N-acetylcysteine instead of theophylline in patients with COPD who are candidates for elective off-pump CABG surgery: Is it possible in cardiovascular surgery unit?

Seyed Jalil Mirhosseini, Seyed Khalil Forouzannia, Marjan Nasirian[1], Sadegh Ali-Hassan-Sayegh[2]

Department of Cardiac Surgery, [2]Medical Student and Researcher of Cardiac Surgery, Yazd Cardiovascular Researches Center, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, [1]Ali Ben Abitaleb Medical College, Islamic Azad University, Yazd, Iran

Address for correspondence:
Dr. Sadegh Ali-Hassan-Sayegh, Shahid Sadoughi Medical University, Yazd, Iran.
E-mail: s.alihassan.cardiosurg@gmail.com

ABSTRACT

Background: Forced expiratory volume in one second (FEV1) is a good predictor of chronic obstructive pulmonary disease (COPD). COPD is characterized by a chronic limitation of airflow. This study was designed to compare the effects and complications of theophylline alone, N-acetylcysteine (NAC) alone, and a combination of the two drugs on the rates of FEV1 in patients with COPD who were candidates for off-pump coronary artery bypass graft (CABG) surgery. **Methods:** This clinical trial was performed on 100 patients who had a smoking history of 27 pack years with a range of 20 to 40 pack years but were not heavy smokers and were candidates for elective off-pump CABG surgery in Afshar Cardiovascular Hospital, Yazd, Iran. The patients with a history of asthma and bronchospasm and non-COPD respiratory disorders were excluded. There were three groups, that is, the theophylline group (n=33) that received theophylline 10 mg/kg TDS after consumption of food, NAC group (n=33) who received NAC 10-15 mg/kg BD after consumption of food, and the combined group (n=32) who received theophylline and NAC together. Data were analyzed by analysis of variance (ANOVA), Chi-square, and exact test for quantitative and qualitative variables. **Results:** One hundred patients with COPD enrolled in this study as possible candidates for CABG surgery. Average age of the patients was 60.36±10.21 years. Of the participants, 83 (83.3%) were male and 17 (17%) were female. Rate of postoperative FEV1 to basal FEV1 was 0.76±0.32, 0.66±0.22, and 0.69±0.24 in the treatments with theophylline, NAC, and the combination, respectively. Theophylline, NAC, and a combination of these drugs can decrease the rate of postoperative FEV1 compared to basal FEV1 significantly. (P=0.0001) **Conclusion:** Theophylline alone, NAC alone, and a combination of these drugs improve pulmonary function, and there are no significant differences between these protocols. Stomach discomfort and cardiac complications in treatment with theophylline alone is significantly higher than NAC alone and the combination.

Key words: *Chronic obstructive pulmonary disease, elective off-pump coronary artery bypass graft, N-acetylcysteine, theophylline*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) in patients who are likely candidates for open heart surgery is characterized by a limitation in airflow and decline in lung capacity. COPD is associated with a significant economic burden, including extension of hospitalization and disability. Cigarette smoking and indoor air pollution provide backgrounds for inducing COPD significantly worldwide.[1,2] Treatment guidelines for COPD recommend theophylline as the principal line of treatment when symptoms are still persistent despite treatment with short - and long-acting inhaled bronchodilators; therefore, physicians have been administering theophylline for the improvement of outcomes of COPD for several years now.[3] Current evidence indicates that COPD is characterized by

Access this article online

Quick Response Code:

Website: www.saudija.org

DOI: 10.4103/1658-354X.114069

systemic inflammation, which is partially initiated by the oxidative stress that is common in COPD patients compared to healthy subjects. Considering the role of inflammation and oxidative stress in the exacerbation of clinical outcomes of pulmonary dysfunction, therefore, supplementation with N-acetylcysteine (NAC) has been shown to increase the levels of glutathione and major antioxidants. Glutathione in NAC is critically important for the removal of toxins including peroxide compounds, and free radical-generating molecules.[4,5] This study was designed to compare the pharmacologic effects and complications of theophylline alone, NAC alone, and a combination of these drugs on the rates of forced expiratory volume in one second (FEV1) in patients with COPD, who are likely candidates for off-pump coronary artery bypass graft (CABG) surgery.

