

EFFECT OF N-ACETYLCYSTEINE ON PULMONARY FUNCTION IN PATIENTS UNDERGOING OFF PUMP CORONARY ARTERY BYPASS GRAFTINGB. Jalakandan¹, K. Bhaskaran²**HOW TO CITE THIS ARTICLE:**

B. Jalakandan, K. Bhaskaran. "Effect of N-Acetylcysteine on Pulmonary Function in Patients Undergoing off Pump Coronary Artery Bypass Grafting". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 79, October 01; Page: 13777-13790, DOI: 10.14260/jemds/2015/1966

ABSTRACT: OBJECTIVE: Postoperative lung injury is one of the most frequent complications of cardiac surgery. Increasingly used Off Pump Coronary Artery Bypass Grafting (OPCABG) has significantly reduced the oxidative stress and the inflammatory response associated with the use of cardiopulmonary bypass (CPB). However, OPCABG is also associated with significant oxidative stress and its related complications. The present study is a prospective, randomized, double blind investigating the effects of N-acetylcysteine (NAC), a potent anti-oxidant on pulmonary functions in patients undergoing OPCABG. **METHODS:** Fifty patients undergoing elective OPCABG were randomized into two groups. Group A (n=25), the control group received 200ml of Normal saline immediately following induction whereas Group B (n=25), the study group received 150mg/kg of NAC in 200ml of Normal saline at the same time. Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Artery Pressure (PAP), Dynamic lung compliance (C Dyn), Static lung compliance (C Stat), Alveolar - arterial oxygen gradient (A-a Do₂) were measured immediately following induction, after admission into ICU, and then 4th hourly till extubation. Malondialdehyde (MDA) and Glutathione (GSH) levels were assayed once immediately following induction and again immediately after shifting to ICU. **RESULTS:** Demographic profile, pre-incision clinical and biochemical values were comparable in both the groups. PCWP, PAP- Diastole were lower and C Dyn and C Stat were significantly higher in study group when compared to control group. No difference in PAP-Systole was found. Both the groups had increased A-a Do₂, but the increase was significantly lower in the study group. At the end of surgery, MDA levels were significantly raised in control group (p<0.001) whereas its levels were maintained in study group (p<0.569). GSH levels were significantly decreased in control group (p<0.001) whereas its levels were significantly increased in study group (p<0.001). **CONCLUSION:** OPCABG was associated with significant oxidative response but the administration of NAC attenuates this stress response by replenishing the GSH stores. NAC improves pulmonary function in terms of increased compliance and increased systemic oxygenation.

KEYWORDS: OPCABG, Oxidative stress, Free radicals, Glutathione, N-Acetylcysteine, Pulmonary pressures, Compliance, Oxygen gradient, Malondialdehyde.

INTRODUCTION: The policies of cost containment, efficient resource utilization and the pressures on intensive care unit (ICU) beds have influenced the development techniques of fast track cardiac anaesthesia. The major determinant of cost is length of ICU stay. The aim is to extubate the patient early and to mobilize and transfer the patient from the ICU and subsequently discharge from the hospital as soon as possible. Postoperative pulmonary function plays an important role in determining the timing of extubation.

Fransen et al.,¹ had observed that the acute phase response of systemic inflammation in CABG patients, which was historically been ascribed to CPB is predominantly caused by surgical procedure

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per se. Many studies have concluded that similar degrees of oxidative injury and pulmonary dysfunction occurs in both OPCABG and conventional CABG group of patients.^{2,3}

Pulmonary dysfunction has been attributed to widespread systemic inflammatory response as the result of oxidative stress.⁴ The nature of these oxidative events leads to depletion of plasma antioxidants.^{5,6} By maintaining high cellular GSH levels, the magnitude of the destructive potentials of ROS can be reduced. NAC, a GSH precursor,⁷ exhibits both direct and indirect antioxidant properties. Many studies have supported the free radical scavenging property of NAC,⁷⁻⁹ and its role in improving systemic oxygenation.^{7,10}

Although most clinical studies had suggested that the drug may be beneficial in facilitating early extubation, no investigation has examined its use in OPCABG. Thus, this prospective study was carried out to examine the pulmonary effects of NAC in patients undergoing OPCABG.

AIMS AND OBJECTIVES: To assess the efficacy of NAC in attenuating oxidative stress response and its role on pulmonary function in patients undergoing OPCABG.

MATERIALS AND METHODS: Fifty adult patients scheduled for CABG were included in this prospective, randomized, double blind, placebo-controlled study. They were randomized into two groups: Group A, the Control group (n=25) and Group B, the Study group (n=25). Randomization was done using sealed envelope technique. The study was approved by the institutional ethics committee, Apollo hospitals and informed consent was obtained from all the patients.

