The effect of intravenous infusion of N-acetyl cysteine in cirrhotic patients undergoing liver resection: A randomized controlled trial

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Abstract

Background and Aims: Liver resection can lead to hepatocellular dysfunction. The aim was to evaluate the effect of N-acetyl cysteine (NAC) on liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), international normalized ratio (INR), C-reactive protein (CRP), and intercellular adhesion molecule 1 (ICAM 1) in cirrhotic patients undergoing liver resection.

Material and Methods: A randomized controlled trial (RCT), Pan African Clinical Trial registry (PACTR201508001251260). 60 Child A patients were studied. NAC group (n = 30) received intravenous infusion of NAC 10 g/24 h in 250 ml of 5% dextrose during surgery and for 2 days. Controls (C) (n = 30) received a similar volume of 5% dextrose. All above parameter were measured during and after surgery.

Results: ALT and AST were significantly elevated after surgery, but to a less extent with NAC versus C (day 3; 118.3 ± 18.6 vs. 145.4 ± 14.0 U/L, P < 0.01) and (121.5 ± 19.5 vs. 146.6 ± 15.1 U/L, P = 0.00), respectively. Lower serum CRP and ICAM 1 with NAC versus C on day 3 (44.2 ± 13.4 vs. 68.7 ± 48.2 mg/l, P = 0.003), (308.8 ± 38.2 vs. 352.8 ± 59.4 ng/ml, P = 0.002), respectively. Hospital stay was shorter with NAC versus C (6.1 ± 0.8 vs. 6.9 ± 1.2 days, P = 0.006). Duration of surgery, INR, and hemodynamics were comparable.

Conclusion: Prophylactic NAC in hepatic patients undergoing liver surgery attenuated postoperative increase in transaminases, ICAM 1, and CRP blood levels. The impact of these findings and the cost benefit of reduced hospital stay on enhanced recovery after surgery needs to be evaluated.

Keywords: Hepatic patients, liver resection, N-acetyl cysteine

Introduction

Hepatocellular carcinoma as a consequence of hepatitis C virus (HCV) is the main indication for liver resection in Egypt.¹,² Resection could lead to a hepatic dysfunction as a result of changes in tissue perfusion and oxygenation that affects the oxidative stress.³,⁴ Oxidative stress is equilibrium between oxidizing (lipid peroxidation) and antioxidizing factors (glutathione [GSH] system).⁵⁻⁷ N-acetyl cysteine (NAC) helps restore intrahepatic GSH stores and can downregulate adhesion molecules.⁸⁻¹¹

The primary goal is to study the effects of NAC infusion in cirrhotic patients undergoing liver resection on liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), international normalized ratio...
Material and Methods

Sixty adult patients Child–Turcotte–Pugh Classification A with cirrhosis confirmed by ultrasonography, scheduled for major liver resection, were enrolled in this double-blinded randomized controlled trial after written informed consents. The study was conducted at National Liver Institute after Local Ethics and Research Committee approval and after registration at Pan African Clinical Trial (PACTR201508001251260). Those with known allergy to NAC, and those refusing to participate in the study were excluded from the study. Pharmacy department supplied the infusions to the anesthesia department before the planned surgery; both the anesthesiologist and assessors were blind to the content of the infusion. Sealed opaque envelopes were only opened by the pharmacist to allocate the patient to his group.

Group I (NAC) received an intravenous dose of NAC (5 g, 200 mg/ml, Zambon S.P.A.,) (10 g/24 h in 250 ml of 5% dextrose each 5 g over 12 h), initiated at the time of hepatic parenchymal dissection, and continued postoperatively for 2 days.12

