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Effects of N-acetyl-L-Cysteine on Postoperative Intraabdominal Adhesion in a Large Animal Model

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Abstract

Objective- Mechanisms that decrease oxidative stress and enhance peritoneal fibrinolysis reduce adhesions. N-acetyl-L-cysteine (NAC) is an antioxidant whose effect on peritoneal fibrinolysis in large animal model has not been established. The aims of this study were to investigate the ability of NAC to decreased adhesion in stablished model of serosal trauma in sheep.
Design- Experimental study
Animals- Eight healthy male sheep weighting 42.67 ± 2.31 kg were used in this study.
Procedures- Established model of serosal trauma were used for adhesion induction. Each sheep intreated group (n=4) received NAC (150 mg/kg) intraperitonealy on operative day and Intravenous infusion during 7days after surgery. Animals in untreated group received normal saline instead of NAC. Blood samples for evaluation of the CBC, total protein and fibrinogen were obtained on perioperative day and at days 1, 2, 4, 7, 11 and 14 after surgery. Animals were killed 14 days postoperatively and Adhesion formation was scored macroscopically and histopathologically.
Results- Evaluation of CBC showed inflammation in 75% of animals in untreated group. CBC of animals in treated group was normal during the study. Measuring the fibrinogen concentration revealed significant differences between untreated and treated groups. Extensive of adhesion formation was 100% in all sheep in both 2 groups. Macroscopic evaluation of severity of adhesion and histopathological assessment of inflammation and fibrosis showed significant reduction in adhesion formation in treated animals.
Conclusions and Clinical Relevance- Results of our study suggest a potential therapeutic use for N-Acetylcysteine in adhesion reduction and prevention in human and veterinary medicine.
Key Words- NAC (N-Acetylcysteine), Intraabdominal Adhesion.

Introduction

Adhesion formation following surgery are a worldwide problem and remain an almost inevitable consequence of most abdominal and pelvic procedures. Studies have found that they occur in more than 94% of patients after abdominal surgery.[1] Adhesions can induce significant clinical problems in human and veterinary medicine.[2]Whilst many methods such as careful operative technique, application of anti-adhesion physical barriers,[1] fibrinolytic agents, wide range of antibiotics and anti-inflammatory drugs[3] have been employed to reduce the formation of adhesions, the incidence of adhesions is still increasing. Clearly, there remains an important need to resolve the problem of postoperative adhesions.

Peritoneal injury such as surgery induces inflammatory response, and in the abdomen this response is at least partly responsible for disrupting the regulation of the peritoneal fibrinolytic system and deposition of the fibrin-rich matrix that serves as a precursor to permanent adhesions[4].Thus, targeting pathways that promote peritoneal fibrinolysis can decrease adhesions. [5]

In the other hand inflammatory process involves the activation of mesothelial cells along with the subsequent recruitment of neutrophils, monocytes/macrophages, and mast cells. These cells secrete inflammatory cytokines and also release reactive oxygen species (ROS), which together appear to enhance the formation and/or maturation of nascent adhesions. Studies

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showing a link between oxidative stress and decreased overall fibrinolytic activity have been shown to reduce experimentally-induced adhesion formation, support this hypothesis.[6]

N-Acetylcysteine (NAC) is a clinically relevant antioxidant that has been used in clinics for more than 50 years for the treatment of numerous disorders[7]. It is also an effective precursor of cysteine that has been used for research on the role of ROS in many disease processes.[8] As a mucolytic, N-Acetylcysteine serves to dissipate disulfide bonds across mucoproteins, loosening and clearing the viscosity of sputum.[9] While the thiol group also confers direct antioxidant properties by scavenging free radicals such as hydroxyl radical (OH^o), Hydrogen peroxide (H_2O_2) and superoxide (O2-), NAC also acts by increasing the cellular content in glutathione (GSH) that is a major intracellular redox buffer.[10] Based on its documented effects on important cellular pathways such as oxidative stress, inflammation, and angiogenesis.[11]

