# STUDY THE N - ACETYLCYSTEINE EFFECTS ON GASTRECTOMY AND SOME BIOCHEMICAL PARAMETERS IN DOGS

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## ABSTRACT

The project of research was carrying out to study the effect of N-acetylcysteine on the wounds which developed in the stomach after gastrotomy. Dogs were used in this study as experimental animals. Dogs were divided into two groups' treatment and control; each group contains 5 animals. The surgical incision was closed by two layers of sutures using absorbent sutures then closed the muscle and skin using traditional steps. The treatment group was treated using 3% of N-acetylcysteine fluid topically on site of operation, as well as N-acetylcysteine (140 mg/kg/ day) was administrated orally for 7 days. Gross examination and clinical signs were recorded after 7 days of operation. Blood samples were collected before the surgery and 7 days after the surgery for complete blood studies on blood samples in both groups. Additionally, tissue samples were taken from operation areas to study the histological change. Results of this study show that the healing of treated groups with N-acetylcysteine was disappeared after 3 days while in control groups the healing sings continued until 7 days after surgery. The mucous membranes in the group treated with N-acetylcysteine were healthier comparative to the control group after 7 days of operation. Openings of the surgical area in the control group suffered from adhesions led to hemorrhage during their separation while in the treated group there were no adhesions. Blood analysis and liver enzymes tests showed an absence of inflammation and regularity of all liver enzymes in the treated group. Finally, the

**169**

treated groups showed the normal arrangement of tissue layers and no adhesion or increasing in collagen fibers.

## INTRODUCTION

N-Acetyl cysteine is inexpensive medication and safety uses, is commercially accessible for long-time. N- Acetyl cysteine was not present naturally but the cysteine is amino acid present normally in meals like chicken and turkey meats, eggs, yogurt and garlic. NAC is a well-tolerated mucolytic drug which moderates clinging secretion of mucous and enhances activity of glutathione S-transferase. The oral administration of this drug, reaction of deacetylation of NAC happens, while passage it through the small intestine as well as liver, thus its 4-10% decreased in bioavailability by NAC which stimulates biosynthesis of glutathione, directly acts as a free radicals scavenger and also promotes detoxification. It acts as powerful antioxidant and a potential treatment option to the diseases (in the diseases when the generation of free radicals) [1,2].

NAC acts to prevents apoptosis of cells and oxygen-related genotoxicity by increasing levels of intracellular glutathione in endothelial cells and decreasing depolarization of mitochondrial membrane [3]. Surgeons of small animal routinely perform the gastrointestinal tract (GI) wounds for neoplasm removal or a foreign body for correction of gastric dilatation-volvulus or to relieve obstruction of the colonic and intestinal tract. Unlike dehiscence of a skin wound, this is often easily remedied with appropriate in the local wound treatment, the dehiscence of wounds of the gastrointestinal tract which leads to infection by bacterial causing peritonitis and increment of the mortality [4].

So far, reoperation required for septic peritonitis, techniques patching for the leakage sites, resuscitation of aggressive fluid and based on culture and sensitivity appropriate the antibiotic therapy. Surgical techniques of innovative such as uses material accelerate healing and prevent adhesion might be necessary to decrease the death rate. In this clinical study, we want to decrease adhesion between the stomach and other organs in the site of operation and in the same time accelerate healing of operation site. This research aimed to study the effects NAC on site operation in gastrostomy in dogs and also its effects on some biochemical parameters.
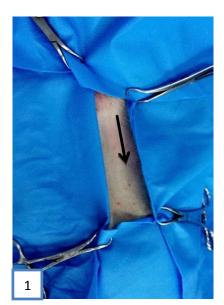
## MATERIALS AND METHODS

**170**

Two gm/10ml ampule of N-Acetylcysteine (Exi-Nace®) was purchased from Exira Pharmaceutical (Iran).

