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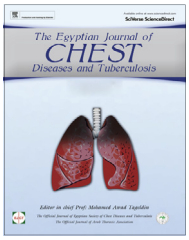

ORIGINAL ARTICLE

High dose N-acetyl cysteine improves inflammatory response and outcome in patients with COPD exacerbations

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KEYWORDS

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Abstract *Introduction:* COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to overall severity in individual patients. Oxidative stress represents one of the key pathogenic mechanisms in the development of COPD. MDA increased production of interleukin (IL)-8 and tumor necrosis factor-a (TNF-a), both attract inflammatory cells and increase oxidant production by these cells. Attenuation of oxidative stress would be expected to result in reduced pulmonary damage and a decrease in local infections, contributing to attenuation of the progression of COPD.

Aim of the study: To compare the effects of high dose NAC versus regular dose on inflammatory response, oxidative stress, pulmonary functions and clinical outcome in patients with COPD acute exacerbations.

Patients and methods: This randomized controlled study included 45 COPD acute exacerbation patients. All patients received standard COPD exacerbation treatment and were randomly assigned to either; control group (A) with no add on therapy, low dose group (B) received NAC 200 mg sachets TID, high dose group (C) received NAC 400 mg sachets TID for 10 days. IL8, malondialdehyde (MDA), arterial blood gases and spirometric parameters were evaluated at baseline and after treatment.

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Results: IL8 levels significantly decreased ($p < 0.001$) in group C (3.47 ± 0.81), versus Group B (5.57 ± 1.66) and group A (8.33 ± 1.69). MDA levels significantly decreased ($p < 0.001$) in group C and group B over time. Pulmonary functions (FEV_1, FVC and FEV_1/FVC) and partial pressure of oxygen PaO_2 significantly improved ($p < 0.001$) in group C versus group B and A over time. The P/F ratio significantly improved ($p < 0.001$) in group C versus group A. No side effects were reported with NAC administration.

Conclusion: High dose NAC improves clinical outcome of COPD exacerbation patients by ameliorating oxidative stress and inflammatory response thereby improving lung spirometry and pulmonary oxygenation.

Introduction

COPD is defined as a common preventable and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1].

An acute exacerbation of COPD is a sustained worsening of a patient's condition, from stable state and beyond normal day-to-day variations, that is acute in the onset and necessitates a change in regular medication [2]. Reduction of exacerbation rates is one of the main treatment goals in COPD [1].

COPD exacerbations are considered to reflect worsening of the underlying chronic inflammation in the airways [3]. Exacerbations and co-morbidities contribute to the overall severity in individual patients [4] this severity is correlated with a decrease in (FEV_1) the most widely used marker of disease severity and progression [5].

Oxidative stress, defined as an imbalance between increased exposure to oxidant and/or decreased antioxidant capacity, represents one of the key pathogenic mechanisms in the development of COPD [6]. COPD patients have shown decreased antioxidant and increased lipid peroxidation products in the sputum and exhaled breath condensate of patients with COPD reflected in increased MDA levels which is a sensitive marker of lipid peroxidation. Markers of oxidative stress are increased even further during exacerbations of COPD, and in patients with a very severe form of this disease [7]. Lipid peroxidation products measured as malondialdehyde (MDA) content correlated inversely with the degree of small airway obstruction [8].

Kluchova et al. reported that MDA levels were significantly higher in patients with severe compared to patients with moderate COPD and there was a significant inverse relationship between FEV_1 and plasma MDA levels which indicate that MDA is a good marker of severity of obstructive lung impairment in patients with COPD [9].

Oxidative stress is closely linked to inflammation. Increased production of interleukin (IL)-8 and tumor necrosis factor-a (TNF-a), both attract inflammatory cells and increase oxidant production by these cells. Attenuation of oxidative stress would be expected to result in reduced pulmonary damage and a decrease in local infections, contributing to attenuation of the progression of COPD [10].

NAC is a thiol reducing agents, it has a mucolytic properties that degrade the three-dimensional network which forms the mucus by reducing the disulfide bonds (S–S) to a sulfhydryl (SH) bond (–SH) that no longer participates in the cross-linking [11]. They may act on the mucus elasticity and viscosity as well as modulate its production and secretion facilitating the removal of pulmonary secretions [12]. Moreover, by maintaining the airway clearance, it prevents bacterial stimulation of mucin production and hence mucus hyper-secretion [11].

