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ORIGINAL ARTICLE

EFFECT OF N-ACETYLCYSTEINE ON OXIDATIVE STRESS IN PATIENTS UNDERGOING OFF PUMP CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT: OBJECTIVE: Increasingly used Off Pump Coronary Artery Bypass Grafting (OPCABG) has significantly reduced the oxidative stress and decreased the inflammatory response associated with the use of Cardiopulmonary by Pass (CPB). However, OPCABG is associated with significant oxidative stress and its associated complications. This present study is a prospective, randomized, double blind investigating the effects of N-acetylcysteine (NAC), a potent anti-oxidant on oxidative stress 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 corresponding time. At the end of surgery, all the patients were shifted to intensive care unit (ICU) and were extubated at the earliest possible time. Malondialdehyde (MDA), a marker of free radical injury and Glutathione (GSH) Levels were assayed from the 2 blood samples obtained (First sample immediately following induction and the second immediately after shifting to ICU). **RESULTS:** Demographic profile, pre-incision clinical and biochemical values were comparable in both the groups. 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:** These results revealed that OPCABG was associated with significant oxidative response and the administration of N-Acetylcysteine attenuates this stress response by replenishing the Glutathione stores.

KEYWORDS: OPCABG, Oxidative stress, Free radicals, Glutathione, N-Acetylcysteine, Malondialdehyde.

INTRODUCTION: Concerns regarding the complications and costs surrounding the use of CPB have led to renewed interest in OPCABG techniques. Though it was initially claimed that OPCABG was associated with reduced cytokine response when compared to on pump CABG,[1-3] subsequent studies have shown that similar degrees of oxidative injury occurs in both OPCABG and conventional CABG group of patients.[4,5]

Oxidative stress results from an imbalance between local anti-oxidant defences and formation of reactive oxygen-derived free radicals. It has been proposed that increased free radical activity represents a potential risk for myocardial and pulmonary complications. These oxidative events leads to depletion of plasma antioxidants.[6,7] To overcome such events and diminish oxidative injury, several studies have investigated and recommended the use of antioxidant supplements.[8,9]

Glutathione, in its reduced form (GSH) plays a central role in cellular defence against specific Reactive oxygen species (ROS), and also acts extracellularly, either directly or via the glutathione peroxidase catalysis, to scavenge the generated ROS. Tissue ischemia depletes intracellular GSH.

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By maintaining high cellular GSH levels, the magnitude of the destructive potentials of ROS can be reduced.

N-acetylcysteine (NAC), a low molecular weight thiol compound, exhibits both direct and indirect antioxidant properties. It acts as a GSH precursor,[10,11] by providing the necessary compound cysteine, a rate-limiting factor in the biosynthesis of GSH. Many studies have supported the free radical scavenging property of NAC,[10,12-14] and its role in improving systemic oxygenation.[10,15-16]

This prospective clinical study was carried out to examine the effects of NAC on oxidative stress in patients undergoing OPCABG.

AIMS AND OBJECTIVES: To assess the oxidative stress with off pump coronary artery bypass grafting surgery and the role of N-acetylcysteine in attenuating this stress response.

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 30-70yrs.
- 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.

ANAESTHESIA AND POSTOPERATIVE CARE: Preoperative assessment and evaluation was done for all the patients. Anti-platelet agents were stopped 5 days before the surgery and anti-diabetic drugs were stopped the night before surgery. Other medications were continued up to the morning of surgery. All the patients received standard anesthesia according to the clinical routine at our department. They were premedicated with Inj. Pethidine (1mg/kg) and Inj. Promethazine (0.5mg/kg) intramuscularly one hour before the scheduled time of surgery.

On arrival into the theatre, all standard 'American Society of Anaesthesiologists' non-invasive monitoring and peripheral intravenous and right radial arterial catheter were placed. Anaesthesia was induced using Fentanyl (5µg/kg) and Thiopentone (5mg/kg), and endotracheal intubation was facilitated with Suxamethonium (1.5mg/kg). After confirmation of the correct position of the endotracheal tube placement, Vecuronium (0.1mg/kg) was given. Anaesthesia was maintained with 66%nitrous oxide, 33% oxygen, continuous Propofol infusion (1-2mg/kg/hr), and Sevoflurane.

Intermittent boluses of Fentanyl, Midazolam and Vecuronium were given at regular intervals.

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All the patients were ventilated in volume control mode (Aestiva 5, Datex Ohmeda) to achieve target $EtCO_2$ of 30-35 mmHg. After patient stabilization and positioning, nasogastric tube, Foley's catheter and temperature probe (Nasopharyngeal) were inserted. A Swan-Ganz catheter (Thermodilution 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.