Group II (controls) received similar volume of glucose 5% as placebo. General anesthesia was induced with propofol 1.5–2 mg/kg and fentanyl 2 µg/kg guided with anesthesia depth monitoring (Entropy, GE, Finland). Rocuronium 0.6 mg/kg (Organon, USA) was used to facilitate endotracheal intubation after achieving maximum neuromuscular block. The lungs were ventilated to maintain normocapnia (end-expiratory partial pressure of carbon dioxide level [32–38 mm Hg] using a constant fresh gas flow of 1 L/min). Maintenance of anesthesia was performed with sevoflurane, fentanyl, and rocuronium keeping entropy reading between 40 and 60. Normothermia was achieved with a forced-air warming device (Bair Hugger, Arizant, UK). Standard monitoring for both groups included electrocardiogram, invasive arterial blood pressure through left radial artery catheter after performing modified Allen’s test, central venous pressure (7 Fr, Arrow International) was placed through the right internal jugular vein by ultrasound-guided method (SonoSite, NanoMax Ultrasound System, USA), pulse oximetry, nasopharyngeal core temperature, inspiratory and expiratory gas concentrations. After surgery, patients were transferred to the intensive care unit, with adequate pain control. The hemodynamic management consisted of maintaining the mean arterial pressure (MAP) at ≥65 mm Hg with adequate vascular filling with crystalloids and colloids (Voluven-Hydroxyethyl Starch 130/0.4, 6%), and dopamine or norepinephrine infusion were used when necessary. Incremental intravenous doses of 20 mg of furosemide were administered if urinary output was <1 ml/kg/h. Baseline liver-specific variables included etiology of chronic liver disease, Child–Pugh score.13 All data were collected by an anesthesia resident blinded to the study design and group allocation. Physiological variables recorded included heart rate (HR), mean arterial blood pressure, and daily collection of serum and plasma samples were undertaken to provide aliquots for routine coagulation and biochemistry analysis; additional aliquots were immediately stored at −80°C for subsequent analysis of serum ICAM 1.

ICAM-1 concentrations were measured by microenzyme-linked immunosorbent assay (micro-ELISA), using the micro-ELISA plate coated with monoclonal antibodies (Human Thrombomodulin Immuonassay kit, Daiichi Fine Chemical Co. Ltd., Toyama, Japan, and Cell-Free TM Human sICAM-1 ELISA, Pierce Endogen, Rockford, IL, USA), according to the manufacturer’s protocol.

Perioperative adverse or side effects such as arrhythmias, nausea, vomiting, flushing, hypotension, cough, and urticaria were all recorded. AST, ALT, serum lactate, CRP, ICAM 1, and serum phosphate were all measured at the following time: T1 – baseline before surgery, T2 – during dissection, T3 – post resection, T4 – postoperative day 1, and T5 – postoperative day 3.

Sample size and power of the study

In this study, α was set to 0.05, and maximum 13 accepted 20% with a minimum power of the study of 80%. A sample size of 30 per group was required in each group to reveal a significant difference in the primary outcome of this RCT, which is the ALT (U/L) to detect a mean difference of 20 U/L and standard deviation of 23.50 U/L and 26.0 U/L in NAC and control groups, respectively.14 Calculation of sample size was done using (IBM Statistical Package for Social Science [SPSS] Version 21, New York, USA, Sample power) software and was also confirmed using LENTHJAVA APPLETS for power and sample size (Free computer software https://homepage.divms.uiowa.edu/~rlenth/Power/index.html).15

Statistical methodology

Data were collected and entered to the computer using SPSS program for statistical analysis (Version 21).16 Data were entered as numerical or categorical as appropriate.

When Kolmogorov–Smirnov test revealed no significance in the distribution of variables, parametric statistics was carried out, while in the not normally distributed data, the nonparametric
An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

As most continuous variables were skewed, nonparametric approaches were used in the study. Baseline characteristics of quantitative variables between two groups were compared using Mann–Whitney U-test. Correction of P value for multiple testing was set to 0.01 to detect significance (Bonferroni correction of multiple comparisons). A consort flow chart will be used.

Results

Patient characteristics and duration of surgery were comparable between the studied groups as shown in Table 1 as well as the other physiological parameters as systemic haemodynamics, transesophageal Doppler variables, and oxygen delivery [Table 2].