Oral NAC administration results in increased plasma cysteine levels, ultimately leading to increases in plasma glutathione (GSH) [13]. NAC exhibits both direct as well as indirect antioxidant properties. Direct effect being due to free thiol group, which interacts with the electrophilic group of reactive oxygen species (ROS) [14]. Indirect antioxidant effect is related to its role as (GSH) precursor, which serves as a central factor in protecting against both internal and external toxic agents [14]. The role of NAC in COPD and COPD exacerbations has shown benefit [15].

Aim of the study

The present study aimed to compare the effect of high dose NAC administration versus standard dose on inflammatory markers, oxidative stress, pulmonary oxygenation and clinical outcome in patients with acute exacerbation of COPD and evaluate NAC tolerability in these patients.

Patients and methods

Design

Prospective, randomized, controlled, double blinded study.

Setting

The study was conducted at the National Institute of Chest and Allergic Diseases hospital (NICD) in Giza – Egypt.

Subjects and methods

All patients presenting to the Chest Department were assessed for eligibility. Inclusion criteria included: (1) COPD diagnosis with a history of $\geqslant 2$ exacerbations/year in 2 years prior to enrollment, (2) an age between 40 and 70 years; (3) a post-bronchodilator $FEV_1/FVC < 70\%$ of predicted; (4) an FEV_1 reversibility $< 12\%$ of the predicted value, 15 min after 400 μg (4 puffs) of Salbutamol; (5) and to be currently experiencing an acute exacerbation of COPD. Exclusion criteria included; allergy or intolerance to NAC, cystic fibrosis, bronchiectasis, history of infection or active infection by TB, history of active peptic ulcer.

Table 1 Patients' demographics.

Parameters	Control ($n = 15$)	Low dose NAC 600 mg/day ($n = 15$)	High dose NAC 1200 mg/day ($n = 15$)	p Value
Age (y)	55.5 ± 9.2	59.6 ± 6.6	62 ± 4.1	0.043*
Sex (male/female)	Male (15)	Male (15)	Male (15)	
Severity (grade)	Severe (15)	Severe (15)	Severe (15)	
Concomitant diseases				
Hypertension (n (%))	4 (26.7%)	6 (40%)	6 (40%)	
Diabetes (n (%))	4 (26.7%)	3 (20%)	5 (33.3%)	
Smoking indices mean (peakyear)	20.87 ± 2.58	21.53 ± 3.314	21.73 ± 3.52	

* $p < 0.005$ is consider significant.

Table 2 On admission data.

Parameters	Control group ($n = 15$)				Low dose group (NAC 600 mg/day) ($n = 15$)				High dose group (NAC 1200 mg/d) ($n = 15$)				p Value
FEV_1	38.8 ± 1.8				38.5 ± 1.3				39.2 ± 1.9				0.554
FVC	58.1 ± 1				58.2 ± 1.3				58.1 ± 1.5				0.96
FEV_1/FVC	49.7 ± 2.4				50.1 ± 1.4				50.1 ± 1.8				0.74
MDA μmol/L	2.37 ± 0.86				2.25 ± 0.95				2.58 ± 0.28				0.482
IL-8 pg/ml	5.36 ± .9				4.92 ± 1.04				5.67 ± 0.66				0.077
PaO_2	63.1 ± 2.1				63.0 ± 2.2				63.7 ± 2.6				0.682
$PaCO_2$	47 ± 2.3				47.1 ± 2.1				46.7 ± 1.5				0.872
P/F	273.8 ± 40.2				283.4 ± 40.9				298.5 ± 36.3				0.232
O_2 device	a	b	c	d	a	b	c	d	a	b	c	d	
	6	5	4	0	8	4	1	2	10	4	0	1	
PH	7.37 ± 0.03				7.36 ± 0.03				7.37 ± 0.03				0.459
SaO_2	90.6 ± 1.8				90.5 ± 2.5				90.6 ± 1.4				0.979

a, Patient on room air; b, patient on 1 L/min nasal canula; c, patient on 2 L/min nasal canula; d, venturi mask; MDA, malondialdehyde; IL8, interleukin 8; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; P/F ratio, partial pressure of oxygen/fraction of inspired oxygen; SaO_2, oxygen saturation; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NAC, N-acetylcysteine.