METHODS

Our randomized double-blind clinical trial was approved by the ethical committee in our university. After giving a written consent, the patients (*n*=100) participated voluntarily for an off-pump CABG surgery in Afshar Cardiovascular Hospital (Yazd, Iran) from January 2010 to June January 2012.. All of the operations were conducted by a certain surgical team. Patients who had a smoking history of 27 pack years with a range of 20 to 40 pack years but were not heavy smokers and were likely candidates for elective off-pump CABG were enrolled in this study. Grading of COPD was defined as mild COPD (FEV1 between 40 and 80%), moderate COPD (FEV1 between 30 and 39%), and severe COPD (FEV1 lower than 29%). The patients were stable for at least eight weeks clinically and were not undergoing oxygen therapy. The patients with a history of asthma and bronchospasm and non-COPD respiratory disorders were excluded from this study. One hundred patients were randomly assigned to three groups, the theophylline group (*n*=33) that received theophylline 10 mg/kg TDS after consumption of food, the NAC group (*n*=33) which received NAC 10-15 mg/kg BD after consumption of food, and the combination group (*n*=32) which received theophylline and NAC together. These drugs were administered 72 hours before surgery. Evaluations through spirometry were done at the time of admission and discharge from hospital. Cardiac and gastrointestinal complications and impact on pulmonary function test of these drugs were recorded in the form of a questionnaire. According to definitions about benefits of drugs on the respiratory system, an improvement in respiratory parameters means an increase in the rate of FEV1 higher than 10% from the basal rate of FEV1 and fewer side effects. Our data were analyzed by SPSS15 software. We used ANOVA, Chi-square, and exact test for quantitative and qualitative variables.

RESULTS

One hundred patients with COPD enrolled in this study as possible candidates for CABG surgery. Average age of the patients was 60.36±10.21 years. Of the participants, 83 (83.3%) were male and 17 (17%) were female. The demographic characteristics of our patients have been presented in Table 1. In the participants, distribution of abundance in grading groups from mild to severe showed that 47 (47%), 43, and 10 cases had mild, moderate, and severe COPD, respectively [Table 2]. Frequency distribution of increase in the rate of FEV1 higher than 10% from basal rate was three cases (9.1%) in the theophylline group, one case (3.1%) in the NAC group, and two cases (6.3%) in the combined treatment group. Information about grading of COPD and increase in the rate of FEV1 higher than 10% from basal rate has been presented in Table 3. Average rate of basal FEV1 in the three groups was 73.4±24.9, 78.4±17.8, and 79.6±31.8 L with theophylline, NAC, and

Table 1: Demographic characteristics of three groups

Variables	Theophylline (*n*=33)	N-acetylcysteine (*n*=33)	Combination (*n*=32)	*P* value
Age (years)	63±9.62	58.4±9.9	59.6±10.8	0.15
Sex (M/F)(*n*)	24/9	30/4	29/4	0.15
Diabetic mellitus [*n* (%)]	11 (33.3%)	13 (38.2%)	11 (33.3%)	0.8
HTN [*n* (%)]	20 (60.6%)	12 (35.3%)	13 (39.4%)	0.08
HLP [*n* (%)]	15 (45.5%)	14 (41.2%)	12 (36.4%)	0.75

HTN – Hypertension; HLP – Hyperlipidemia; M – Male; F – Female

Table 2: Frequency distribution of grading of COPD

Variables [*n* (%)]	Theophylline (*n*=33) (%)	N-acetylcysteine (*n*=33) (%)	Combination (*n*=32) (%)
Mild COPD	14 (42.4)	18 (52.9)	15 (45.5)
Moderate COPD	14 (42.4)	13 (38.2)	16 (48.5)
Severe COPD	5 (15.2)	3 (8.8)	2 (6.1)

COPD – Chronic obstructive pulmonary disease

Table 3: Frequency distribution of increase in rate of FEV1 higher than 10% and grading of COPD

Variables [*n* (%)]	Theophylline (*n*=33) (%)	N-acetylcysteine (*n*=33) (%)	Combination (*n*=32) (%)	*P* value
Mild COPD	0 (0)	0 (0)	0 (0)	0.8
Moderate COPD	1 (7.1)	1 (8.3)	2 (12.5)	0.9
Severe COPD	2 (40)	0 (0)	0 (0)	0.58

FEV1 – Forced expiratory volume in one second; COPD – Chronic obstructive pulmonary disease

combination therapy, respectively. Therefore, there are no significant differences in the rate of basal FEV1 following treatment with a combination of NAC and theophylline versus NAC or theophylline alone (P=0.58). Average rate of FEV1 after off-pump CABG was the same statistically in the three groups [Table 4]. Ratio of rate of postoperative FEV1 to basal FEV1 was 0.76±0.32, 0.66±0.22, and 0.69±0.24 in the treatments with theophylline, NAC, and the combination, respectively (P=0.32). Theophylline, NAC, and a combination of these drugs can decrease the rate of postoperative FEV1 compared to basal FEV1 significantly (P=0.0001 for the three protocols) [Table 5]. The incidence of nausea, vomiting, and arrhythmias after surgery in the theophylline group was significantly higher than that in the NAC and combination groups [Table 6]. In all patients, average duration of operation, intubation, and stay in the intensive care unit (ICU) and hospital were 181.95±33.2 minutes, 7.16±5.5 hours, 59.3±18.5 hours, and 5.4 8±1.47 days, respectively. Details of information about surgery, intubation time, and stay in the ICU and hospital in the three groups have been presented in Table 7. There were eight (24.2%), one (3%), and two cases (6.2%) of postoperative pulmonary dysfunction (pneumonia or atelectasis or aspiration) in the theophylline, NAC, and combination groups, respectively. These findings indicate that theophylline maybe more suitable compared to the NAC or combination groups for reduction in pulmonary dysfunction.