Table 1: Demographic data and preoperative criteria in studied groups

| Variables                      | NAC (n=30) | Control (n=30) | Significance | P       |
|-------------------------------|------------|---------------|--------------|---------|
| Age (years)                   |            |               |              |         |
| Mean±SD                       | 50.2±7.1   | 51.5±8.1      | Z=0.007      | P=0.994 (NS) |
| Gender (%)                    |            |               |              |         |
| Males                         | 22 (73.33) | 22 (73.33)    | NA           |         |
| Females                       | 8 (26.67)  | 8 (26.67)     |              |         |
| BMI (kg)                      |            |               |              |         |
| Mean±SD                       | 28.4±1.4   | 28.9±2.3      | Z=0.223      | P=0.816 (NS) |
| Operative time (h)            |            |               |              |         |
| Mean±SD                       | 5.6±0.6    | 6.7±1.0       | Z=1.554      | P=0.120 (NS) |
| Liver resection of (%)        |            |               |              |         |
| Formal left hepatectomy       | 22 (73.33) | 12 (40.00)    | χ²=15.227    | P (MC)<0.001* |
| Left lateral resection        | 0          | 12 (40.00)    |              |         |
| Nonanatomical resection       | 8 (26.67)  | 6 (20.00)     |              |         |

Data are presented as mean±SD, n (%), and Mann–Whitney U-test was used comparing age, gender, BMI, and operation time. *P (significant if ≤0.01). Z=Mann–Whitney test, χ²=Pearson Chi-square. NA=Nonapplicable statistics due to exact match. NAC=N acetyl cysteine, BMI=Body mass index, SD=Standard deviation, NS=Not significant, MC=Monte Carlo, P=Probability of error

The blood levels of ALT, AST, and lactate were all significant elevated above baseline values in both groups after liver surgery, but this increase was significantly less within the NAC group as compared to controls on day 1 and day 3 postoperatively [Table 3].

CRP, ICAM 1, and phosphate were also affected by surgery and demonstrated a significant increase above baseline values throughout the study period in both groups, but this increase was significantly lower within the NAC group when compared to controls on postoperative day 3 [Table 4].

Hospital stay was shorter with NAC versus controls (6.1 ± 0.8 vs. 6.9 ± 1.2 days, P = 0.006) and the incidence of chest infection was lower within NAC group 2 cases (6.7%) when compared to controls 6 (20.0%) but failed to reach statistical significance, P = 0.255.

Discussion

Most of the liver resections enrolled in this RCT were performed to treat primary neoplasms as a consequence of chronic HCV infection, which represented 80% of the etiology due to the high incidence of HCV infection in Egypt.

The ability of the remaining liver cells to produce substances such as clotting factors is reduced for several days following trauma to the cells during the tumor resection as evident in the results of both groups in this current study. The elevation in INR, serum lactate, and serum liver enzymes is a reflection of this temporary liver dysfunction.

Reducing this liver dysfunction and preserving the remaining liver cell function is an important priority, particularly in cirrhotic patients undergoing liver resection to help enhance
recovery after surgery, this led several researchers in the field to investigate the role of NAC. Robinson et al.[12] in their earlier work were able to demonstrate that the hepatic ischemia-reperfusion injury during liver resection procedure is mediated through the generation of reactive oxygen species (ROS), these ROS lead to the depletion of hepatic GSH stores.

Elevation of serum concentrations of ALT and AST reflects hepatocytes loss and their activities in serum are considered one of the most frequently used indicators for evaluation of liver injury. [23] Results from our RCT showed that AST and ALT were significantly increased in both groups during hepatic dissection and post resection up to day 3 due to the injury of hepatocytes. One of the main findings of this current RCT was the observed attenuation in posthepatectomy liver dysfunction when NAC was administered intra- and post-operative as indicated from the reduced postoperative levels of hepatic transaminases and the decrease in the associated inflammatory process.

This could be attributed to the ability of NAC to replenish intracellular GSH stores, thus offering a protection for liver cells against the released oxygen free radicals associating the surgical trauma that can disrupt cellular metabolism and cause lipid peroxidation. NAC is known to improve the hepatic microcirculation with a significant reduction in the number of non-perfused sinusoids. This improvement in the microvascular perfusion within the liver decreases the number of leukocytes adhering to the vascular endothelium, which helps lower the associated inflammatory process. [24]

Ibrahim et al. [25] in their study found similar results and demonstrated that liver functions were well preserved with the administration of NAC to their study group of cirrhotic patients undergoing major abdominal surgery. In other different types of surgeries as laparoscopic, Beyaz et al. [14] also found that NAC preserved hepatic function during isoflurane anesthesia, and additionally in liver transplant surgery, Stravitz et al. [26] was able to show that NAC could improve transplant-free survival in patients with non-acetaminophen acute liver failure (ALF) by ameliorating the production of interlukin-17.