Inclusion Criteria:

- Age group 30-70 yrs.
- Elective OPCABG.
- Normal Left Ventricular systolic function.

Exclusion Criteria:

- Pre-existing pulmonary disease (Parenchymal/vascular).
- Recent Myocardial Infarction (<4 weeks).
- Morbid obesity (Body Mass Index >35).
- Significant valvular heart disease.
- Redo OPCABG.
- OPCABG involving harvest of both mammary arteries.

ANAESTHESIA AND POSTOPERATIVE CARE: Preoperative assessment and evaluation was done for all the patients. On arrival into the theatre, all standard 'American Society of Anaesthesiologists' non-invasive monitoring and peripheral intravenous and right radial arterial catheter were placed. All the patients received standard anesthesia according to the clinical routine at our department. They were ventilated in volume control mode (Aestiva 5, Datex Ohmeda) with FiO₂ of 0.33, to achieve target EtCO₂ of 30-35 mmHg. A Swan-Ganz catheter (Thermoflution Paceport Catheter, Edwards Life science, Irvine, CA, USA) was floated through the right internal jugular vein. Group A, patients were administered placebo of 200 ml normal saline before skin incision and Group B, patients received N-acetylcysteine 150mg/kg in 200 ml Normal saline at the same time, over a period of 20 minutes.

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After completion of CABG, all the patients received standard post-operative care in ICU. Patient management was by a single team according to strict, unbiased, blinded, criteria-driven protocols. Patients were ventilated mechanically initially with a FiO_2 of 1.0 until satisfactory oxygen saturation was obtained and then with a FiO_2 of 0.5. Tracheal extubation was accomplished when the patient was hemodynamically stable, responsive and cooperative, demonstrated adequate pulmonary function (Normal arterial blood gases), had core temperature $>36^\circ C$, and without excessive chest tube drainage. During the postoperative period, any hemodynamic instability was treated using appropriate inotropes based on cardiac output studies.

SURGICAL PROCEDURE: The patients were operated through a median sternotomy by three different surgeons. Left internal mammary artery and/or radial artery and/or saphenous vein grafts were harvested and used. The revascularisation was performed on the beating heart using the Medtronic Octopus device (Medtronic, Minneapolis, USA). An intracoronary shunt tube was used to maintain distal perfusion. Heparin 2mg/kg was administered to maintain ACT over 300s. Finally, the need to rotate the heart into the right chest to facilitate grafts to the posterolateral vessels, sometimes produced hemodynamic compromise necessitating inotropic support and extra intravenous fluids. All proximal anastomoses were performed by the use of a side-biting clamp. After all the anastomoses were completed, Heparin was neutralised with Protamine 1.5mg/1mg of Heparin.

DATA COLLECTION: Systolic and Diastolic Pulmonary artery pressure, and pulmonary capillary wedge pressure were measured from the Swan Ganz catheter. Dynamic lung compliance, static lung compliance, and alveolar – arterial oxygen gradient were determined using following standard equations.

- Dynamic lung compliance C_{Dyn} (ml/cm H₂O):

$$C_{Dyn} = \text{Tidal Volume} / (\text{P}_{peak} - \text{PEEP}).$$
- Static lung compliance C_{stat} (ml/cm H₂O):

$$C_{stat} = \text{Tidal Volume} / (\text{P}_{plateau} - \text{PEEP}).$$
- Alveolar – arterial oxygen gradient A-aDO₂ (mm Hg):

$$\text{A-aDO}_2 = \text{PAO}_2 - \text{PaO}_2.$$

$$\text{PAO}_2 = \text{PiO}_2 - (\text{PaCO}_2 / 0.8).$$

$$\text{PiO}_2 = \text{FiO}_2 \times (\text{PB} - 47).$$

PEEP-Positive End Expiratory Pressure, PO₂-Partial Pressure of Oxygen, PAO₂-Alveolar PO₂, PaO₂-Arterial PO₂, PiO₂-Partial Pressure of inspired Oxygen, FiO₂-Fraction of inspired Oxygen, PaCO₂-Partial Pressure of carbon di-oxide, PB- Barometric pressure.

These data were obtained once before the study drug administration, at arrival in the ICU, and then 4th hourly thereafter till extubation.

Samples: Arterial samples collected from the radial arterial line was analyzed for blood gases just before the administration of the study drug, at arrival in the ICU and then 4th hourly thereafter till extubation. Mixed venous blood was sampled from the Swan Ganz catheter just before the administration of the study drug, and at arrival in the ICU. The obtained heparinized blood were

immediately centrifuged at 3,000 rpm for 10 min, and were stored at -80°C for the analysis of malondialdehyde and glutathione levels.

