Original Article

Assessment Effect of N Acetyl Cysteine on Liver Function Test in Patient with Elective Coronary Artery Bypass Grafting with Cardiopulmonary Bypass

Mohammad Fathi[1], Maryam Baniani[1], Mohammad Forouzeshfard[2], Samira Rajaei[3], Kamran Ghods[4], Ali Dabbagh[1*]

Abstract

Background: Liver ischemic insults are important sources of liver injuries leading to production of reactive oxygen species (ROS) and mediating liver cell injury. Glutathione mediated mechanisms are among the most important defense mechanisms of the liver; N-acetylcysteine (NAC) provides cysteine for glutathione defense mechanisms. Patients undergoing cardiac surgery are at increased risk of liver ischemia. This study was performed to assess the role of NAC in prevention of liver ischemia.

Materials and Methods: In a double blind, randomized clinical trial, 90 patients entered the study in two groups (45 in each). Patients in the NAC group received 150 mg/Kg NAC after induction of anesthesia and the other group, the same volume of placebo. Serum levels of aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and bilirubin were checked before and after the surgery. ANOVA was used for data analysis and p value less than 0.05 was considered statistically significant.

Results: No difference between the two groups regarding basic variables; however, the postoperative values of AST and ALT were lower in the NAC group with statistically significant difference. Also, postoperative levels of total bilirubin were lower in the NAC group compared with the control group; a statistically significant difference.

Conclusion: Patients undergoing CABG are advised to receive prophylactic 150 mg/Kg NAC to improve their postoperative levels of AST, ALT and bilirubin.

Keywords: glutathione antioxidant mechanism, N-acetylcysteine; Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), bilirubin, liver ischemia.

1. Anesthesiology Research Center, Cardiac Anesthesiology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Anesthesiology Department, Semnan University of Medical Sciences, Semnan, Iran
3. Immunology Department, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Surgery, Semnan University of Medical Sciences, Semnan, Iran

Corresponding Author:
Ali Dabbagh, MD; Professor, Fellowship in Cardiac Anesthesiology, Anesthesiology Research Center, Cardiac Anesthesiology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: alidabbagh@sbmu.ac.ir
Received: May 31, 2016
Accepted: June 7, 2016

Please cite this article as: Fathi M, Baniani M, Forouzeshfard M, Rajaei S, Ghods K, Dabbagh A. Assessment Effect of N Acetyl Cysteine on Liver Function Test in Patient with Elective Coronary Artery Bypass Grafting with Cardiopulmonary Bypass. J Cell Mol Anesth. 2016;1(3):103-8.

Introduction

Liver ischemic insults are important source of liver injuries; mainly through inflammatory pathways and oxidative stress chain of injury which leads to production of reactive oxygen species (ROS); these ROS's mediate endoplasmic reticulum stress response leading to liver cell injury (1-4). One of the most

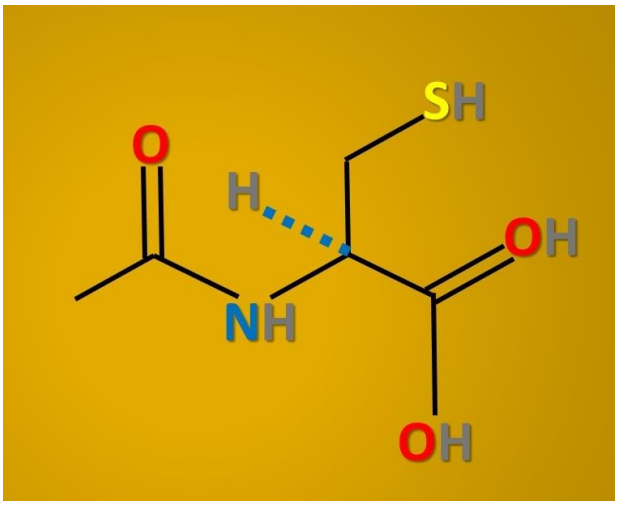

Figure 1. N Acetylcysteine (NAC) molecule.

important defense mechanisms that is used by liver is the glutathione mediated mechanisms; N-acetylcysteine (NAC) provides cysteine for defense mechanisms exerted by glutathione (2, 5-9). NAC has similar structure with cysteine (Figure 1), being an appropriate lysine releasing agent which supports the glutathione mediated protective mechanisms (10).

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at increased risk of mesenteric ischemia. Many strategies have been used for organ protection in these groups of patients; however, some controversies exist. Among the organs at risk of ischemia is the liver; this is why liver protection is always at the top list of organs aimed to be protected in such patients. Serum levels of Aspartate aminotransferase i.e. AST (formerly known as SGOT) and Alanine aminotransferase i.e. ALT (formerly known as SGPT) are still among the very sensitive and predictive biomarkers of liver injury.