To the best of our knowledge there are two studies that evaluated the effect of N-Acetylcysteine on intraabdominal adhesion. Pata et al (2004), demonstrated that the intramuscular administration of NAC decreased adhesion formation in a rat model of adhesion formation.[12] In the second study, Daniel et al (2011) administered NAC intraperitoneally and showed decreased adhesion formation as a result of increase in peritoneal fibrinolytic activity and antioxidant defenses without affecting normal anastomotic wound healing in the same animal model.[13] Evaluation of the ability of N-Acetylcysteine to prevent postoperative intraabdomnal adhesion formation in large animal model to our knowledge has never been studied. Considering the potent antioxidant and fibrinolytic properties of NAC, we hypothesized that it would decrease intraabdominal adhesions in large animal when administered intravenously. Since intra abdominal adhesion is an important clinical challenge in both human and veterinary surgery, we decided to choice sheep for our study because it can be an appropriate animal model for quickly and effectively extrapolation of results from the experimental model to the clinical medicine.

Materials and Methods

Materials

N-Acetylcysteine in the dosage form of 2gr/10ml ampule (Exi-Nace®) obtained from Exir Pharmaceutical Co (Pharmaceutical Company in Iran).

Animals

A total of eight male sheep were involved in the study. Each was aged between 9 and 10 months old with an average weight of 42 kg (range 40–45.4 kg). The sheep were randomized into two groups of four animals each. No differences were observed between the groups with respect to age and weight. The animals were housed at hospital of Veterinary Faculty of Tehran University in Mardabad, Karaj. They had free access to food and water. They were determined to be healthy based on physical, examination findings, normal complete blood count (CBC), and serum biochemistry results (Total protein, Albumin, Fibrinogen, ALT, AST, ALP, BUN and Creatinine). The study protocol was approved by the ethics committee of animal studies at Tehran University of Medical Sciences.

Adhesion operation

Food was withheld from the sheep for 24 hours before surgery. Adhesion induction model of Moll et al (1991), as an established model of serosal trauma, were used for this study[14]. The surgical procedure was performed under local anesthesia by 2%Lidocaine (1cc/1cm incision). The animals were prepared for aseptic surgery and positioned on left lateral recumbency. A 10 cm ventrolateral incision was made and the abdomen opened. The jejunum was exteriorized from the abdominal cavity. Five separated area of the jejunum for a length of 5 cm, 15cm distance from each other, were abraded using sterile dry gauze until they lost their shine, and hemorrhagic points became visible without perforation, then 3 simple interrupted 2-0 plain gut sutures that did not penetrate the intestinal lumen were placed in each abraded area (Fig.1). After that, the jejunum was returned to its anatomic position in the abdomen. Before abdominal closure, animals in treated group were received 150mg/kg N-Acetylcysteine in 500ml normal saline intraperitoneally. In untreated group, an equal volume of normal saline alone was used instead of NAC. Following surgery and during 7days postoperative, intravenous infusion of NAC (150 mg/kg/day) was used in the treated group. Animals were killed 14 days postoperatively and adhesion formation was scored.

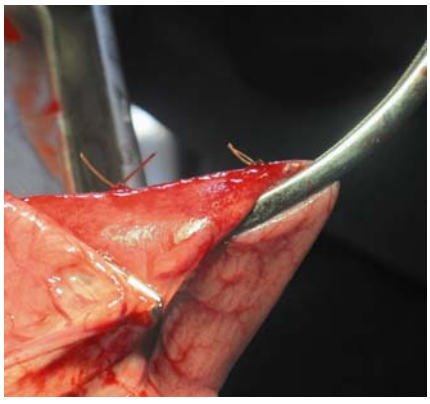

Figure 1- Adhesion induction model of Moll et al. Note hemorrhagic points and gut sutures in abraded area

Evaluation of postoperative inflammation

Blood samples were collected before surgery and at days 1, 2, 4, 7, 11 and 14 after surgery. CBC and Level of total protein and fibrinogen and their changes were measured for evaluation of postoperative inflammation during postoperative days.