**Animals of experiment:** Ten dogs were involved in the study. The age of dogs was between (8-9) months old and an average weight of 20 kg (range 15–25.4 kg). The dogs were randomly divided into two groups (five animals each). No observed differences were showed between the groups with respect to age and weight. The dogs were housing in the facility of the animal at Basra University in Veterinary Medicine College. They provided free access to food and water. They were determined to be healthy based on physical examination findings.

**Technique operation:**The animals were given a mixture of ketamine HCl 50 mg/kg B.W (Alfasan Company) and xylazine Hcl 10 mg/kg B.W (Alfasan Company). The abdominal area was prepared under aseptic technique. The surgical incision was done ventrally in the midline of abdominal region along the xiphoid to pubis, and then isolated the stomach from remaining contents of abdominal with moistened laparotomy sponges. Sutures the place to blocked and assist in the manipulation of the stomach and prevent helps spillage of gastric contents.  The incision of gastric was done in an area of hypovascular of the ventral aspect of the stomach between the lesser and greater curvatures and a stab incision made into the lumen of gastric with a scalpel and enlarge the incision by Metzenbaum scissors.  The stomach closed with 2-0 absorbable suture material (polyglycolic acid) in a 2-layer inverting as eromuscular pattern. The such as layers of serosa, muscularis, and submucosa sutured as the first layer, using a Cushing pattern was used and then follow it with a Lembert pattern that incorporates the serosal and muscularis layers. After closing stomach utilize N-acetylcysteine (0.5%) 5CCs topical by rubber dropper on the site of operation. Close abdominal wall by routine methods then the treated groups use treated daily with 140 mg/kg N-acetylcysteine using oral method (figure 1,2 and 3).

**Clinical signs:** The clinical points of interest such as; heat, appetite, weight, mucus membrane, and heart rate were evaluated at 0, 3 and 7 days after surgery and record.

**Microscopic examination:**After 7 days the surgical operation, the surgical site was reopened to make macroscopic examination of the site of operation and check the healing process as well as evaluate whether adhesion present or not.
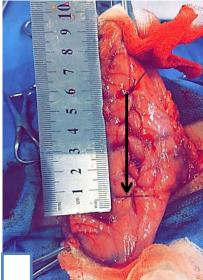
**171**

Figure 1,2,3 : show stages gastrotomy operation in dogs

**Biochemical measurements:** These measurements were done on the serum isolation from blood by enzymatic kits as follow:

**1- Serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) estimation (U/I):**AST and ALT are measured by monitoring the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenyl-hydrazine [5].

**2- Serum Alkaline Phosphatase (ALP) estimation (U/I):**The measurement of ALP was work by using the determination of colorimetric the activity of alkaline phosphatase [6].

**3-Total cholesterol measurements (TC):**Serum total cholesterol was enzymatically measurement by using a linear chemical kit, the principle measurement of TC is presented by Tietiz [7].

**5- Serum triglyceride measurement (TG):** The concentration of serum triglyceride was measured by using a special chemical kit based on Stein [8].

**6- Estimation of serum lipoprotein cholesterol:** There are 3 types of lipoprotein cholesterol measured as followed:

**172**

**A- Serum High-Density Lipoprotein Cholesterol (HDL-C):** The HDL is play important role in the lipid metabolism is the uptake and transport of cholesterol from peripheral tissues to the liver through a process known as reveres cholesterol transport [6].

**B- Serum Low-Density Lipoprotein Cholesterol (LDL-C):** Serum LDL concentration calculated can be by method mentioned by Ram [9].