Plasma MDA and GSH levels were estimated by the method of Yagi,¹¹ and the method of Beutler and Kelley,¹² respectively.

Statistical Analysis: The statistical package employed by us was Statistical package for social scientists windows version 12.0 software (SPSS Inc, Chicago, Illinois). Results were expressed as mean \pm standard deviation. Statistical analysis was performed using the paired 't' test for numeric variables and one way analysis of variance repeated measure for Continuous variables and categorical variables by Chi-square and Fisher's exact test. Statistical significance was assumed when $P < 0.05$.

OBSERVATIONS: Demographic profile of both control and study groups were comparable and the difference was not statistically significant (table 1 and 2). Similarly duration of surgery and mechanical ventilation were comparable between both the groups (table 3).

Clinical Parameters: Pre-incision values of PCWP and PAP were comparable in both the groups. In control group, PCWP values did not differ significantly throughout the postoperative period. Whereas in study group, the PCWP values were significantly lower than pre-incision values (Table 4, fig. 1). Comparing both the groups, PCWP was significantly lower in the study group throughout the postoperative period.

PAP-Systole in the entire postoperative period did not differ significantly both within the group and between the groups (Table 5, fig. 2). In control group, PAP-Diastole values were significantly high in the entire postoperative period whereas in study group, the PAP-Diastole did not differ statistically when compared to pre-incision values (Table 6, fig. 3). Comparing both the groups in the postoperative period, PAP-Diastole was higher in the control group and it was statistically significant at 0, 4, 8th postoperative hour.

Pre-incision values of Cdyn and C Stat were comparable in both the groups.

In control group, there was a significant reduction in the compliance in the immediate postoperative period whereas in study group, significant reduction in the compliance was only at 12th postoperative hour (Table 7, fig. 4). Comparing both the groups, the reduction in Cdyn in study group was lower when compared to control group and it was statistically very significant at 8th postoperative hour ($p= 0.002$).

In control group, there was a reduction in the Cstat in the postoperative period. In study group, there was an actual increase in compliance except for a mild decrease at 0 and 12th postoperative hour, which were not statistically significant. Comparing both the groups, Cstat was higher in the study group in the postoperative period (Table 8, fig. 5) and it was statistically significant at 4th and 8th postoperative hour.

Pre-incision baseline A-aDO₂ values were comparable. In both the groups, there was a sharp rise in A-aDO₂ at arrival in the ICU, when patients were mechanically ventilated with FiO₂ of 1.0. Subsequently, at 4, 8, 12, 16th postoperative hour, when the patients were ventilated with FiO₂ of 0.50, there was a fall in A-aDO₂ but was still higher when compared to their respective pre-incision values and were statistically significant (Table 9, fig. 6). In the postoperative period, both the groups had a higher A-aDO₂, but the increase in study group was lower when compared to control group, especially at 0 and 4th postoperative hour and was statistically significant ($p<0.05$).

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Biochemical Parameters: Pre-incision plasma levels of MDA and GSH were comparable between both the groups.

Following surgery, MDA levels increased significantly in control group but in study group there was a non-significant decrease (Table 10, fig. 7). Comparing both the groups in the postoperative period, the MDA levels were significantly higher in the control group ($p=0.033$).

The control group had a very significant decline in GSH levels following surgery Whereas in study group, there was a very significant rise in GSH levels (Table 11, fig. 8). Comparing both the groups postoperatively, GSH levels was very high in the study group and the difference was statistically very significant ($p=0.005$).

DISCUSSION: Postoperative pulmonary dysfunction is a well-recognized and significant clinical problem.¹³ The pathophysiology of postoperative pulmonary dysfunction after CABG is complex and reflects the combined effects of general anaesthesia, surgical injury, median sternotomy, and CPB to produce hypoxia, atelectasis, pleural effusion and dysfunction of the diaphragm.¹⁴ Studies have shown that both OPCABG and conventional CABG produces similar degrees of pulmonary dysfunction.^{2,3,14,15}

Postoperative pulmonary dysfunction has been attributed to widespread systemic inflammatory response, as a result of oxidative stress,⁴ which results from an imbalance between local antioxidant defenses and formation of reactive oxygen derived free radicals. ROS are highly reactive and, when generated close to cell membranes, can induce lipid peroxidation (Oxidation of membrane phospholipids) and the accumulation of their products including MDA,^{16,10,17} 4-hydroxy-2-nonenal, acrolein, hydroperoxides,⁵ and F₂-isoprostanes.^{6,7,9} Elevated levels of these products acts as an indirect measure of free radical activity.^{4,17} In addition to their cytotoxic properties, lipid peroxides are increasingly recognized as being important in signal transduction for a number of important events in the inflammatory response in the lungs.