Macroscopic Scoring of Adhesion

Adhesion scores were determined by one of the investigators blind to randomization of groups. Macroscopic classification described by Zühlke et al (1990) was used for measuring the severity of adhesion in all abraded area of jejunum (Table-1).[15]

Histopathologic scoring of adhesion

For histhopathological evaluation the samples were obtained from area of abraded jejunum and adjacent tissue that involved in adhesion. The samples were fixed in 10% buffered formalin and immersed in paraffin. Several paraffin sections were made by microtome. These sections were stained by Haematoxylin-Eosin (HE). Histopathologic examinations were performed by a pathologist blinded to the study groups. Histological classification of adhesion was carried out using two criteria of inflammation and fibrosis (table-2).[16] Since in histopathological evaluation of adhesion in treated group different severity of inflammation and fibrosis were observed between 1- area of abraded jejunum near the gut sutures and 2- area of abraded jejunum far from gut sutures, degree of inflammation and fibrosis was scored separately for each of this area.

Statistical analysis

Data analysis was performed using the IBM SPSS version 21. All variables were expressed as mean ± SD. Independent samples T test was performed to determine differences in plasma fibrinogen level in untreated and experiment groups. Mann Whitney U test was conducted to compare scores of macroscopic classifications of adhesion and also inflammations and fibrosis evaluation in the studied groups. P values<0.05 considered significant and P values<0.001 were considered highly significant.

Results

CBC, total protein and fibrinogen levels

There were no mortalities due to local anesthesia or surgical procedures. No mortality was recorded. Inflammation was seen in 2 animals of untreated group, 2 days after surgery in CBC and continued for one week. One of sheep in this group showed inflammation 4 days after surgery and maintain during the study. CBC of animals in treated group was normal during the study. Mean plasma fibrinogen concentration in untreated and treated group was 0.5±0.16 and 0.26±0.1 respectively. The significant differences were observed between two groups (P< 0.05).

The grade of adhesion
Result of macroscopic scoring

Macroscopic evaluation revealed adhesion formation in all abraded jejunums in both untreated and treatment groups. It means extensive of adhesion formation was 100% in all sheep and no differences was determined between 2 groups. According to the Züuhlke et al (1990) scaling, the distribution (Table 3) and the scoring of abdominal adhesion bands (Fig. 2) were evaluated. The adhesion score (mean ± SD) in untreated and treated groups was 3.45±0.6048 and 1.4 ± 0.88258 respectively. Significant differences were found between the mean adhesion score in treated and untreated groups (P<0.05). The representative illustrations of grades of adhesion bands have been also shown in Figs. 3 and 4.

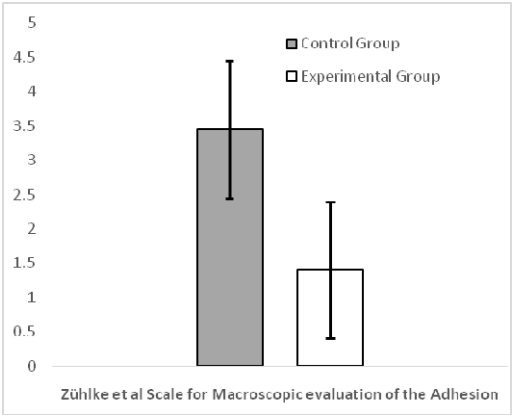

Figure 2- Macroscopic scoring of abdominal adhesion bands. Mean±SD

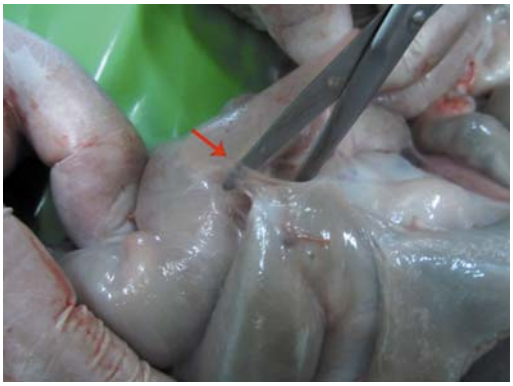

Figure 3- Grade 1 adhesions according to the Züuhlke et al scaling. Gentle, blunt dissection was required to free adhesion bands

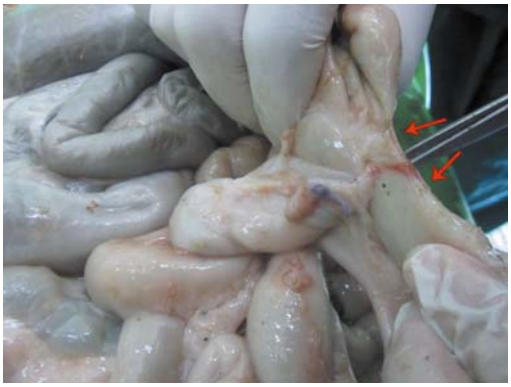

Figure 4- Grade 4 adhesions according to the Züuhlke et al scaling. Adhesion was not dissectible without damaging organs.