**C- Serum Very Low-Density Lipoprotein (VLDL):** this concentration was calculated as TG/5 described by Firedwald *et al*. [10].
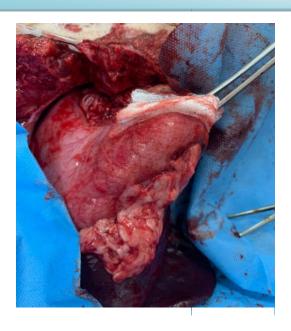
**Statistical Analysis:** Expressed of the results were as mean ± standard deviation (M±SD). By using independent *t*-test analyzed for the experiment; the statistical analysis was using One-way ANOVA by SPSS (Special Program for Statistical System) version 21.0. The least significant difference test (LSD) was used to determine the differences between groups in ANOVA-test, the level of significant set on $p < 0.05$ [11].

**Histopathological Study:** The histopathological study was performed after seven days from surgical operation. Specimens, which taken from the site of operation of stomach, were fixed in 10 % formalin and the tissue was processed in ordinary ways and then stained with Hematoxyline – Eosin (H & E) stains [12].

## RESULTS

**Clinical signs** Heat, appetite, weight, mucus membrane and heart rate recorded before and after the operation in all animals. In summary heat disappeared after 3 days in treated groups but persisted until day 7 in control groups. Appetite evaluation saw no changes at day 7 in the two groups. Body weight decreased in control groups more than treated groups. The mucus membrane of two groups after 3 day had had abnormal structure while after 7 days the treated group had less changes compared to control group. Finally, the study did not find any different in heart rate among groups.

**Microscopic examination:** After 7 days the surgical operation was opened, and Gross examination was performed. In summary, we were found adhesion in control group and healing development in site of operation low, but in treated group only one dog found small adhesion with easy separated also, the site of surgery found in good healing condition (figure 4-treated ,5- Control).

**Effect of N-acetylcysteine on blood picture**

The effect of NAC in (table 1) showed no significant difference between before and after treatment of operation in RBC s and WBCs while significant (P<0.05) increased in Hb concentration after 7 day of operation in treated groups with NAC. The table appeared significantly increased (p<0.05) in lymphocyte, eosinophils and neutrophils in G control after 7 day of operation while no significant difference in treated group

**Table 1: Effect of NAC on blood picture in dog:**

| groups | | RBC X $10^6$ mm$^3$ | WBC X $10^9$ mm$^3$ | Hb | Lymph. M$^3$ | Eosino. M$^3$ | Neutr. M$^3$ |
|---|---|---|---|---|---|---|---|
| Control group | 0 day | 6.5×10$^6$ $^{Aa}$ 0.68 ± | 10.90 $^{Aa}$ ±0.77 | 14.77 $^{Aa}$ ±0.68 | 2750 $^{Aa}$ ±238.0 | 555.00$^{Aa}$ ±58.02 | 10.67 $^{Aa}$ ±0.53 |
| | 7 days | 8.95×10$^6$ $^{Bb}$ 0.12 ± | 6.570 $^{Bb}$ ±0.67 | 14.65 $^{Aa}$ ±0.86 | 5150 $^{Bb}$ ±810.34 | 802.50$^{Bb}$ ±81.80 | 12.37 $^{Bb}$ ±0.48 |
| Treatment group | 0 day | 7.0×10$^6$ $^{Aa}$ ±0.97 | 10.97 $^{Aa}$ ±0.65 | 14.17 $^{Aa}$ ±0.84 | 2800 $^{Aa}$ ±294.39 | 580.00 $^{Aa}$ ±77.88 | 10.75 $^{Aa}$ ±0.42 |
| | 7 days | 7.32×10$^6$ $^{Aa}$ ±0.55 | 10.87 $^{Aa}$ ±0.47 | 16.57 $^{Bb}$ ±0.93 | 8425 $^{Aa}$ ±859.39 | 552.50 $^{Aa}$ ±79.58 | 11.05 $^{Aa}$ ±0.44 |

**\*small litters denote to significant differences within groups.**

**\*large litters denote to significant differences between groups.**

**Effect of N-acetylcysteine on lipid profile:**

The results in table (1) revealed the effect of N- acetylcysteine on total cholesterol (TC) which significantly (p<0.05) decreased after 7days of operation and treatment in G2 compared with control group. Also the results showed significantly (p<0.05) decreased in TG, VLDL and LDL while increased significantly (p<0.05) the level of serum HDL in treated group compared to same group before treatment (0days) and control group.