Increased amounts of ROS can reduce the synthesis of elastin and collagen. Fragmentation of major constituents of the lung skeleton may also occur. Increased levels of ROS may also increase Interleukin (IL)-1 and IL -8 production,¹⁸ and also other cytokines,^{19,20} in several cell systems. Other changes include changes in protein structure, leading to altered antigenicity and thus immune responses, contraction of smooth muscle, impairment of β -adrenoceptor function, stimulation of airway secretion, pulmonary vascular smooth muscle relaxation or contraction, and activation of mast cells. Antiproteases such as α_1 -proteinase inhibitor (α_1 -PI) and secretory leukoprotease inhibitor may be inactivated by ROS. The permeability is increased. Sequestration of neutrophils may occur in the lung microcirculation. Finally, oxidative stress activates the transcription factor nuclear factor- κ B (NF- κ B), which switches on the genes for Tumor necrosis factor (TNF)- α 1, IL-8 and other inflammatory proteins, enhancing inflammation.²¹ These data strongly suggest that oxidative stress plays an important pathogenetic factor in causing pulmonary dysfunction.

Sustained oxidative challenge results in depletion of GSH and other antioxidants from the lungs. GSH is an important water-phase antioxidant and essential cofactor for antioxidant enzymes catalase and Superoxide dismutase. Its high redox potential renders GSH both a potent antioxidant per se and a convenient cofactor for enzymatic reactions that require readily available electron pairs, the so-called "reducing equivalents". Through its significant reducing power, GSH also makes major contributions to the recycling of other antioxidants that have become oxidized. This could be the

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basis by which GSH helps to conserve lipid-phase anti-oxidants such as alpha-tocopherol (Vitamin E), and the carotenoids.

The availability of amino acids for GSH synthesis is a fundamental factor in its regulation. Cellular levels of glutamic acid and glycine, but not cysteine, are plentiful. Consequently, GSH synthesis depends on the availability of cysteine. NAC is a thiol [Sulphydryl (SH)-containing] compound which has the chemical formula $C_5H_9NO_3S$ and a molecular weight of 163.2, acts as a precursor of GSH as it can penetrate cells easily and is subsequently deacylated to form cysteine. The required quantity of cysteine may thus be administered to maintain adequate levels of GSH.

NAC exhibits both direct and indirect antioxidant properties. NAC exerts an indirect antioxidant effect related to its role as a GSH precursor,⁷ as discussed above. It exerts its direct effect through its free thiol group, which is capable of interacting with the electrophilic groups of ROS.²² Many studies have supported the use of NAC, as a free radical scavenger, especially in cardiac surgeries,⁷⁻⁹ which has led to improvement in pulmonary function.^{7,10} As a source of sulphydryl groups, it also enhances glutathione-S-transferase activity and promotes detoxification. NAC is well documented in neutralization of pro-inflammatory cytokines like TNF- α and NF- κ B. It is well documented in renal function preservation and lung function preservation when given pre and peri procedurally. PM Suter et al,²³ concluded that administration of NAC, in patients with acute lung injury, has improved systemic oxygenation and reduced the need for ventilatory support.

Possible adverse reactions include an urticarial rash, nausea, and vomiting and an anaphylactoid reaction. Studies had observed that NAC infusion did not induce any severe adverse reactions.²³ After a single intravenous dose of NAC, plasma concentration declined in a poly-exponential decay manner with mean terminal half-life $T_{1/2}$ of 5.6 hours.

We have used NAC, as a single dose of 150mg/kg before skin incision. And the same dose has been employed in various studies related to this property of NAC in cardiovascular surgeries,^{7,24} septic shock patients,²⁵ and in ventilation of cardiac risk patients.²⁶

In our study, patient characteristics, duration of surgery and mechanical ventilation were comparable in both the groups and did not differ significantly. The duration of mechanical ventilation was longer in our study. Though the extubation was attempted at the earliest appropriate time once the patients meets the criteria, the time to extubation was also influenced by the surgeons decision. Nicholson DJ et al,²⁷ had compared the effects of short-term mechanical ventilation and early extubation on pulmonary function in patients undergoing CABG and concluded that extending mechanical ventilation does not affect pulmonary function.