The effects of NAC on organ protection have been studied in a number of organs (11-15); however, assessment of NAC effects on liver function in CABG patients has not been studied yet. So, this randomized clinical trial was designed and performed to assess the role of NAC in prevention of liver ischemia monitored by serum levels of Aspartate aminotransferase i.e. AST (formerly known as SGOT), Alanine aminotransferase (formerly known as SGPT) and total bilirubin before and after CABG with CPB.

Methods

The research project was approved by the ethics committee on research studies, School of Medicine, SBMU, Tehran, Iran; Numbered M-540 and dated January 17, 2015.

The main goal of the study was to assess the effects of NAC on liver function test after CABG with CPB; however, the subordinate goals were measuring liver function tests in the NAC group before and after CABG with CPB and comparing with liver function tests in the control group.

Among the total of patients entered the cardiac operation room in Modarres hospital, Tehran, Iran, for CABG with CPB in 2015, a total of 90 patients were selected based on inclusion and exclusion criteria.

Inclusion criteria for the study were: Elective CABG using CPB, Age 30-65 years, Heart failure was ruled out (right sided or left sided, including low left ventricular ejection fraction, i.e. preoperative LVEF<25%), Normal renal function, Normal hepatic function, Diabetes mellitus was ruled out, Treated or controlled hypertension, Treated or controlled thyroid status, Treated or controlled rhythm disorders, Treated or controlled hepatic status, History of drug or substance abuse was ruled out.

And exclusion criteria were: Emergent or urgent progress of disease after primary allocation, Patient refusal to continue study, Newly administered steroids, anti-inflammatory agents or anticonvulsants or other drugs affecting liver function.

Sample size determination was done after a power analysis: power= 0.8; β= 0.2; α= 0.02, using sample size software (PASS 2005, NCSS LLC, Kaysville, Utah, USA). Then, using this equation: $n= 2[(Z\beta+Z\alpha)\ \sigma/\Delta]^2$ and considering the following items, the final sample size in each group was 44 which was rounded to 45 in each group (16, 17):

- $Z\alpha= 1.96$
- $Z\beta= 0.84$
- σ (estimated standard deviation based on similar studies) = 5
- Δ= the estimated effect size (i.e. the minimal difference desired between the two study interventions or the clinical outcomes of the two groups)= 3

The sample size (i.e. 90 study patients) was randomly assigned into two study groups using the table of random numbers (simple randomization). And all continuous data with normal distribution were expressed as mean±SD.

All the patients entered the operating room after a primary anesthesia visit and also, a blood sampling to assess baseline serum levels of AST, ALT and bilirubin. The anesthesia method, the surgeon and the cardiopulmonary bypass protocol was planned to be as similar as possible. Total bypass time and aortic cross clamp time, also, baseline patient characteristics were recorded. The AC group received 150 mg/Kg NAC through the central line after induction of anesthesia and intubation; while the control group received the same volume of normal saline as placebo.

The patients were transferred to the cardiac intensive care unit afterwards and then, if they matched the extubation criteria, were weaned and extubated.

Also, ANOVA was used for comparison between groups and post-hoc analysis for further analysis. Also, Chi-square, and Fisher exact tests were used. All statistical analyses were performed by SPSS software (Version 11.5, SPSS, Inc, Chicago, IL). Meanwhile a P value less than 0.05 was statistically considered significant.

Results

There was no statistically significant difference between the two groups regarding basic variables (Table 1).

The results of liver function tests were compared and are demonstrated in Tables 2-4. AST levels were not different between the two groups in the preoperative period. However, postoperative results were significantly different. Post hoc analysis demonstrated difference between the groups as demonstrated in Table 2 with significantly lower postoperative results in the NAC group.

ALT levels were not different between the two groups in the preoperative period. However, postoperative results were significantly different. Post hoc analysis demonstrated difference between the groups as demonstrated in Table 3 with significantly lower postoperative results in the NAC group.

Bilirubin levels were not different between the two groups in the preoperative period. However, postoperative results were significantly different. Post hoc analysis demonstrated difference between the groups as demonstrated in Table 4 with significantly higher postoperative results in the control group.

Table 1: Basic Variables in the Two Groups.