Lee et al. [27] were also able to demonstrate that intravenous NAC managed to improve the transplant-free survival in patients with an early stage of non-acetaminophen-related ALF.

Table 2: Heart rate (beat/min), mean arterial blood pressure (mmHg), systemic vascular resistance (dyn s/cm²), corrected flow time (ms), and oxygen delivery (ml/min) in studied groups

| Variables                  | Mean±SD          | Z (Mann–Whitney test) | P    |
|----------------------------|------------------|-----------------------|------|
|                            | NAC (n=30)       | Control (n=30)        |      |
| HR (beats/min)             | 78±7             | 80±7                  | 1.244| 0.213 (NS) |
| T1                         |                  |                       |      |
| T2                         | 79±6             | 82±6                  | 1.819| 0.069 (NS) |
| T3                         | 80±6             | 83±5                  | 1.440| 0.150 (NS) |
| MAP (mmHg)                 | 79±7             | 78±7                  | 0.720| 0.471 (NS) |
| T1                         |                  |                       |      |
| T2                         | 78±7             | 76±7                  | 0.667| 0.505 (NS) |
| T3                         | 76±7             | 75±5                  | 0.874| 0.382 (NS) |
| SVR (dyn s/cm²)            | 805±129          | 822±158               | 1.037| 0.300 (NS) |
| T1                         |                  |                       |      |
| T2                         | 732±132          | 728±139               | 0.044| 0.965 (NS) |
| T3                         | 719±124          | 714±134               | 0.126| 0.900 (NS) |
| Ftc (ms)                   | 319±13           | 316±16                | 0.492| 0.622 (NS) |
| T1                         |                  |                       |      |
| T2                         | 321±13           | 318±14                | 0.896| 0.370 (NS) |
| T3                         | 317±18           | 311±16                | 1.377| 0.168 (NS) |
| DO₂ (mL/min)               | 744±142          | 755±146               | 0.969| 0.333 (NS) |
| T1                         |                  |                       |      |
| T2                         | 755±138          | 759±147               | 0.466| 0.641 (NS) |
| T3                         | 757±141          | 759±146               | 0.540| 0.589 (NS) |

Table 3: Lactate dehydrogenase (U/L), serum lactate (mg/dL), and international normalized ratio (%) for the studied groups

| Variables                  | Mean±SD          | Z (Mann–Whitney test) | P    |
|----------------------------|------------------|-----------------------|------|
|                            | NAC (n=30)       | Control (n=30)        |      |
| LDH (U/L)                  | 216.8±32.0       | 218.7±29.0            | 0.074| 0.941 (NS) |
| T1                         |                  |                       |      |
| T2                         | 238.1±41.3       | 244.2±61.1            | 0.400| 0.689 (NS) |
| T3                         | 282.2±37.5       | 281.5±66.5            | 1.134| 0.257 (NS) |
| T4                         | 257.7±36.1       | 276.1±62.7            | 0.947| 0.344 (NS) |
| T5                         | 228.0±23.0       | 256.3±59.9            | 1.229| 0.219 NS  |
| Lactate (mg/dL)            | 13.9±2.8         | 13.8±3.2              | 0.419| 0.676 NS  |
| T1                         |                  |                       |      |
| T2                         | 21.4±6.0         | 22.1±6.4              | 0.512| 0.609 (NS) |
| T3                         | 37.2±11.9        | 35.6±14.0             | 0.851| 0.395 (NS) |
| T4                         | 26.2±7.7         | 26.3±15               | 3.221| 0.001*    |
| T5                         | 19.4±5.2         | 27.5±10.3             | 3.178| 0.001*    |
| INR (%)                    | 1.1±0.0          | 1.1±0.0               | 0.742| 0.458 (NS) |
| T1                         |                  |                       |      |
| T2                         | 1.2±0.0          | 1.1±0.0               | 2.050| 0.040 (NS) |
| T3                         | 1.3±0.1          | 1.4±0.1               | 1.004| 0.316 (NS) |
| T4                         | 1.4±0.1          | 1.4±0.0               | 1.107| 0.268 (NS) |
| T5                         | 1.3±0.1          | 1.3±0.1               | 1.358| 0.174 (NS) |