Result of histopathological scoring

The inflammation score of untreated group was dominant at serosal surface of jejunum. After 2 weeks, serosa surface of jejunum was surrounded by inflammatory cells such as giant cells, neutrophils, plasma cells, and lymphocytes (Fig. 5). Microabscesses that indicated grade 3 inflammation were noted in 40% of samples obtained from area of abraded jejunum (Fig. 6). The mean ± SD of score in the untreated group was 2.25±0.71635. Inflammation of abraded jejunum in treated group was seen with different severity in 2 separated areas (Fig. 7). Around the gut suture, inflammation was similar to that of untreated group. The mean ±SD of scores in this area of abraded jejunum of treated group was 1.95±0.51042. No significant differences were observed between them (P>0.05).The area of abraded jejunum far from gut suture show notable reduction in inflammation when compare with untreated group. The mean ± SD of inflammation scores in this area was 1.15±0.58714 and there was significant difference between this group and untreated group. The distribution (Table 4) and the scoring of inflammation (Fig. 8) were evaluated according to the criteria mentioned by Hooker et al (1999).[34]

Evaluation of severity of fibrosis showed severs and dens fibrous connective tissue in untreated group (Fig.9). The mean ± SD of score of fibrosis in this group was 2.45±0.51042. Histopathological examination of fibrosis in treated group found similar results of inflammation scoring. Near the gut suture, we found sever fibrosis with excess fibroblast and collagen fibers but in area far from gut suture significant decline in severity of fibrosis was seen (Fig. 10).The mean ± SD of scores of fibrosis were 2.2 ± 0.52315 for area near the gut suture and 1.2 ±0.41039 for area far from gut suture. The fibrosis score in this area was significantly less than that in untreated group (P<0.05).While the fibrosis score of area near the gut suture did not differ significantly with untreated group (P>0.05). The distribution (Table 5) and the scoring of fibrosis (Fig. 11) were evaluated according to the criteria mentioned by Hooker et al (1999).[34]

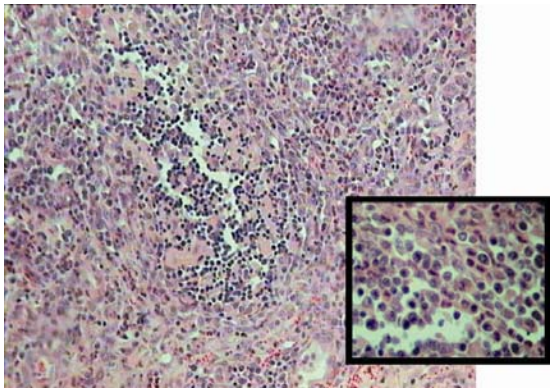

Figure 5- Sever inflammatory response with accumulation of mononuclear cell, plasma cells, lymphocytes, neutrophils, macrophages and epithelioid cells. 40× & 100×

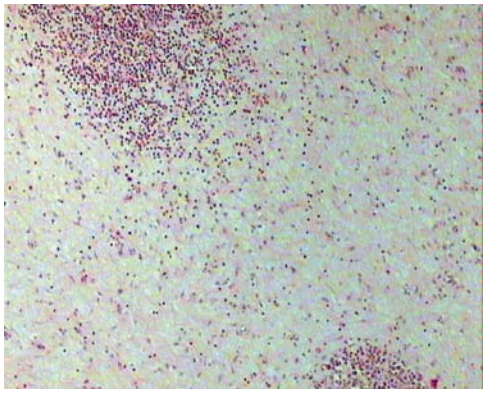

Figure 6- Microabscesses that indicated grade 3 inflammation was noted in histopathological evaluation in untreated group. 40×