In our study, PCWP was significantly lower in the study group and PAP diastolic pressures were significantly high in the control group in the early postoperative period. PAP-systole pressures did not differ significantly between the groups. This rise in PAP-Diastole in the control group has also been observed by G W Staton et al,²⁸ in their study on pulmonary outcomes following OPCABG vs conventional CABG. Kretzschmar M, et al⁷ had studied the effect of NAC (150mg/kg) on ischemia-reperfusion syndrome in patients undergoing abdominal aortic aneurysmectomy and concluded that mean PAP in the control group were significantly higher when compared to the NAC treated group. Angdin et al,²⁹ had demonstrated that thiol supplementation with NAC reduces endothelial dysfunction and thereby improves endothelium dependant vasodilation.

C Dyn decreased in the postoperative period in both the groups but the decrease was much lower in the study group. C Stat had decreased significantly in the control group but increased in the study group. Thus compliance was better preserved in NAC treated group. This reduction in both C

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Dyn and C Stat following OPCABG in control group has also been observed by Kochamba G S, et al¹⁵ in their comparative study on pulmonary abnormalities following CABG with CPB vs mechanical stabilization.

In both the groups, there was a sharp rise in A-aDO₂ at arrival in the ICU. This may be because patients were mechanically ventilated initially with the FiO₂ of 1.0 till the satisfactory oxygen saturation was obtained. Subsequently, at 4, 8, 12, 16th postoperative hour, when the patients were ventilated with FiO₂ of 0.50, there was a fall in A-aDO₂ in both the groups but was still higher when compared to their respective preincision values and were statistically significant. But the increase in A-aDO₂ in study group was lower when compared to control group, especially at 0 and 4th postoperative hour, which were statistically significant (p<0.05). Cakir O et al.,¹⁰ in their study on the effect of NAC on pulmonary function in patients undergoing CABG with CPB, had observed the similar,²³ increase in A-aDO₂ in their study.

MDA, an important decomposition product of lipid peroxides, is an indirect measure of free radical activity.^{6,16} In the control group, there was a statistically very significant (p<0.001) increase in MDA levels but in the study group there was a non-significant decrease. Thus in the postoperative period, the MDA levels were significantly higher in the control group (p=0.033), implying an attenuated oxidative injury in the NAC treated group. Cakir O et al.,¹⁰ and Kretzschmar et al.,⁷ also had observed a significantly higher MDA levels in the control group and no change in NAC treated group. In control group, there was a statistically very significant (p<0.001) reduction in GSH levels, thereby implying depletion of plasma antioxidants due to oxidative injury. In study group, there was a statistically very significant rise (p=0.001) in GSH levels, implying the role of NAC as a GSH precursor⁷. The difference was statistically very significant (p=0.005). Kretzschmar et al.,⁷ also had observed this similar response in their study.

To conclude, even OPCABG is associated with significant oxidative stress. Administration of N-acetylcysteine, by replenishing the glutathione stores attenuates this stress response, and thereby improves pulmonary function and systemic oxygenation. But, there was no difference in terms of ventilation time. However, further studies are needed to appreciate its use in OPCABG.

The nature of these oxidative events lead to depletion of plasma antioxidants.^{5,6} To counterbalance this sequence of events and diminish oxidative injury, several studies have investigated and recommended the use of antioxidant supplements.¹⁸ To prevent elevations in proinflammatory cytokines and complement activation during cardiac surgery, several agents viz. Steroids,²³ aprotinin,¹⁶ pentoxiphylline,²⁴ N-acetylcysteine were tried for their beneficial role.

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Variables	Control	Study	p value
Age	56.48±6.69	59.76±8.05	0.496
Weight	65.52±10.76	63.04±9.82	0.399
Height	162.92±8.75	162.96±9.98	0.988

Table 1: Demographic Profile

Sex	Control	Study	p value
Male	21	18	0.496
Female	4	7	
Total	25	25	

Table 2: Sex Distribution

Mean duration(min)	Control	Study	p value
Surgery	325.8±69.637	345.0±66.427	0.3079
Mechanical ventilation	1220.60±186.057	1159.80±233.419	0.2763

Table 3: Duration of surgery and ventilation

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Duration(hours)	Control	Study	p value
Pre-incision	9.36±1.96	10.28±1.86	0.095
0	9.28±1.21	8.12±1.99*	0.015*
4	9.64±2.27	7.88±1.72*	0.003*
8	9.44±2.10	8.08±1.44*	0.010*
12	9.27±1.88	8.12±1.27*	0.036*
16	10.57±1.81	8.75±0.95*	0.099

Table 4: PCWP (mmHg)

*Statistically significant.