Data presented as mean±SD. Z=Mann–Whitney test, P=Probability of error, NS=Nonsignificant difference (at P=0.01 after Bonferroni correction for multiple comparison), T1=Baseline, T2=Dissection, T3=Postresection, T4=Postoperative day 1, T5=Postoperative day 3, LDH=Lactate dehydrogenase, INR=International normalized ratio, NAC=N-acetyl cysteine, SD=Standard deviation
Using NAC by other researchers in liver transplantation showed that ischemic reperfusion injury is not totally preventable, but its negative effects may be reduced.[28,29]

In contrast Grendar et al.,[9] and Khan et al.,[30] in their studies failed to show a benefit of NAC infusion in the setting of liver resection and liver transplantation, respectively. There was no significant difference in peak serum transaminases in both studies.

One of the other markers selected in this current RCT was ICAM 1, which is recognized as an important leukocyte adhesion molecule that mediates leukocyte migration to areas of inflammation and its release into the circulation had been reported to correlate with the degree of tissue injury. High serum levels of ICAM 1 after graft reperfusion during adult living donor liver transplantation is suggested to be an evidence of endothelial cell damage in the newly transplanted liver cells.[31]

This marker serum ICAM 1 was found in this current RCT to significant increase in blood above baseline values in both groups during dissection and postresection with a significantly reduction in response to NAC infusion, this was statistically significant on postoperative day 3.

This downregulated expression of ICAM 1 caused by NAC has been previously described by other researchers,[11] attributing it to the known anti-inflammatory action of NAC that suppress the cytokine expression/release and consequently inhibits the adhesion molecules expression.[32] Weigand et al.[31] and Radomska et al.[34] demonstrated similar findings with patients in their studies whom received NAC infusions.

In another context, hepatic tissues are known to have a great capability to convert lactate to pyruvate through lactate dehydrogenase enzyme. Consequently, the impairment of liver functions after liver resection is expected to reduce the clearance of lactate.[35] This was supported by the findings in this current RCT shows that there is a significant increase in serum lactate above baseline level within both groups, but the increase was significantly reduced with NAC infusion.

A vasodilator action for NAC was observed and reported by several authors. They suggest that this vasodilator action could be due to its direct effect on vasculature or indirectly by enhancing nitric oxide release.[36] Cirrhotic patients are known to be depleted in sulfated amino acids.[37] NAC acts by sulfhydryl repletion to cause vasodilatation. This vasodilator effect of NAC on tissues such as liver can help improve tissue perfusion and its ability to metabolize and clear markers as lactate, ICAM 1, and others.

Ibrahim et al.[25] demonstrated that NAC preserved postoperative renal function in cirrhotic patients undergoing major abdominal surgeries assessed by cystatin C concentration and cystatin C glomerular filtration rate. However, in our RCT, no significant difference was observed in serum creatinine between both groups.

Hypophosphatemia can develop after liver resection as reported in George and Shiu retrospective study.[38] The mechanism by which phosphorus in blood decreases after liver resection has not been elucidated, but several studies suggest that the rapid changes of extracellular phosphorus pool are related to various factors including phosphate flux into liver for regeneration and energy metabolism.[39] Serum phosphorus concentration for that needs to be frequently checked and replaced. Results from this current study were in support of the above assumptions and showed that serum phosphate level was significant decreasing below baseline values among patients enrolled in the trial. This decrease was postresection and mainly during the postoperative day 3 in both groups. The decrease was significantly less within the NAC prophylactically treated group compared to controls. This indicates that NAC could have a role in preserving hepatic cells integrity in face of the surgical injury and improve conditions for regeneration.