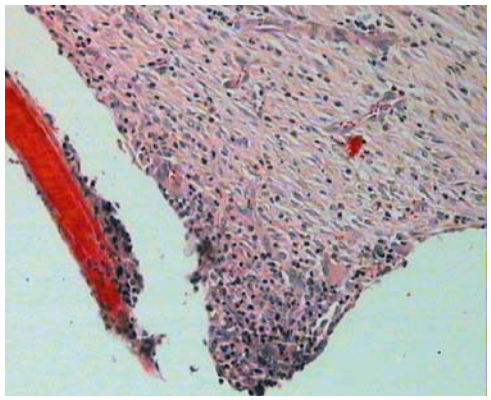

Figure 7- Sever and moderate inflammatory reaction in abraded jejunum near and far from the gut suture in treated group. 100×

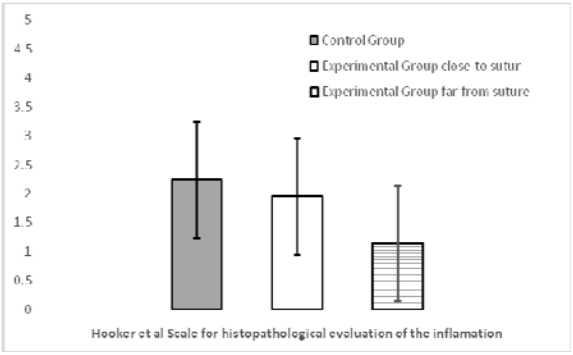

Figure 8- Histopathological scoring of inflammation. Mean±SD

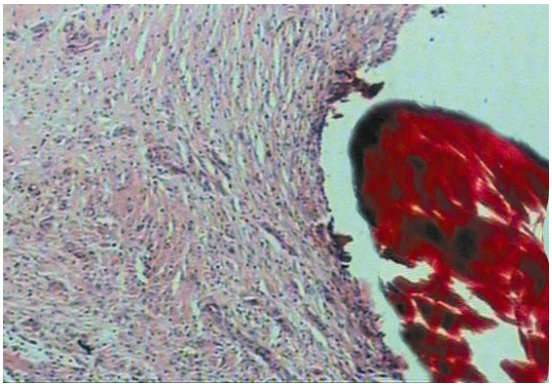

Figure 9- Sever fibrosis with excess fibroblast and collagen fibers in all area of abraded jejunum in untreated group. 40×

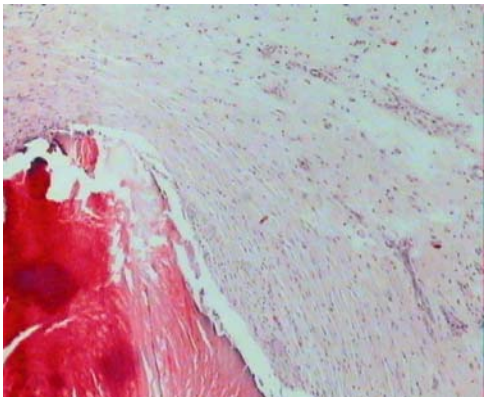

Figure 10- Different severity of fibrosis was found in abraded jejunum in treated group. Note the amount of fibroblast and collagen fibers in area near the gut suture and far from gut suture. 40×

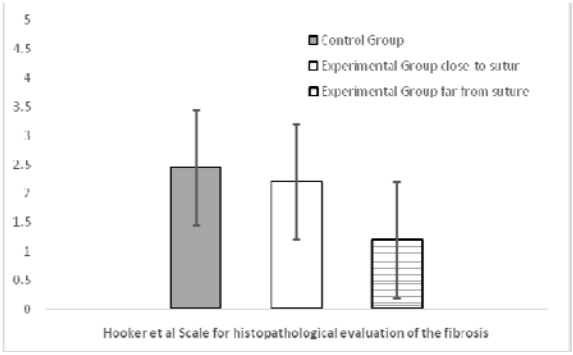

Figure 11- Histopathological scoring of Fibrosis. Mean±SD

Table 1- Macroscopic classifications of adhesion

Grade	Severity	Extension
0	No adhesion	No adhesion in abraded area of jejunum
1	Filmy adhesions: gentle, blunt dissection required to free adhesions	adhesions in only one abraded area of jejunum
2	Mild adhesions: aggressive blunt dissection required to free	adhesions in two abraded area of jejunum
3	Moderate adhesions: sharp dissection required to free adhesions	adhesions in three abraded area of jejunum
4	Severe adhesions: not dissectible without damaging organs	adhesions in four abraded area of jejunum
5	----------	adhesions in all five abraded area of jejunum