**175**

Table 2: N-acetylcysteine effect on lipid profile in dog:

| groups | | TC (mg/dI) | TG (mg/dl) | HDL (mg/dl) | VLDL (mg/dl) | LDL (mg/dl) |
|---|---|---|---|---|---|---|
| Control Group (1) | 0 day | 77.02 [Aa] ±2.09 | 75.62 [Aa] ±1.75 | 35.65 [Aa] ±1.33 | 68.23 [Aa] ±2.50 | 29.52 [Aa] ±0.83 |
| | 7 days | 78.38 [Aa] ±1.15 | 76.06 [Aa] ±1.25 | 36.32 [Aa] ±1.19 | 70.37 [Aa] ±4.32 | 30.58 [Aa] ±0.78 |
| NAC Group (2) | 0 day | 77.45 [Aa] ±1.71 | 74.10 [Aa] ±4.27 | 35.36 [Aa] ±2.13 | 70.43 [Aa] ±3.32 | 30.13 [Aa] ±1.14 |
| | 7 days | 67.12 [Bb] ±1.41 | 65.65 [Bb] ±2.30 | 43.26 [Bb] ±2.47 | 56.78 [Bb] ±2.51 | 21.47 [Bb] ±0.99 |
| LSD | | 9-90 | 8-44 | 6-94 | 11-45 | 8-04 |

*small litters denote to significant differences within groups.

*large litters denote to significant differences between groups.

Effect of N-acetylcysteine on liver enzymes:

In table (2), the results showed the effect of N-acetylcysteine on liver enzymes (ALP, AST and ALT). Significant ($p<0.05$) decreased in ALP, AST and ALT concentrations in groups treated with N-acetylcysteine compared to G1 group.

Table 3: N-acetylcysteine effect on liver enzymes in dogs:

| groups | | ALP(U/l) | AST(U/l) | ALT(U/l) |
|---|---|---|---|---|
| Control Group (1) | 0 day | 37.70 ± 2.77 [A] | 41.01±0.71 [A] | 53.87±2.35 [A] |
| | 7 days | 37.35 ± 0.78 [A] | 41.35±0.81 [A] | 55.15±0.60 [A] |
| NAC Group (2) | 0 day | 38.96±1.65 [A] | 40.71±0.79 [A] | 53.77±2.07 [A] |
| | 7 days | 29.75±0.92 [B] | 33.93±1.15 [B] | 39.46±0.60 [B] |
| LSD | | 7.60 | 6.78 | 14.30 |

*large litters denote to significant differences between groups.

**Histopathological change:** After 7 days, the stomach of dogs in treated group with NAC showed normal structure of stomach layers, no adhesion and increase collagen fibers, but in control groups fibers adhesion presented on the outer layer of the stomach in addition to hemorrhage and increase inflammatory cells (Figures 6,7 and 8).
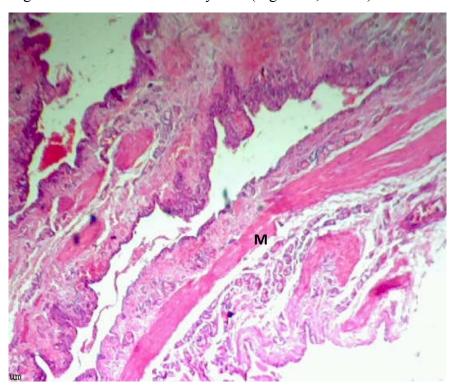