Eligible patients were randomly assigned to either of group A, B or C. Group A (control); received COPD exacerbation standard treatment according to GOLD 2011 [4]. Group B; received standard treatment + low dose NAC (600 mg/ day). Group C; received standard treatment + high dose NAC (1200 mg/day), all for a continuous 10 days period.

Drug administration

Administered NAC sachets (200 mg each) were obtained from SEDICO pharmaceutical company (Egypt). Standard COPD exacerbation medication included; Systemic glucocorticoids oral prednisolone 30–40 mg/day, short acting B2 agonist (SABA) salbutamol and antibiotics [4].

The study was approved by the hospital Ethics Committee and patients gave an informed consent. COPD was diagnosed based on the GOLD criteria [4].

Baseline evaluation included; history taking, physical examination, routine laboratory workup, and chest radiography.

The following parameters were evaluated for all patients on admission (T_0), and after 10 days (T_{10}) of treatment and these included; spirometric pulmonary function tests (SPFTs), MDA levels in the plasma by spectrophotometery [16], arterial blood gases (ABGs) and IL8 levels in the plasma. Patients were monitored for incidence of NAC related side effects and drug interactions.

Statistical analysis

Data were analyzed using SPSS version 17. Nominal and ordinal data were presented as percentage, and continuous data were presented as means ± SD. ANOVA test with repeated measures was used to compare means between the groups over time. p-value < 0.05 was considered significant for all statistical test results. Pearson's correlation coefficient was done to correlate between various parameters.

Results

Forty-five acute COPD exacerbation patients matched the inclusion criteria and were included and randomized to one of 3 groups A–C with 15 patients in each group.

Patients' demographics are presented in (Table 1).

On admission, there was no significant difference between the 3 groups in any of the following parameters; FEV_1%, FVC%, FEV_1/FVC ratio, MDA levels, IL-8 levels, PaO_2, $PaCO_2$, P/F ratio, pH, SaO_2 (Table 2). Control group age was significantly lower (55.5 ± 9.2) than high dose group (62 ± 4.1), ($p < 0.05$). All patients included in the study were male patients with severe COPD. Mean Smoking index (pack-year) was not significantly different between 3 groups; (control; 20.87 ± 2.58, low dose; 21.53 ± 3.314, high dose; 21.73 ± 3.52).

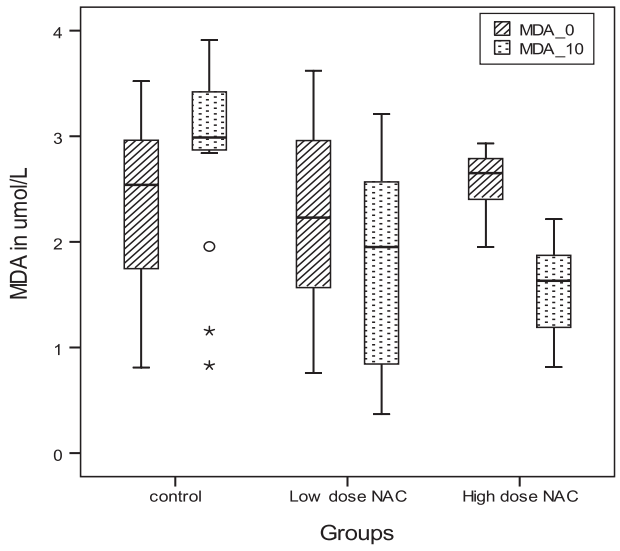

Figure 1 MDA levels in the 3 groups before & after treatment. MDA_0: MDA on admission; MDA_10: MDA after treatment.