Table 2- Histopathologic classifications of adhesion

Grade	Inflammation	Fibrosis
0	No inflammation	No fibrosis
1	Presence of giant cells, occasional lymphocytes, and plasma cells	Minimal, loose
2	Presence of giant cells, plasma cells, eosinophils, and neutrophils	Moderate
3	Presence of many inflammatory cells and microabscesses	Florid dense

Table 3- Frequency of adhesion scores for macroscopic classification

Adhesion score	Group1 (Control)		Group2 (Experiment)	
	Frequency	(%)	Frequency	(%)
0	0	0	0	0
1	0	0	16	80
2	1	5	1	5
3	9	45	2	10
4	10	50	1	5
	20	100	20	100

Table 4- Frequency of inflammation scores for histopathological classification

Inflammation score	*Group1*		*Group2*		*Group3*	
	Frequency	(%)	Frequency	(%)	Frequency	(%)
0	0	0	0	0	2	10
1	3	15	3	15	13	65
2	9	45	15	75	5	25
3	8	40	2	10	0	0
total	20	100	20	100	20	100

Table 5- Frequency of fibrosis scores for histopathological classification

Inflammation score	*Group1*		*Group2*		*Group3*	
	Frequency	(%)	Frequency	(%)	Frequency	(%)
0	0	0	0	0	0	0
1	0	0	1	5	16	80
2	11	55	14	70	4	20
3	9	45	5	25	0	0
total	20	100	20	100	20	100

Discussion

Intra-abdominal adhesion formation after abdominal surgery continues to be a source of great clinical problems in both human and veterinary medicine. Sheep was used in this study because it is suitable animal model for evaluation of adhesion. The results could be translated to human and also domestic animals such as cow and horse.[17]

While experimental expedience may be one criterion for the selection of an ideal animal model, it could be argued that these strengths, whilst important, are not as critical as the ability to translate experimental findings which are relevant in the biomedical context from the sheep to the human. There are many published evidence which suggests that translation of results from the 'sheep to the bedside' is entirely feasible.[17,18]

N-Acetylcysteine is used in a variety of clinical settings. According to the published data its ability of adhesion prevention in large animal model has, to our knowledge, never been studied. Given its potent antioxidant properties and the mounting evidence that antioxidants decrease adhesions, we hypothesized that N-Acetylcysteine would decrease adhesions.

Studies consistently have demonstrated that peritoneal fibrinolytic system has a key role in adhesion formation.[19,20] Peritoneum has an inherent fibrinolytic activity similar to that found in vascular endothelium.[21] In adhesion-free peritoneal healing, there is a balance between fibrinogenesis and fibrinolysis. If fibrin

exudate overwhelms fibrinolytic activity, organization leading to adhesion rather than resolution of the fibrin-cellular matrix occurs. Peritoneal fibrinolysis parameters (tPA, tPA activity, PAI-1, and tPA/PAI-1 complex) are potential markers for the identification of patients at risk for developing adhesions.[22,23,24] Daniel et al, in their study on rat adhesion model showed that NAC increased peritoneal fibrinolytic activity by morethan 2-fold compared to operative controls, which was associated with a significantly increased tPA/PAI-1 protein ratio. Further analyses demonstrated that NAC increased the tPA/PAI-1 ratio due to disproportionately low PAI-1 protein levels both in vivo and in vitro.[13] Dose-dependent decrease in PAI-1 protein levels has been described previously in human umbilical vein endothelial cells treated with NAC.[25] Similar to endothelial cells, peritoneal mesothelial cells are major sources for tPA and PAI-1.[26,27] Daniel et al (2011) indicated that regulation of fibrinolysis within the peritoneum may therefore be controlled, at least in part, by mesothelial cells, as suggested by their in vitro data with HMCs.[13]