Duration (hours)	Control	Study	p value
Preincision	22.12±2.97	23.20±3.96	0.282
0	22.44±4.11	23.52±5.02	0.409
4	23.64±4.05	22.96±4.67	0.585
8	24.68±3.76	23.12±4.16	0.171
12	23.68±4.44	23.28±4.04	0.767
16	21.86±5.64	22.50±1.91	0.833

Table 5: PAP-SYSTOLE (mmHg)

Duration (hours)	Control	Study	p value
Pre-incision	9.08±2.88	10.32±2.23	0.096
0	11.08±2.76*	9.60±2.29	0.045*
4	11.96±3.14*	10.16±2.34	0.026*
8	12.64±2.39*	10.60±2.10	0.002*
12	11.73±2.72*	11.12±2.71	0.492
16	11.71±1.89*	12.00±1.63	0.807

Table 6: PAP-DIASTOLE (mmHg)

*Statistically significant.

Duration (hours)	Control	Study	p value
Pre-incision	31.55±5.75	32.80±8.05	0.530
0	29.27±6.63	28.99±8.78	0.899
4	26.47±5.97*	29.12±8.18	0.198
8	27.21±5.61*	30.12±8.91	0.002*
12	28.63±8.49	28.73±6.94*	0.967
16	30.28±6.36	29.32±5.88	0.810

Table 7: Cdyn (ml/cm of H₂O)

* Statistically significant.

Duration (hours)	Control	Study	p value
Pre-incision	37.16±7.43	38.65±10.39	0.561
0	36.68±8.81	38.50±10.69	0.515
4	32.94±7.20*	40.84±12.74	0.010*
8	34.10±8.84	41.64±12.41	0.017*
12	36.66±10.41	37.36±11.53	0.844
16	38.00±9.36	42.14±14.53	0.575

Table 8: Cstat (ml/cm of H₂O)

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* Statistically significant.

Duration (hours)	Control	Study	p value
Pre-incision	85.99±37.08	80.56±30.56	0.575
0	353.63±61.71*	315.25±51.35*	0.021*
4	122.66±33.4*	102.92±22.19*	0.017*
8	110.48±18.26*	103.95±21.45*	0.252
12	118.43±24.37*	108.24±17.13*	0.152
16	146.68±19.76*	123.71±10.37*	0.062

Table 9: A-aDO₂ (mmHg)

* Statistically significant.

	Control	Study	p value
Pre	1.40±0.63	1.70±0.87	0.164
Post	2.26±1.03	1.58±1.12	0.033*
p value	< 0.001*	0.569	

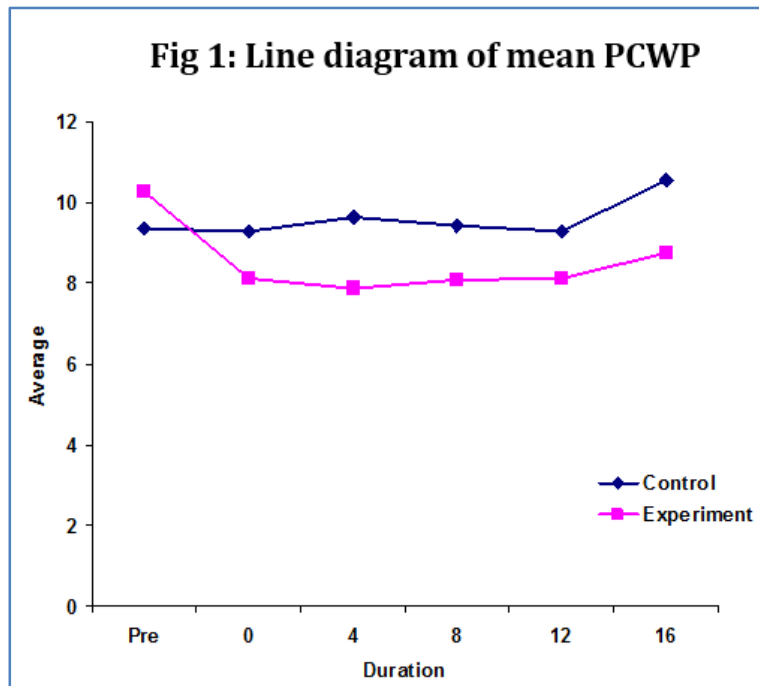
Table 10: MDA (nmol/ml)