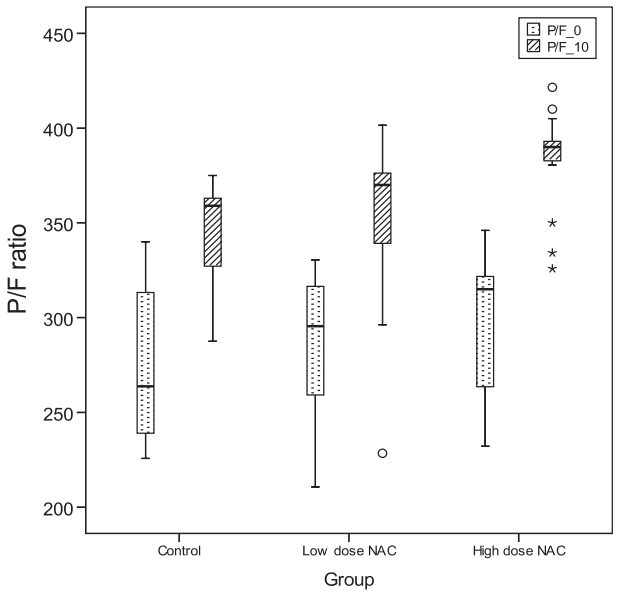

Figure 3 P/F ratio levels in the 3 groups before & after treatment. P/F_0: P/F at admission; P/F_10: P/F after treatment.

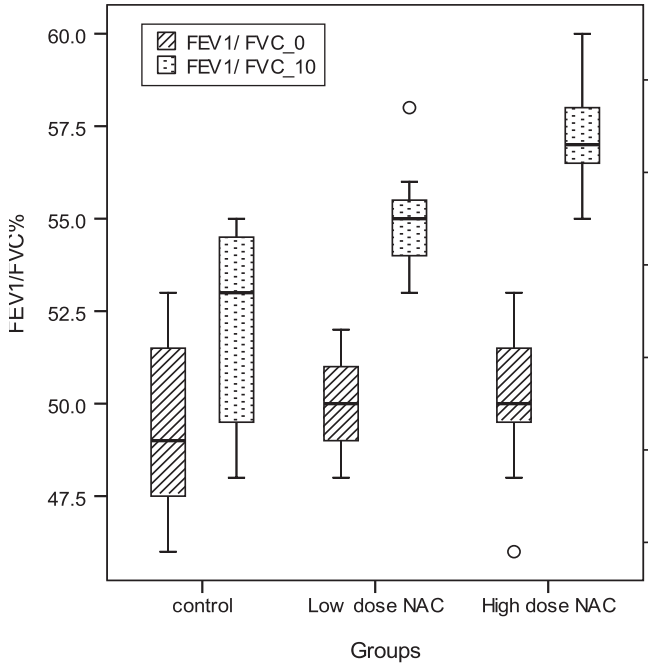

Figure 2 FEV_1/FVC values in the 3 groups before & after treatment. FEV1/FVC_0: FEV1/FVC at admission, FEV1/FVC_10: FEV1/FVC after treatment.

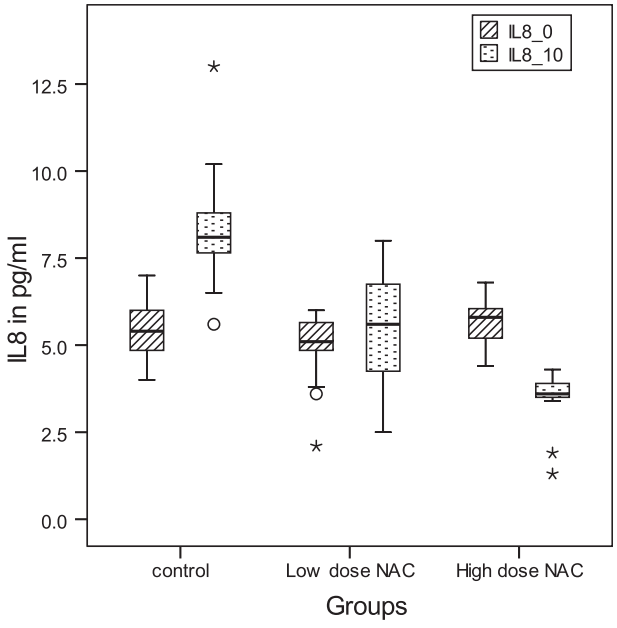

Figure 4 IL-8 ratio levels in the 3 groups before & after treatment. IL-8_0: IL-8 at admission, IL-8_10: IL-8 after treatment.

After 10 days of NAC treatment, serum IL8 levels significantly decreased ($p < 0.001$) in group C (3.47 ± 0.81), versus Group B (5.57 ± 1.66) and group A (8.33 ± 1.69). Plasma MDA levels significantly decreased ($p < 0.001$) in group C and group B over time. Pulmonary functions (FEV_1%, FVC% and FEV_1/FVC%) and partial pressure of oxygen PaO_2 significantly improved ($p < 0.001$) in group C versus group B and A over time. The P/F ratio significantly improved ($p < 0.001$) in group C versus group A. No side effects were reported with NAC administration (see Figs. 1–4 and Table 3).