Abdominal surgery causes injury to the peritoneum, leading to activation of the surrounding mesothelium and underlying endothelium. This results in the localized release of inflammatory cytokines such as tumor necrosis factoralpha and interleukin-6 into the abdominal cavity, the subsequent recruitment of neutrophils, macrophages, and eosinophils, and the release of a fibrinous exudate into the peritoneum.[28] This process is associated with significant oxidative stress, both from the activation of the mesothelium and underlying endothelial cells and, more importantly, from the infiltration and subsequent activation of neutrophils and macrophages.[29] There are numerous reports dating back nearly 50 years demonstrating that vitamin E prevents adhesions[30,31], and more recent studies have shown that other antioxidant treatments such as methylene blue and catalase/superoxide dismutase can also inhibit adhesion formation.[32,33]

Daniel et al showed that NAC significantly decreased peritoneal oxidative stress, as reflected by decreased levels of 8-isoprostane (markers of oxidative stress) in both peritoneal tissue and fluid.[31] The relationship between oxidative stress and fibrinolytic activity within the peritoneum is not well defined, but some evidence indicated that oxidative stress decrease fibrinolytic activity. In vitro studies have shown that oxidants can directly inactivate tPA[34] or decrease tPA activity by direct modification of fibrin binding sites. [35] In addition oxidative stress can also upregulate PAI-1 expression in endothelial cells.[36,37] In accordance with these findings, neutralizing peritoneal oxidant screated postoperatively with antioxidants such as NAC would decrease peritoneal oxidative stress and increase peritoneal fibrinolytic activity.

The results of this study showed that NAC decreases intraabdominal adhesions in large animal model. Macroscopic evaluation of adhesion showed that in treated animals 80% of adhesions had grade 1 severity that could be free by gentle dissection. Only 1 abraded jejunum (5%) developed sever adhesion that required aggressive sharp dissection to separate involved tissue. It was seen in area that gut suture was placed. Sever grade 3 adhesion in untreated group occurred more frequently. Half of abraded jejunum in this group developed adhesion that required aggressive sharp dissection to be separated. In 45% of abraded jejunum moderate adhesion was seen that required aggressive blunt dissection to be free. Macroscopic assessment of severity of adhesion showed that N-Acetylcysteine decreased severity of adhesion in treated sheep. Some different results were found in histopathological assessment of 2 separated areas in abraded jejunum of treated group. Severity of inflammation near the gut suture in abraded jejunum was dominant but it was reduced some distance from the gut suture in the same jejunum. Significant reduction in severity of inflammation was only found in this point of abraded jejunum. Histopathological assessment of fibrosis showed similar results. There were no significance differences in severity of fibrosis near the gut suture in abraded jejunum of treated group and that of untreated group but marked reduction in severity of fibrosis was notable in area of abraded jejunum far from the gut suture. In overall evaluation NAC caused an appropriate reduction in postoperative adhesion bands, inflammatory response and fibrosis in the treated sheep but with consideration of the unexpected results in abraded jejunum near the gut suture in treatment group it may be better kept in mind that NAC may have limited potency for prevention and decreasing the adhesion that depend on degree of tissue inflammation and trauma. In addition evaluation of extension of adhesion revealed that all abraded jejunum in both groups had adhesion with different degree of severity. It seems that NAC affects adhesion maturation rather than the formation of nascent fibrinous adhesions, i.e., it induces the breakdown of the fibrinous protoadhesions rather than allowing them to become organized during the period between 1 and 7 daypost-surgery.

Two previous studies regarding to evaluation of NAC on postoperative abdominal adhesion, have tested intramascular, intraperitoneal and oral administration[13]. The results of Daniel et al showed that oral delivery of NAC did not decrease adhesions compared to intraperitoneal NAC. This finding was not unexpected, because it is unclear whether per os administration of NAC achieves therapeutic levels in the peritoneum[13].

Within the literature, oral delivery of very few substances has been shown to decrease adhesions.[38,39] In contrast, intraperitoneal administration of pharmaceutical compounds has a greater efficacy in decreasing adhesions.[40-41] Local and systemic drug delivery used for adhesion prevention has their own advantages and disadvantages. The application of drugs

directly at the site of peritoneal damage throughout and at the end of abdominal or pelvic surgery allows for achieving suitable concentrations just where it is needed. However, repeated topical applications are obviously not conceivable. [42] Systemic administration is surely a more reliable method for ensuring adequate hematic drug concentrations for a sufficient time. However, this approach is somehow limited by the fact that, at the injured peritoneal sites, blood flow is reduced or even cut off due to suturing and microvessels obstruction and to the presence of some degree of ischemia.[43] The combination of intraperitoneal and intravenous infusion for administration of NAC, were selected for this study, because it could be more practical than repeated intraperitoneal application. No systemic clinical side effects was observed and drug related toxicity were seen (omit this please) during the study.