	NAC group N=45	Control group N=45	P value
Gender (M/F)	28/17	30/15	>0.05
Age	53±8	51±10	>0.05
Weight	73±11	71±12	>0.05
LVEF, %	43±7	45±6	>0.05
CPB time	96±14	93±16	>0.05
ACC time	51±8	49±9	>0.05

LVEF: left ventricular ejection fraction; CPB: cardiopulmonary bypass; ACC: aortic cross clamp

Discussion

The current study demonstrated improved liver function tests in CABG patients with CPB receiving NAC compared with the control group. Also, less increase in postoperative bilirubin was seen in the NAC group. Decreased AST and ALT after CABG in the NAC group is remarkably important, leading to real outcome improvements in our study; especially in patients who are at risk of decreased visceral perfusion during the operation (especially during CPB) with real risk of ischemia and injury to the liver (1); though in other clinical states there are some controversies in favor or against NAC (18, 19). However, our findings demonstrated that NAC improvement in LFT's is a

Table 2: AST levels (SGOT) in the two groups.

	NAC group N=45	Control group N=45
Preoperative AST	28±8 *	30±9
Postoperative AST	19±6 *	38±14 *

* P value=0.01; post hoc analysis demonstrated difference between the groups with asteroid

Table 3: ALT levels (SGPT) in the two groups.

	NAC group N=45	Control group N=45
Preoperative ALT	32±9 *	31±10
Postoperative ALT	21±7 *	40±12 *

* P value=0.01; post hoc analysis demonstrated difference between the groups with asteroid

very impressive outcome which could help us prevent ischemic insults to the liver tissue. This is primarily due to the effects of NAC on glutathione system which is a liver protective mechanism; however, anti-inflammatory effects of NAC may have roles; which were not studied here.

These results were in concordance with other studies assessing the effect of NAC on lung function (10-13, 20, 21); these researches have demonstrated the antioxidant and anti-inflammatory role of NAC in organ protection in many organ systems including liver; a finding in concordance with our results (22). On the other hand, the results of this study were in concordance with other studies that have assessed the effects of NAC on liver function. Most of the studies assessing the role of NAC on liver function deal with the role of NAC on liver protection during drug induced liver injury (DILI) especially due to acetaminophen overdose (19, 23-25). However, there are studies assessing the protective effects of NAC during anesthesia, both in liver transplant and other surgical procedures under general anesthesia; which are in favor of improved liver function with administration of NAC (26-28).

Based on our study, patients undergoing CABG are advised to receive prophylactic NAC to improve their postoperative levels of AST, ALT and bilirubin.

The lab tests in this study are both sensitive and specific; however, some studies have used micro RNA assays for assessment of liver function; which assess cellular mechanisms of liver function; so, if we could use these tests, our study could be much more valuable; however, we could not use such techniques in our patients.

Conclusion

On the other hand, anti-inflammatory effects of NAC were not assessed in our study; if they were

Table 4: Total bilirubin levels in the two groups.

	NAC group N=45	Control group N=45
Preoperative Total bilirubin	0.73±0.08	0.72±0.09 *
Postoperative Total bilirubin	0.71±0.06	1.02±1.1 *

* P value=0.03; post hoc analysis demonstrated difference between the groups with asteroid

measured, they could help us detect the anti-inflammatory effects of NAC on liver function in these patients.