DISCUSSION

COPD is a chronic disease of the lungs and airways that induces a socioeconomic burden. Oxidative stress has been implicated in the pathogenesis and progression of COPD.[6,7] Anti-inflammatory actions of theophylline at low serum concentrations have an effect on pulmonary disorders, but one of the most important complications of this drug is cardiac arrhythmia.[8] NAC, a glutathione precursor, has been used in patients with COPD who are possible candidates for CABG to reduce symptoms of pulmonary dysfunction.[7] A study carried out by Tang *et al.* indicated that cardiac complications especially arrhythmia can be a predictor of mortality following COPD.[9] Ferrari *et al.* reported that atrial and ventricular arrhythmias in COPD patients were common complications in treatment with theophylline.[10] In our study, incidence of stomach discomfort and cardiac disorders was more in treatment with theophylline than NAC. A study performed by Sessler *et al.* reported that sinus tachycardia, supraventricular ectopic beats, and ventricular premature beats were prevalent among patients with theophylline toxicity.[11] A study conducted by Thomas *et al.* showed that theophylline increased the rate of FEV1 significantly.[12] Our study reports that theophylline and NAC increased postoperative rate of FEV1 compared to the basal FEV1. Fink *et al.* reported that cardiopulmonary procedures may exacerbate COPD in patients who are candidates for surgery; therefore, administration of theophylline improves respiratory functions.[13] In our study, the surgical procedure was CABG without cardiopulmonary bypass. A study carried out by Wang *et al.* indicated that theophylline could improve arterial blood gas tension and lung function, whereas the incidence of drug-related side effects was higher.[14] Zhou *et al.* reported that insomnia, stomach

Table 4: Average rate of FEV1 (L) after CABG

Variables	Theophylline (*n*=33)	N-acetylcysteine (*n*=33)	Combination (*n*=32)	*P* value
Rate of FEV1	53.4±22.1	50.7±15.2	56.2±35	0.69

FEV1 – Forced expiratory volume in one second; CABG – Coronary artery bypass graft

Table 5: Average rates of basal and postoperative FEV1 in the three groups

Variables	Basal FEV1	Postoperative FEV1	*P* value
Theophylline (*n*=33)	73.4±24.9	53.4±22.18	0.0001
N-acetylcysteine (*n*=33)	78.6±18.2	50.7±15.2	0.0001
Combination (*n*=32)	80.6±31.7	56.2±35	0.0001

FEV1 – Forced expiratory volume in one second

Table 6: Evaluation of side effects of drugs in patients with COPD

Variables [*n* (%)]	Theophylline (*n*=33) (%)	N-acetylcysteine (*n*=33) (%)	Combination (*n*=32) (%)	*P* value
Nausea	4 (12.1)	0 (0)	1 (3)	0.04
Vomiting	5 (15.1)	1 (8.3)	1 (3)	0.04
Arrhythmias	5 (15.1)	0 (0)	0 (0)	0.03

COPD – Chronic obstructive pulmonary disease

Table 7: Operative and postoperative information

Variables	Theophylline (*n*=33)	N-acetylcysteine (*n*=33)	Combination (*n*=32)	*P* value
Duration of operation (minutes)	182.4±28.1	182.2±9.5	181.2±31.9	0.98
Duration of intubation (hours)	6.3±4.03	7.9±5.8	7.2±6.5	0.13
ICU stay (hours)	58.4±16.3	55.3±16.6	64.4±21.7	0.13
Hospital stay (days)	5.3±1.1	5.1±1.04	5.9±1.9	0.12
Need for chest tube [*n* (%)]	31 (93.9%)	32 (94.1%)	31 (93.9%)	0.99