Figure (6) section of stomach of dog treated with N-acetylcysteine show normal layers of the mucosa, sub mucosal layer and muscular layer (M). (H&E) 100 X
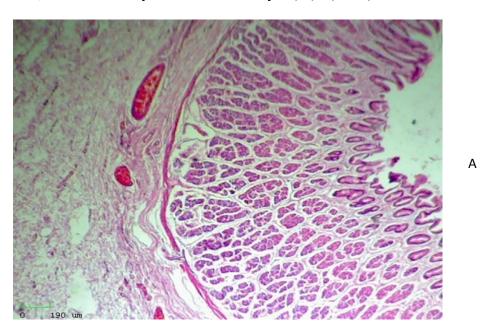


Figure (7): section of stomach of dog treated with N-acetylcysteine shows atrophy of the mucosal layer (A) and increased collagen fibers (C) and congested blood vessels. (H&E) 100X
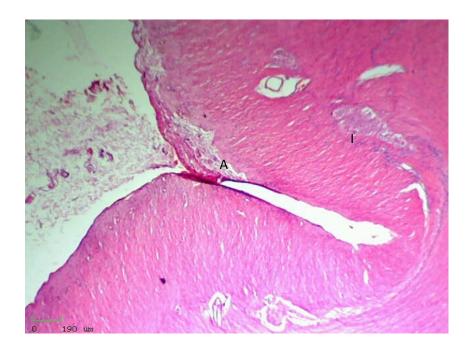
Figure (8) section of stomach of group control, shows adhesion fibers (A) on the outer layer of the stomach and hemorrhage with inflammatory cells (I). (H&E) 100X

## DISCUSSION

The results of this research, the evaluated of NAC effect on the wound-induced in the stomach during gastrostomy operation. After gastrostomy operation, NAC was used in treatment groups by two methods; topical after the closed site of operation in the stomach and oral daily dosage for 7 days. Cysteine supplies by NAC for glutathione replenishment and also it prevents damage, inflammation and reactive oxygen species (ROS) in the wound healing process that formation and generation by a number of cells of inflammatory such as macrophages, endothelial cells, neutrophils and fibroblasts. Glutathione act as antioxidant agent which prevents the damage cellular components caused by ROS. The role of angiogenesis plays in the proliferation of wound healing [13] .

Clinical signs found heat disappeared after 3 days in the treated group which indicated on inflammation reduced by use NAC, however, in control group heat continued until day

**178**

7. Weight and mucous membrane in the group treated with NAC showed progression as compared to the standard group indicated that NAC could be used as a supplement dietary after surgery these results agree with [14].

Gross examination on the site of operation after 7 days found treated group by NAC did not have adhesion between the stomach and other organs in the abdominal cavity or between stomach and peritoneum. Also, the liner of the wound in the stomach in the treated group healthier than the same site in the group of control this finding agreement with [15].

The effect of NAC on blood picture showed no significant differences between before and after treatment of operation in RBC s and WBCs while significant ($p<0.05$) increased in Hb concentration after 7 days of operation in treated groups with NAC was found. Moreover, significant ($p<0.05$) increases in lymphocyte, eosinophils and neutrophils in group control after 7 days of operation were found while no increases found in group treated with NAC.[16] found neutrophils is regarded as the first line of defense in the immune system and the most abundant leukocytes in the circulation. It captures and destroys invading microorganisms through phagocytosis and intracellular degradation, the release of granules, and the formation of neutrophil extracellular traps after detecting pathogens. Also, the Neutrophils participate as inflammatory mediators. The classical view for these leukocytes is that neutrophils constitute a homogenous population of terminally differentiated cells with a unique function.