### Table 4: C-reactive protein (mg/L), intercellular adhesion molecule 1 (ng/mL), serum phosphate (mg/dL), and studied groups

| Variables | Mean±SD | Z (Mann–Whitney) | P |
|-----------|---------|------------------|---|
| **CRP (mg/L)** | | | |
| T1 | 2.7±2.2 | 2.3±1.9 | 0.845 | 0.398 (NS) |
| T2 | 7.1±4.9 | 3.7±2.9 | 2.875 | 0.004* |
| T3 | 32.8±11.3 | 25.3±22.8 | 2.303 | 0.021 (NS) |
| T4 | 48.9±14.4 | 52.5±27.9 | 0.089 | 0.929 (NS) |
| T5 | 44.2±13.4 | 68.7±48.2 | 3.003 | 0.003* |
| **ICAM 1 (ng/mL)** | | | |
| T1 | 250±35 | 260±48 | 0.518 | 0.605 (NS) |
| T2 | 292±33 | 377±61 | 4.961 | 0.000* |
| T3 | 383±40 | 399±72 | 0.303 | 0.762 (NS) |
| T4 | 352±35 | 369±62 | 0.481 | 0.631 (NS) |
| T5 | 308±38 | 352±59 | 3.165 | 0.002* |
| **Phosphate (mg/dL)** | | | |
| T1 | 4±0.3 | 4±0.4 | 2.264 | 0.024 (NS) |
| T2 | 4±0.2 | 3±0.6 | 1.780 | 0.075 (NS) |
| T3 | 3±0.5 | 4±0.3 | 3.612 | <0.001* |
| T4 | 2±0.5 | 3±0.5 | 1.433 | 0.152 (NS) |
| T5 | 2±0.3 | 3±0.4 | 2.660 | 0.008* |

Data presented as mean±SD, Z=Mann–Whitney test, P=Probability of error, *P<0.01 is significant. NS=Non-significant difference (at P=0.01 after Bonferroni correction for multiple comparison), T1=Baseline, T2=Dissection, T3=Postresection, T4=Postoperative day 1, T5=Postoperative day 3, CRP=C-reactive protein, ICAM 1=Intercellular adhesion molecule 1, NAC=N Acetylcysteine, SD=Standard deviation
The other important observation was the lower number of patients with chest infection within the NAC group compared to controls despite not reaching statistical significance. The ability of NAC to break disulfide bonds in mucus and hence liquefy bronchial secretions and allow it to be coughed up easily with minimal effort and pain from the abdominal surgical wound could explain this finding reported in our trial.

NAC antioxidant and anti-inflammatory characteristics could also improve the chest conditions by maintaining the endothelium-dependent vasodilatation in the pulmonary circulation to prevent or attenuate the deterioration of lung mechanics and gas exchange as reported in an animal experimental study among end toxemic sheep.[40]

Regarding the hemodynamic changes observed during the trial, both the NAC group and the control group showed a significant increase in HR and a significant decrease in mean arterial blood pressure during dissection and immediately after resection in comparison with baseline values. These changes are similar to those reported by El Sharkawy et al.[4]

This can be explained by release of vasodilators from vascular endothelium of the injured liver. Splanchnic arterial vasodilatation produced by vasodilators decreased effective arterial blood volume and mean arterial blood pressure,[41] but NAC administration was unable affect or alter these observed hemodynamic changes. Beyaz et al.[14] and Steib et al.[42] demonstrated similar results.

The utilization of transesophageal Doppler for guided fluid and hemodynamic management during surgery helped both groups to establish a stable cardiovascular environment to allow for comparison between both groups and to study NAC effects. Keeping a stable mean arterial blood pressure is vital for the remaining liver cells to keep it viable and allow the process of regeneration.

Conclusion

Intravenous administration of NAC in cirrhotic patients during and after liver resection surgery attenuated the anticipated postoperative hepatic dysfunction as indicated from the reduced increase in transaminases, ICAM 1, and CRP blood levels. A larger scale study is recommended to investigate the economic impact of NAC practice in this population in view of associated reduction in chest infection and hospital stay.

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Conflicts of interest
There are no conflicts of interest.

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