Acknowledgment

The authors would like to acknowledge the kind help of all personnel of Anesthesiology Research Center, SBMU, Tehran, Iran; also, the kind help of physicians and nurses in OR and CVICU of Modarres Hospital, SBMU, Tehran, Iran is highly acknowledged.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. de Andrade KQ, Moura FA, dos Santos JM, de Araujo OR, de Farias Santos JC, Goulart MO. Oxidative Stress and Inflammation in Hepatic Diseases: Therapeutic Possibilities of N-Acetylcysteine. International journal of molecular sciences. 2015;16(12):30269-308.
2. Sun Y, Pu LY, Lu L, Wang XH, Zhang F, Rao JH. N-acetylcysteine attenuates reactive-oxygen-species-mediated endoplasmic reticulum stress during liver ischemia-reperfusion injury. World journal of gastroenterology. 2014;20(41):15289-98.
3. Sener G, Tosun O, Sehirli AO, Kacmaz A, Arbak S, Ersoy Y, et al. Melatonin and N-acetylcysteine have beneficial effects during hepatic ischemia and reperfusion. Life sciences. 2003;72(24):2707-18.
4. Reyes RC, Cittolin-Santos GF, Kim JE, Won SJ, Brennan-Minnella AM, Katz M, et al. Neuronal Glutathione Content and Antioxidant Capacity can be Normalized In Situ by N-acetyl Cysteine Concentrations Attained in Human Cerebrospinal Fluid. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2016;13(1):217-25.
5. Kerksick C, Willoughby D. The antioxidant role of glutathione and N-acetyl-cysteine supplements and exercise-induced oxidative stress. Journal of the International Society of Sports Nutrition. 2005;2:38-44.
6. Kerksick C, Willoughby D. The Antioxidant Role of Glutathione and N-Acetyl-Cysteine Supplements and Exercise-Induced Oxidative Stress. Journal of the International Society of Sports Nutrition. 2005;2(2):1-7.
7. Matuszczak Y, Farid M, Jones J. Effect of n-acetylcysteine on glutathione oxidation and fatigue during handgrip exercise. Muscle Nerve. 2005;32.
8. Quadrilatero J, Hoffman-Goetz L. N-Acetyl-L-cysteine prevents exercise-induced intestinal lymphocyte apoptosis by maintaining intracellular glutathione levels and reducing mitochondrial membrane depolarization. Biochem Biophys Res Commun. 2004;319.
9. Quadrilatero J, Hoffman-Goetz L. N-Acetyl-L-Cysteine inhibits exercise-induced lymphocyte apoptotic protein alterations. Med Sci Sports Exerc. 2005;37.
10. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. Brain and behavior. 2014;4(2):108-22.
11. Forgiarini LF, Forgiarini LA, Jr., da Rosa DP, Silva MB, Mariano R, Paludo Ade O, et al. N-acetylcysteine administration confers lung protection in different phases of lung ischaemia-reperfusion injury. Interact Cardiovasc Thorac Surg. 2014;19(6):894-9.
12. Sanguinetti CM. N-acetylcysteine in COPD: why, how, and when? Multidisciplinary respiratory medicine. 2015;11:8.
13. Laubach VE, Sharma AK. Mechanisms of lung ischemia-reperfusion injury. Current opinion in organ transplantation. 2016;21(3):246-52.
14. Lancaster EM, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. Archives of toxicology. 2015;89(2):193-9.
15. Chayanupatkul M, Liangpunsakul S. Alcoholic hepatitis: a comprehensive review of pathogenesis and treatment. World journal of gastroenterology. 2014;20(20):6279-86.
16. Friede T, Kieser M. Sample size recalculation in internal pilot study designs: a review. Biometrical journal Biometrische Zeitschrift. 2006;48(4):537-55.
17. Schafer H, Timmesfeld N, Muller HH. An overview of statistical approaches for adaptive designs and design modifications. Biometrical journal Biometrische Zeitschrift. 2006;48(4):507-20.
18. Chughlay MF, Kramer N, Spearman CW, Werfalli M, Cohen K. N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review. Br J Clin Pharmacol. 2016;81(6):1021-9.
19. Chughlay MF, Kramer N, Werfalli M, Spearman W, Engel ME, Cohen K. N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review protocol. Systematic reviews. 2015;4:84.
20. Wang Q, Hou Y, Yi D, Wang L, Ding B, Chen X, et al.

Protective effects of N-acetylcysteine on acetic acid-induced colitis in a porcine model. BMC gastroenterology. 2013;13:133.
21. Cuzzocrea S, Mazzon E, Dugo L, Serraino I, Ciccolo A, Centorrino T, et al. Protective effects of n-acetylcysteine on lung injury and red blood cell modification induced by carrageenan in the rat. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001;15(7):1187-200.
22. Guo H, Zhang J, Boudreau M, Meng J, Yin JJ, Liu J, et al. Intravenous administration of silver nanoparticles causes organ toxicity through intracellular ROS-related loss of inter-endothelial junction. Particle and fibre toxicology. 2016;13:21.
23. Sarges P, Steinberg JM, Lewis JH. Drug-Induced Liver Injury: Highlights from a Review of the 2015 Literature. Drug Saf. 2016.
24. Ghannoum M, Kazim S, Grunbaum AM, Villeneuve E, Gosselin S. Massive acetaminophen overdose: effect of hemodialysis on acetaminophen and acetylcysteine kinetics. Clinical toxicology (Philadelphia, Pa). 2016:1-4.
25. Cairney DG, Beckwith HK, Al-Hourani K, Eddleston M, Bateman DN, Dear JW. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. Clinical toxicology (Philadelphia, Pa). 2016;54(5):405-10.
26. Ibrahim ES, Sharawy A. Effectiveness of intravenous infusion of N-acetylcysteine in cirrhotic patients undergoing major abdominal surgeries. Saudi J Anaesth. 2015;9(3):272-8.
27. Aksit H, Bildik A. Determination of DNA damage in experimental liver intoxication and role of N-acetyl cysteine. Cell biochemistry and biophysics. 2014;70(2):1119-25.
28. Santiago FM, Olmedo C, Muffak-Granero K, Comino A, Villar JM, Garrote D, et al. Intraoperative pH values after N-acetylcysteine administration during liver transplantation. Transplantation proceedings. 2010;42(8):3164-6.