Discussion

The major findings of the current study includes: (a) NAC treatment significantly decreased elevated MDA levels versus control; (b) high dose NAC was superior to low dose & control groups in improving SPFTs; (c) IL-8 levels decreased significantly in high dose NAC group; (d) PaO_2 significantly improved in the high dose group versus low dose group and

Table 3 Parameters after treatment in the 3 groups.

Parameter	Control (n = 15)	Low dose (n = 15)	High dose (n = 15)	p Value	p Values		
					Between groups	Time	Interaction
FEV_1	43.5 ± 2.7	45 ± 1.3	48.5 ± 2.7	< 0.001 *	< 0.001	< 0.001	< 0.001
FVC	63.9 ± 3	65.7 ± 2.2	68.3 ± 1.1	< 0.001 *	< 0.001	< 0.001	< 0.001
FEV_1/FVC	52 ± 2.6	54.9 ± 1.3	57.3 ± 1.3	< 0.001*	< 0.001	< 0.001	< 0.001
(MDA) μmol/L	2.86 ± 0.88	1.82 ± 0.97	1.55 ± 0.47	0.056	0.056	< 0.001	< 0.001
IL-8 pg/ml	8.33 ± 1.69	5.57 ± 1.66	3.47 ± 0.81	< 0.001*	< 0.001	0.031	< 0.001
PaO_2	71.8 ± 2.1	74.5 ± 3.6	78.3 ± 3.2	< 0.001*	< 0.001	< 0.001	< 0.001
$PaCO_2$	44.1 ± 3	43.2 ± 4.2	43.5 ± 3	0.807	0.807	< 0.001	0.734
P/F	343.3 ± 30.1	350.9 ± 45	382.7 ± 26.5	0.025*	0.025	< 0.001	0.424
PH	7.43 ± 0.02	7.41 ± 0.04	7.41 ± 0.02	0.055	0.055	< 0.001	0.305
SaO_2	93 ± 1.3	93.4 ± 1.8	94.2 ± 1	0.508	0.508	< 0.001	0.088

* $p < 0.005$ is consider significant.

control. P/F ratio significantly improved in the high dose group versus control group.

In the current study, at baseline the three groups were comparable in their demographic characteristics regarding sex and disease severity, except for the control group whose age was significantly lower than the high dose group. Patients included were all males between the age of 40–70 years, complying with the GOLD guidelines, that reported a COPD prevalence that was higher in males, smokers and an age over 40 years than non-smokers, females and an age under 40 [4,17].

While exacerbations of COPD are considered to reflect worsening of the underlying chronic inflammation and is associated with disease severity, this is usually correlated with a decrease in (FEV_1) the most widely used marker of disease severity and progression [5].

At baseline the 3 groups' SPFTs were low, in accordance with other studies of COPD exacerbations that reported a serious negative impact on patient's lung volume, and a doubling in the rate of decline in the FEV_1 [5].

In the current study, after 10 days of treatment, NAC 1200 mg group showed the

highest improvement in lung functions as reflected by a significant increase in all SPFTs versus low dose or control groups which is similar to the results of Zuin and Colleagues (2005), that reported an increase in FEV_1 only in NAC 1200 mg group after 5 days and an increase in FEV_1 after 10 days in both low and high NAC groups [15].

Moreover, in the study by Stav and Raz (2009), in moderate-to-severe COPD patients, treatment with NAC 1200 mg, improved patients' physical performance and endurance time to exercise [18]. FVC was higher especially after exercise in the NAC treated group compared to placebo. In contrast to the study by Decramer et al. (2005), that has failed to show an improved effect with NAC treatment [19], a meta-analysis, documented that the use of NAC significantly reduced the numbers of exacerbations in COPD patients [20].

Alveolar oxygenation is reflected by P/F ratio, which is said to be an independent factor for predicting whether avoiding intubation will be possible [21]. In the current study, the three groups were comparable at baseline in their P/F ratio, after treatment with NAC, the high dose group showed a significant increase in P/F ratio relative to low dose and control groups indicating an improvement in alveolar oxygenation.