After completion of CABG, Propofol infusion was stopped and patients were transferred to the ICU, where all the patients received standard post-operative care. 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. Postoperative pain relief was achieved with intravenous Fentanyl infusion (0.75µg/kg/hr) and intermittent boluses of Fentanyl, as and when required. 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°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). To provide better access to lateral and posterior target vessels, the pericardium was retracted by two or three deep sutures and two sponges were placed under the heart. An intracoronary shunt tube was used to maintain distal perfusion. Silicone snare sutures were placed proximal to the anastomoses, in order to provide a bloodless field. 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: Mixed venous blood were sampled from the Swan Ganz catheter just before the administration of the study drug, and at arrival in the ICU. The obtained heparinized blood was immediately centrifuged at 3,000 rpm for 10 min, and the plasma samples were stored at – 80°C for the analysis of malondialdehyde and glutathione levels. Plasma MDA levels was estimated by the method of Yagi,[17] and plasma GSH levels was measured according to the method of Beutler and Kelley.[18]

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±standard deviation. Statistical analysis was performed using the paired 't' test for numeric variables and categorical variables by Chi-square and Fisher's exact test. Statistical significance was assumed when $P < 0.05$.

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Observations: Fifty patients scheduled to undergo CABG were included in this randomized placebo-controlled study. Demographic profile of both control and study groups were comparable and the difference was not statistically significant (Table 1, 2). Similarly duration of surgery and mechanical ventilation were comparable between both the groups (Table 3).

The biochemical parameters–Malondialdehyde and Glutathione levels were analyzed once before the study drug administration, and at arrival in the ICU.

Malondialdehyde: Pre-incision levels of MDA were 1.40±0.63 and 1.70±0.87 nmol/ml of plasma in control and study groups respectively, which shows statistically non-significant difference (p=0.164). In the control group, there was an increase in the levels of MDA in the postoperative period when compared to pre-incision levels. It was statistically very significant (p<0.001). Whereas in study group, there was a decrease in the postoperative period, and was not statistically significant (p=0.569) (table 4). While comparing both the groups in the postoperative period, the MDA levels were significantly higher in the control group (p=0.033).

Glutathione: Pre-incision values of GSH levels were comparable and the difference was not statistically significant (p=0.225). They were 32.79±15.78 and 28.18±10.14 nmol/ml in control and study groups respectively. In control group, there was a reduction in GSH levels in the postoperative period, when compared to pre-incision values. They were statistically very significant (p<0.001). Whereas in study group, there was a rise in GSH levels in the postoperative period, when compared to pre-incision values (table 5). The increase was statistically very significant (p=0.001). While comparing both the groups in the postoperative period, there was a significant rise in GSH levels in study group, in contrast to significant decline in control group. The difference was statistically very significant (p=0.005).

DISCUSSION: With the re-emergence of OPCABG, interest has grown in the isolated effects of CPB on oxidative stress. Earlier, few studies had observed reduced cytokine response and significantly lower number of circulating neutrophils and monocytes as well as levels of neutrophil elastase, following OPCABG compared to on-pump CABG.[19,20] But Fransen et al,[21] 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 per se and both OPCABG and conventional CABG produces similar degrees of oxidative injury.[4,5,22]

Oxidative stress results from an imbalance between local antioxidant defences and formation of reactive oxygen derived free radicals, which are generated and released by activated inflammatory cells. ROS are highly reactive and can induce lipid peroxidation (oxidation of membrane phospholipids) and the accumulation of their products including MDA,[7,16,23,24] 4-hydroxy-2-nonenal, acrolein, hydroperoxides[6] and F_2-isoprostanes[7,10,14] acts as an indirect measure of free radical activity.[8,9,25]

Experiments have demonstrated that oxidative stress may cause alterations in essential components of the lung, contributing to pathological abnormalities and functional changes. ROS can reduce the synthesis as well as can fragment elastin and collagen. In addition, ROS may affect the structure of components of the extracellular matrix, such as hyaluronate. Lipid peroxidation may initiate the release of arachidonic acid from membrane phospholipids, leading to release of prostaglandins and leukotrienes and also increase Interleukin (IL)-1 and IL -8 production,[26] in several cell systems.

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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 may be inactivated by ROS. Sequestration of neutrophils may occur in the lung microcirculation. The increased numbers and prolonged presence of these inflammatory cells contributes to the cycle of locally increased ROS production, attraction of new inflammatory cells, etc. Finally, oxidative stress activates the transcription factor nuclear factor-κB (NF-κB), which switches on the genes for Tumor Necrosis Factor (TNF)-α1, IL-8 and other inflammatory proteins, enhancing inflammation.[27]

To counterbalance this sequence of events and diminish oxidative injury, several studies have investigated and recommended the use of antioxidant supplements,[8,9] viz. Steroids,[28] aprotinin,[23] pentoxiphylline,[29] N-acetylcysteine.

Sustained oxidative challenge results in depletion of GSH and other antioxidants. By maintaining high cellular GSH levels, the magnitude of the destructive potentials of ROS can be reduced. Glutathione is an important water-phase antioxidant and essential cofactor for antioxidant enzymes catalase and Superoxide dismutase. The oxidized glutathione (GSSG)/reduced glutathione (GSH) ratio may be a sensitive indicator of oxidative stress. Glutathione (GSH) has facile electron-donating capacity, linked to its sulfhydryl (-SH) group and hence called "Reducing equivalents".