In conclusion, the results of this study suggest a potential new therapeutic use for N-Acetylcysteine in reduction and prevention of intraabdominal adhesion formation in sheep.

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چکیده

تاثیر N- استیل سیستئین بر چسبندگی بعد از جراحی محوطهٔ بطنی در مدل حیوانی بزرگ

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هدف- مکانیسم‌هایی که استرس اکسیداتیو را مهار و فعالیت فیبرینولیتیک را تقویت می‌کنند باعث کاهش چسبندگی می‌شوند. N- استیل سیستئین یک آنتی‌اکسیدانت است که خاصیت فیبرینولیتیک و مقابله با چسبندگی آن در مدل حیوانی بزرگ به اثبات نرسیده است. هدف این مطالعه بررسی توانایی این دارو در کاهش چسبندگی در مدل تخریش سروزی در گوسفند می‌باشد.

طرح- مطالعهٔ تجربی

حیوانات- هشت عدد گوسفند نر بالغ با میانگین وزنی ۴۲/۶۷ کیلوگرم وارد این مطالعه شدند.

روش کار- مدل چسبندگی از پیش تعریف شدهٔ سایش سروزی برای این مطالعه انتخاب گردید. حیوانات گروه آزمون (گوسفند ۴) داروی N- استیل سیستئین با دز ۱۵۰ میلی‌گرم بر کیلوگرم وزن بدن که در ۵۰۰ میلی‌لیتر سالین نرمال مخلوط شده بود را داخل محوطهٔ بطنی و قبل از بخیهٔ برش شکم دریافت کردند. حیوانات گروه کنترل (گوسفند ۴) به همین میزان سالین نرمال را در زمان یاد شده دریافت کردند. N- استیل سیستئین با دز ۱۵۰ میلی‌گرم بر کیلوگرم در روز و به صورت تزریق داخل رگی در دورهٔ ۷ روزه بعد از جراحی در گوسفندان گروه آزمون مورد استفاده قرار گرفت. نمونه‌های خون برای ارزیابی محتوی سلولی خون، پروتئین تام و فیبرینوژن در روز قبل جراحی و در روزهای ۱-۲-۴-۷-۱۱ و ۱۴ بعد از جراحی از حیوانات مورد مطالعه اخذ گردید. ۱۴ روز بعد از جراحی حیوانات مورد مطالعه ذبح شده و تشکیل چسبندگی به صورت ماکروسکوپیک و میکروسکوپیک (هیستوپاتولوژیک) مورد بررسی و درجه‌بندی قرار گرفت.

نتایج- بررسی محتوی سلولی خون و فیبرینوژن و پروتئین تام نشان‌دهندهٔ وقوع التهاب در ۷۵ درصد از حیوانات گروه کنترل بود. ارزیابی موارد یاد شده در حیوانات گروه آزمون روند التهابی را آشکار نساخت. اندازه‌گیری غلظت فیبرینوژن تفاوت معنی‌داری را در دو گروه آزمون و کنترل نشان داد. گسترش چسبندگی در تمامی حیوانات مورد مطالعه ۱۰۰ درصد بود و ۲ گروه از این جهت تفاوتی نداشتند. بررسی ماکروسکوپیک شدت چسبندگی و ارزیابی هیستوپاتولوژیک شدت التهاب و فیبروزه شدن کاهش برجسته و معنی‌داری را در وقوع چسبندگی در حیوانات گروه آزمون نشان داد.

نتیجه‌گیری- نتایج این مطالعه نشان دهندهٔ توانایی بالقوه داروی N-استیل سیستئین برای مقابله با وقوع چسبندگی بعد از جراحی محوطهٔ بطنی در طب انسانی و دامپزشکی می‌باشد.

کلید واژگان- N - استیل سیستئین، چسبندگی داخل محوطهٔ بطنی.