The effect of N-acetylcysteine on total cholesterol (TC) significantly decreased after 7 days of operation in the treated group compared to group of control. Also, the data of results appeared significantly decreased in TG and VLDL and LDL while significantly increased in the level of serum HDL in the treated group with NAC compared to pretreatment period (0 days) and control group. This result means decreasing of T.C., T.G., V.L.D.L. and L.D.L after NAC treatment causing low-stress factor may be affected on wound healing in the stomach, while the increase in HDL means increasing in improvement factors and accelerate healing in the site of operation. Infectious diseases, inflammatory disorders, and the alterations in lipoprotein levels and lipid in the plasma of blood are very similar to decreasing in plasma HDL which consistently observed. Consistent increases in lipoprotein levels and small dense LDL. Furthermore, elevated a tendency for plasma TG levels and LDL-C levels decreased. The underlying disease severity is linked to consistently these lipids abnormalities. Additionally, treatment of the

**179**

underlying disease leads to a reduction in inflammation resulting in a return of the lipid profile towards normal [17].

The study showed the effect of N-acetyl cysteine on liver enzymes (ALP, AST, and ALT). The decreases significantly in ALP, AST and ALT concentration were found in groups treated with NAC compared to group of control. Elevated liver enzymes are common in liver problems and inflammations in the body these caused due to increased ALP, AST, and ALT but in this study, liver enzyme did not show any changes and treated groups had healthy parameters [18].

The histopathological study after 7 days of the stomach in dogs in treated group with NAC showed normal layers, no adhesion and increase collagen fibers, but the control group showed adhesion fibers on the outer layer of the stomach, hemorrhage and increase inflammatory cells. NAC is a powerful antioxidant agent and a scavenger of free radicals. NAC in recently, it has anti-inflammatory activities in the cells and tissues. NAC therapy has a dual action as an effective anti-inflammatory, an antioxidant agent and may be a promising therapeutic option for wounds in the stomach [19].

## دراسة تأثير N - acetylcysteine على استئصال المعدة وبعض المعايير الكيموحيوية في الكلاب

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## الخلاصة

هدفت هذه الدراسة إلى تنفيذ تأثير N-acetylcysteine على الجروح التي تكونت في المعدة بعد استئصال المعدة. استخدمت الكلاب في هذه الدراسة كحيوانات تجريبية. تم تقسيم الكلاب إلى مجموعتين : مجموعة العلاج ومجموعة السيطرة. كل مجموعة تحتوي على ٥ حيوانات. تم إغلاق الشق الجراحي بواسطة طبقتين من الخيوط الجراحية باستخدام خيوط ماصة ثم أغلقت العضلات والجلد باستخدام الخطوات التقليدية. تمت معالجة مجموعة العلاج باستخدام ٣ ٪ من سائل N-acetylcysteine موضعيا في موقع العملية، وكذلك كان يعطى N-acetylcystine ١٤٠ ملغم / كغم / يوم) عن طريق الفم لمدة ٧ أيام. تم تسجيل الفحص الإجمالي والعلامات السريرية بعد ٧ أيام من

العملية. تم جمع عينات الدم قبل الجراحة و بعد ٧ أيام من الجراحة لإجراء دراسة الدم بشكل كامل على عينات الدم في كلا المجموعتين. بالإضافة إلى ذلك، أخذت عينات الأنسجة من مناطق العمليات لدراسة التغير النسيجي. أظهرت نتائج هذه الدراسة أن شفاء المجموعة التي عولجت بـ N-acetylcysteine قد شفيت بعد ٣ أيام بينما استمرت مجموعة السيطرة بالشفاء حتى ٧ أيام بعد الجراحة. كانت الأغشية المخاطية في المجموعة المعالجة أكثر صحة مقارنةً بمجموعة السيطرة بعد ٧ أيام من العملية. الشق الجراحي في المنطقة الجراحية في مجموعة السيطرة عانت من الالتصاقات أدت إلى نزيف أثناء الانفصال بينما في المجموعة المعالجة لم تكن هناك أي التصاقات. أظهرت اختبارات تحليل أنزيمات الكبد والدم غياب الالتهاب وانتظام جميع إنزيمات الكبد في المجموعة المعالجة. أخيرًا أظهرت المجموعات المعالجة الترتيب الطبيعي لطبقات الأنسجة وعدم الالتصاق أو الزيادة في ألياف الكولاجين.

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