contribution

EAK: study design, supervision, interpretation of results; SS: study design, supervision, interpretation of results; AAS: study design, data collection, data analysis, interpretation of results; GAM: statistical advisement; NM: study design, supervision, interpretation of results; MM: study design, supervision, interpretation of results; AH: interpretation of results, drafting of the article.

Conflict of Interest

The authors declare that they have no competing interests.

Funding Source

This study was conducted under order and supervision of Kashan University of Medical Sciences and all advantages referred back to this university.

Ethics Approval and Consent to Participate

This study was performed under supervision of University of Medical Sciences, and the ethics committee has approved study design by registering code IR.KAUMS.MEDNT.REC.1398.124.

Provenance and Peer Review

Not commissioned, externally peer reviewed.

Consent for Publication

All patients signed written consent form for participation in this study.

Availability of Data and Material

The data used to support findings of this study are available in the medical file archive unit of Beheshti Hospital, Kashan, Iran.

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