Through its significant reducing power, it contributes to the recycling of other antioxidants that have become oxidized. GSH is synthesized intracellularly from the amino acids, glycine and glutamate, and the thiol-providing amino acid cysteine. Although glutamate and glycine are abundant intracellularly, an adequate transmembranous supply of cysteine becomes a rate-limiting factor in the biosynthesis of GSH.

In the case of depletion of GSH levels or increased demand, it may be increased by delivering additional cysteine. However, it is impossible to administer the active form of cysteine, l-cysteine, because of low intestinal absorption, poor water solubility and rapid hepatic metabolism. NAC, with the acetyl radical linked to amine function, eliminates these disadvantages. NAC is a thiol [Sulfhydryl (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 subsequently deacylated to form cysteine.

NAC exhibits both direct and indirect antioxidant properties. NAC exerts an indirect antioxidant effect related to its role as a GSH precursor,[10,11] as discussed above. It exerts its direct effect through its free thiol group, which is capable of interacting with the electrophilic groups of ROS.[30] Many studies have supported the use of NAC, as a free radical scavenger, especially in cardiac surgeries.[10,12-14] As a source of sulfhydryl 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-κB. It is well documented in renal function preservation and lung function preservation when given pre and peri procedurally.

Possible adverse reactions include an urticarial rash, nausea, and vomiting and an anphylactoid reaction (Involving hypotension, tachycardia, bronchospasm and facial edema). Medved et al.,[11] in their study found that NAC infusion did not induce any severe adverse reactions. After a single intravenous dose of NAC, plasma concentration declined in a poly-exponential decay manner with mean terminal half-life T1/2 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.[10,31] and septic shock patients.[32]

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.

MDA, an important decomposition product of lipid peroxides, is an indirect measure of free radical activity.[7,23,24] In the control group, there was a statistically very significant ($p<0.001$) increase in the levels of MDA in the postoperative period but in the study group there was a decrease in the postoperative period, and was not statistically significant ($p=0.569$). 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[16] in their study on the effect of NAC on pulmonary function in patients undergoing CABG with CPB, had also observed significantly higher MDA levels in the control group when compared to NAC treated group. Kretzschmar et al.,[10] also had observed this similar response in their study on the effect of NAC in ischemia-reperfusion syndrome in patients undergoing abdominal aortic aneurysmectomy.

In control group, there was a statistically very significant ($p<0.001$) reduction in GSH levels in the postoperative period, 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 in the postoperative period, implying the role of NAC as a GSH precursor.[10,11] Thus in the postoperative period, there was a significant rise in GSH levels in study group, in contrast to the significant decline in control group.

The difference was statistically very significant ($p=0.005$). Kretzschmar et al.,[10] also had observed this similar response in their study on the effect of NAC in ischemia-reperfusion syndrome in patients undergoing abdominal aortic aneurysmectomy.

In summary, even OPCABG is associated with significant oxidative stress, administration of N-acetylcysteine by replenishing of the glutathione stores attenuates the stress response. However, further studies are needed to appreciate its use in OPCABG.

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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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	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 4: 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 5: GSH (nmol/ml)

* Statistically significant

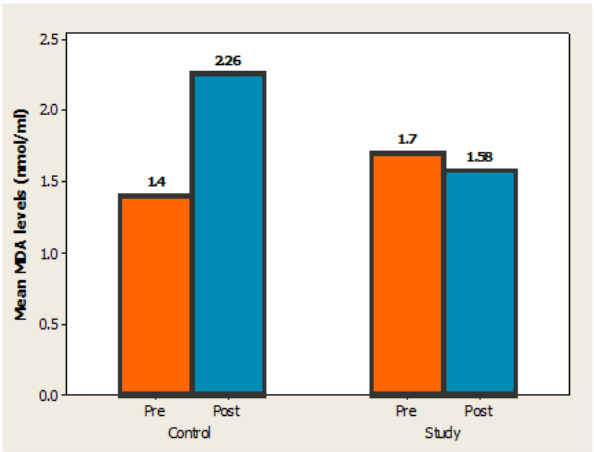

Fig. 1: Bar diagram showing malondialdehyde levels

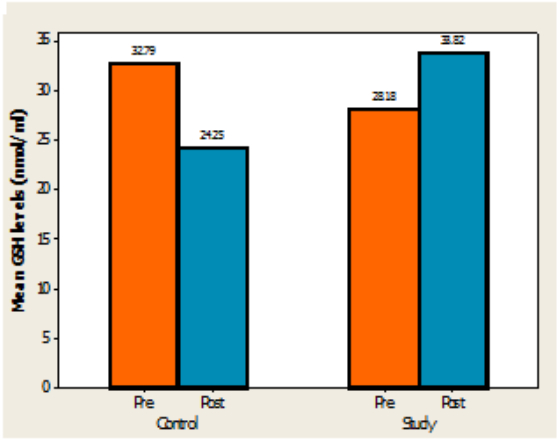

Fig. 2: Bar diagram showing mean glutathione levels

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