Increased oxidative stress plays a role in enhancing the inflammatory response leading to progression and increasing the severity of COPD [22]. COPD patients are subjected to enhanced oxidative stress and increased level of MDA which is a sensitive marker of lipid peroxidation [9]. Moreover, exacerbations of COPD lead to further elevations in various markers of oxidative stress [7].

In our study, prior to treatment, MDA levels were high in the 3 groups when measured in plasma indicating a high oxidative stress burden in COPD exacerbation patients, coinciding with other studies [9,23], that showed that MDA levels were linked to COPD severity.

After 10 days of NAC treatment, our results showed a significant decrease in MDA levels in the high and low dose groups relative to the control, indicating that NAC administration improved the oxidative stress burden. This decline was dose dependant as the high dose group showed a more decline in MDA levels than the low dose yet the difference was not significant. These results are consistent with Patil and Colleagues (2011) that showed a significant decrease in serum MDA levels from baseline to post-treatment levels, yet with the maximum decline observed in the low dose group [24].

IL-8, is a pro-inflammatory cytokine and a potent chemoattractant for neutrophils. IL-8 plays a primary role in the activation of both neutrophils and eosinophils in the airways of COPD patients and may serve as a marker in evaluating the severity of airway inflammation [25].

There is a controversy about the role of IL-8 in COPD exacerbations, as some studies have reported increased levels [26], whereas others have not reported this finding [27]. Qui and Colleagues (2003), reported increased neutrophil recruitment and gene expression of neutrophil chemoattractant receptors in bronchial biopsies from patients with acute severe COPD exacerbations compared with those with stable COPD and non-smoking healthy subject [28].

In the present study, IL-8 levels were high in the three groups at baseline indicating an increased inflammation in COPD exacerbation patients complying with the results of other studies [26,29], that documented high IL- 8 in COPD exacerbation patients. Bhowmik and Colleagues, demonstrated that patients with more frequent exacerbations have higher baseline sputum interleukin (IL)-6 and IL-8 levels, and these cytokines may predict the frequency of future exacerbations [30]. Moreover, it was shown that intubated patients with severe exacerbations, undergo an up-regulation of gene expression for IL-8 [28] and also a significant correlation was shown to exist between increased levels of systemic IL-8 and

enhanced peripheral muscle weakness [31], indicating that ameliorating inflammatory effects induced by IL-8 might contribute to a better outcome in COPD exacerbations.

In our study, the high dose group showed a significant decrease in IL-8 levels after treatment as compared to their pre-treatment values, on the contrary, the control and the low dose group showed a significant increase in IL8 levels after treatment relative to their pre-treatment levels, indicating that high doses may be required to efficiently reduce levels of inflammatory mediators and modulate the inflammatory process. These results are in accordance with the results of Zuin et al. (2005) that reported a significant decrease in IL-8 levels only in the high dose group with an increase in levels in the control group and no change in the low dose group [15].

In contrast to our results, van Overveld et al. (2005), have demonstrated a significant decrease in sputum IL-8 with low dose NAC treatment [32] which elaborates that low NAC doses may improve the inflammatory response in the lungs yet might not be sufficient to ameliorate the overall oxidative stress burden.

The current study also demonstrated a highly significant moderate negative correlation between IL-8 levels after treatment and the SPFs, indicating that ameliorating the inflammatory response may significantly improve lung functions and COPD patients' clinical outcome.

Coinciding with our results, are the results of Drost et al. [33], that reported a linear relationship between IL-8 levels in large airway samples and in BAL fluid with the measured FEV_1/FVC ratio[33]. Conflicting with our results, are the results of Akbulut et al. (2009), who found no correlation between IL-8 levels and FEV_1, FEV_1/FVC values [29].

In our study neither low nor high dose NAC caused any side effects except for one patient in the high dose group who developed a 2-day duration of rhinorrhea indicating the safety and tolerability of high dose NAC. These results were consistent with those of Bachh et al. (2007), who observed no side effects with low dose NAC [14] also the results of Zuin et al. (2005), which reported that both low and high NAC are equally well tolerated, with a report of only one adverse event in the high dose group and two in the placebo group [15].

Stav and Raz (2009), stated that apart from mild epigastric discomfort that was reported by a few patients in the high dose NAC group, no other complaints or findings were recorded [18].

Conclusion

High dose NAC improves clinical outcome of COPD exacerbation patients by ameliorating oxidative stress and inflammatory response, hence improving lung spirometry and pulmonary oxygenation.

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