*Statistically significant

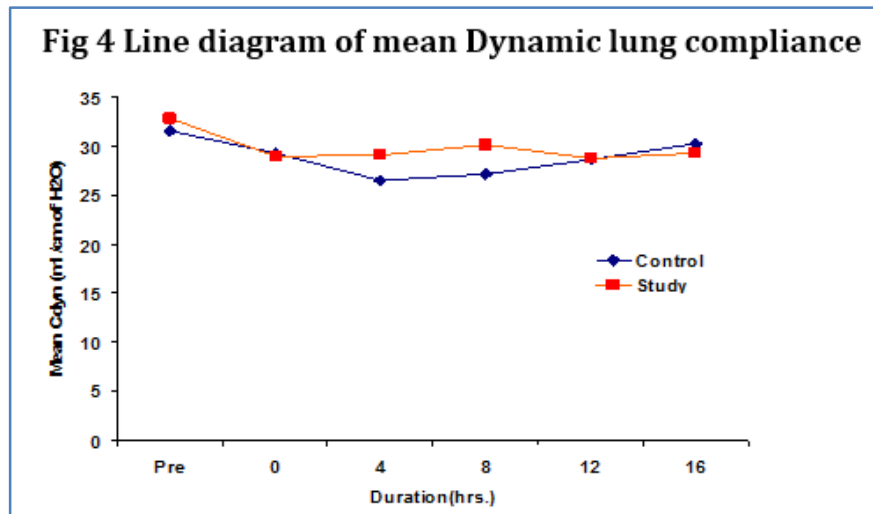
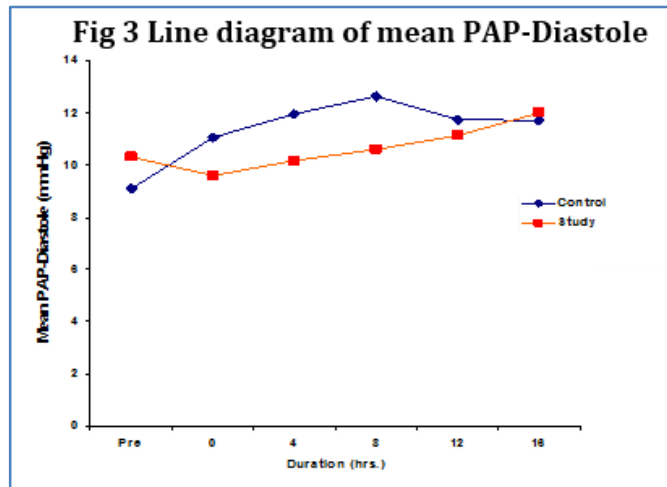
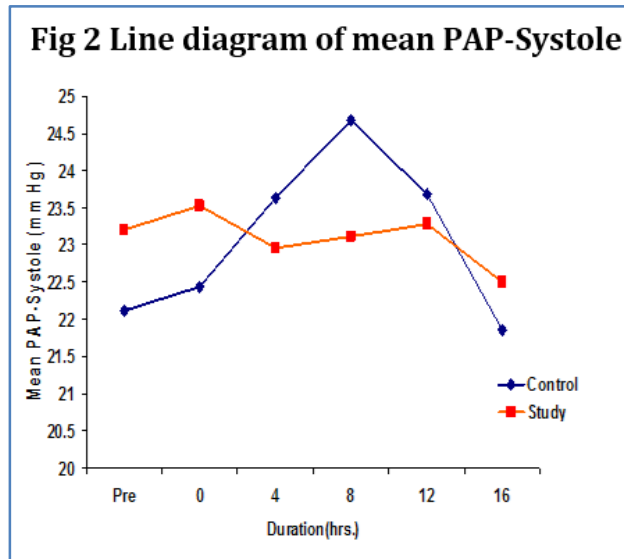
	Control	Study	p value
Pre	32.79±15.78	28.18±10.14	0.225
Post	24.25±11.56	33.82±11.70	0.005*
P value	< 0.001*	0.001*	

Table 11: GSH (nmol/ml)