ICU – Intensive care unit

discomfort, and palpitation were common adverse effects of theophylline; however, slow-release oral theophylline may be safe and acceptable in the long-term treatment of COPD.[15] A study conducted by Ferarri *et al*. suggested that NAC had antioxidant, microcirculatory inhibition of aggregation of platelets and decrease in ischemic events significantly.[10] Our findings show that NAC can improve pulmonary dysfunction, but there were no significant differences compared to theophylline. A study about the mechanism of NAC carried out by Sadowska *et al*. indicated that NAC may induce expression of mucin by affecting oxidative stress and inflammation; therefore, NAC provided enough lung capacity in COPD patients.[16] In our study, the rate of postoperative FEV1 to basal FEV1 was 0.76±0.32, 0.66±0.22, and 0.69±0.24 in treatments with theophylline, NAC, and the combination, respectively. Theophylline, NAC, and a combination of the drugs can decrease the rate of postoperative FEV1 compared to basal FEV1 significantly. A study by Dhalla *et al*. indicated that NAC with anti-inflammatory effects managed pulmonary parameters effectively.[17] This finding is in line with our results. Our study suggests that the efficacy of NAC is more than theophylline for reduction in pneumonia, atelectasis, and aspiration. Finally, we conclude that theophylline alone, NAC alone, and a combination of the two improve pulmonary function, and there are no significant differences between these protocols. Stomach discomfort and cardiac complications in treatment with theophylline alone are significantly higher than NAC alone and the combination. We recommended that NAC is a safe and acceptable drug for patients with COPD who are candidates for off-pump CABG surgery.

REFERENCES

1. Rycroft CE, Heyes A, Lanza L, Becker K. Epidemiology of chronic obstructive pulmonary disease: A literature review. Int J Chron Obstruct Pulmon Dis 2012;7:457-94.
2. Lou P, Zhu Y, Chen P, Zhang P, Yu J, Zhang N, *et al*. Prevalence and correlations with depression, anxiety, and other features in outpatients with chronic obstructive pulmonary disease in China: A cross-sectional case control study. BMC Pulm Med 2012;12:53.
3. Cyr MC, Beauchesne MF, Lemière C, Blais L. Effect of theophylline on the rate of moderate to severe exacerbations among patients with chronic obstructive pulmonary disease. Br J Clin Pharmacol 2008;65:40-50.
4. Millea PJ. N-acetylcysteine: Multiple clinical applications. Am Fam Physician 2009;80:265-9.
5. Keranis E, Makris D, Rodopoulou P, Martinou H, Papamakarios G, Daniil Z, *et al*. Impact of dietary shift to higher-antioxidant foods in COPD: A randomised trial. Eur Respir J 2010;36:774-80.
6. Kerstjens HA, Postma DS. [Medical maintenance treatment of chronic obstructive pulmonary disease (COPD)]. Ned Tijdschr Geneeskd 2002;146:1631-5.
7. Dekhuijzen PN, van Beurden WJ. The role for N-acetylcysteine in the management of COPD. Int J Chron Obstruct Pulmon Dis 2006;1:99-106.
8. Wieshammer S, Dreyhaupt J, Basler B. Theophylline and cardiac stress in patients with dyspnea: An observational study. Pharmacology 2010;86:189-95.
9. Tang LD, Sun JZ, Wu K, Sun CP, Tang ZM. Beneficial effects of N-acetylcysteine and cysteine in stunned myocardium in perfused rat heart. Br J Pharmacol 1991;102:601-6.
10. Ferrari R, Ceconi C, Curello S, Guarnieri C, Caldarera CM, Albertini A, *et al*. Oxygen-mediated myocardial damage during ischaemia and reperfusion: Role of the cellular defences against oxygen toxicity. J Mol Cell Cardiol 1985;17:937-45.
11. Sessler CN, Cohen MD. Cardiac arrhythmias during theophylline toxicity. A prospective continuous electrocardiographic study. Chest 1990;98:672-8.
12. Thomas P, Pugsley JA, Stewart JH. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. Chest 1992;101:160-5.
13. Fink G, Kaye C, Sulkes J, Gabbay U, Spitzer SA. Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease. Thorax 1994;49:332-4.
14. Wang CH, Zhang Q, Li M, Fu PF, Yan ZM, Peng AM, *et al*. [Meta-analysis of efficacy and safety of oral theophylline in chronic obstructive pulmonary disease]. Zhonghua Yi Xue Za Zhi 2010;90:540-6.
15. Zhou YM, Wang XP, Zeng XY, Qiu R, Xie JF, Liu SM, *et al*. [Theophylline in the treatment of chronic obstructive pulmonary disease: A randomized, double-blind, placebo-controlled study]. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:577-82.
16. Sadowska AM. N-Acetylcysteine mucolysis in the management of chronic obstructive pulmonary disease. Ther Adv Respir Dis 2012;6:127-35.
17. Dhalla NS, Golfman L, Takeda S, Takeda N, Nagano M. Evidence for the role of oxidative stress in acute ischemic heart disease: A brief review. Can J Cardiol 1999;15:587-93.

How to cite this article: Mirhosseini SJ, Forouzannia SK, Nasirian M, Ali-Hassan-Sayegh S. N-acetylcysteine instead of theophylline in patients with COPD who are candidates for elective off-pump CABG surgery: Is it possible in cardiovascular surgery unit?. Saudi J Anaesth 2013;7:151-4.

Source of Support: Nil, **Conflict of Interest:** None declared.