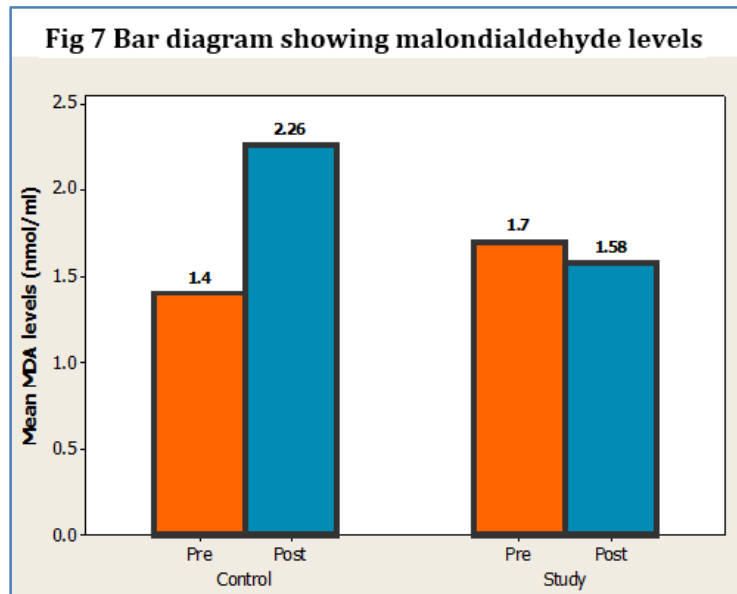
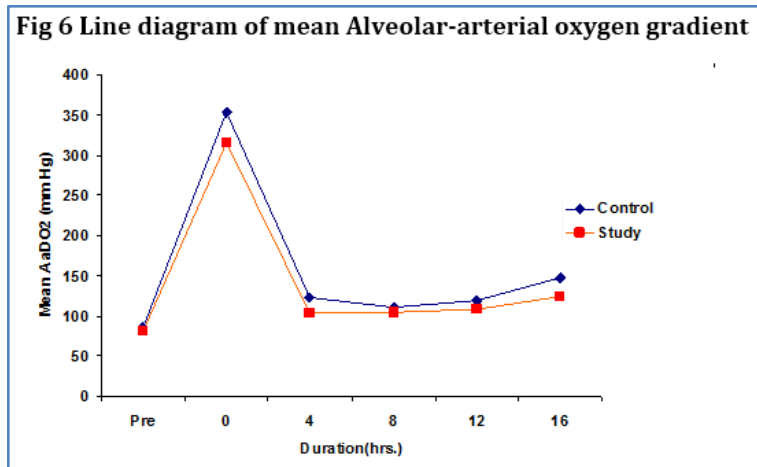
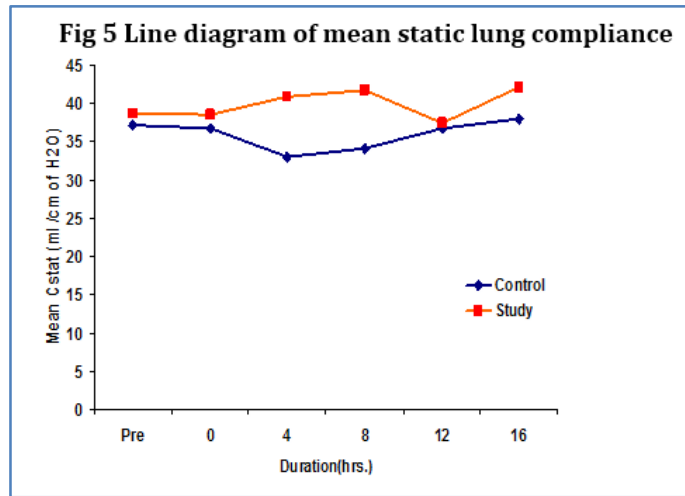
* Statistically significant.

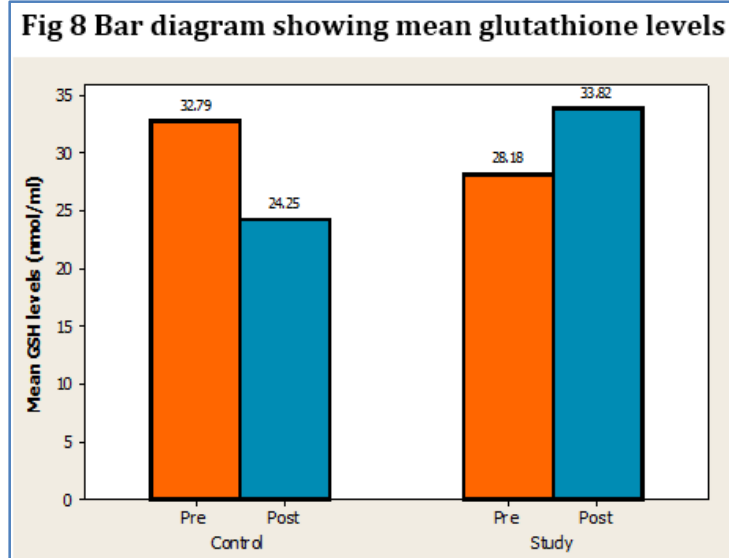


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FINANCIAL OR OTHER**COMPETING INTERESTS:** None**NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:**

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Date of Submission: 10/09/2015.
 Date of Peer Review: 11/09/2015.
 Date of Acceptance: 23/09/2015.
 Date of Publishing: 29/09/2015.