Iraqi Journal of Veterinary Sciences

www.vetmedmosul.com

Pathological and histomorphometric study of comparative gastric ulcer induced by indomethacin, aspirin, and ethanol in rats

M. G. Saeed, E.K. Al-Hamdany and H. Kh. Ismail

Department of Pathology and Poultry Diseases, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

Article information

Article history:
Received July 09, 2022
Accepted October 21, 2022
Available online February 26, 2023

Keywords:
Gastric ulcers
Indomethacin
Aspirin
Ethanol
Rats

Correspondence:
M. G. Saeed
mgsaeed@uomosul.edu.iq

Abstract

This study aimed comparison the gastric ulcer induced by indomethacin, aspirin, and ethanol on the level of pathological changes, ulcers surface area, and index. Forty rats were divided into 4 groups: the control group received normal saline, the remaining were the gastric ulcer groups, the Indomethacin group 40 mg/kg, the Aspirin group100 mg/kg, and the 80% ethanol group 5 ml/kg, all doses were orally administrated one time. The result revealed the ethanol group had the largest ulcer surface area, whereas the indomethacin group had a significantly lowest ulcer index after 3 hrs., and no significant differences among the groups after 24 hrs. Gastric ulcers were in the ethanol group after 3 hours, while the gastric ulcers were approximate in treated groups after 24 hrs. Histopathological changes revealed erosions or gastric ulcers with necrosis, hemorrhage, and inflammation, as well as complete ulcer exfoliation of mucosa reaching the muscularis in the indomethacin and ethanol groups after 24 hrs. The PAS/AB stain showed intense, slight, and moderate mucus reactivity in the indomethacin, aspirin, and ethanol groups, respectively, after 3 hrs., while decreased mucus reactivity in all treated groups after 24 hrs. The COX-2 expression increased in the indomethacin and aspirin groups except in the ethanol groups. We conclude that gastric ulcer surface area was severer in the ethanol group after 3 hrs., whereas severe gastric ulcers and a decline in mucus production after 24 hrs. The indomethacin group had a modest rise in COX2 expression, which was stronger in the aspirin and weak in the ethanol groups.

DOI: 10.33899/ijvs.2022.134659.2389,

Introduction

Gastric ulceration is a necrotizing mucosa lesion leading to inflammation and hemorrhage because of damage and perforation of the gastric mucosa (1). When the stomach is exposed to excessive acid and intense pepsin activity, gastrointestinal toxicity of non-steroidal anti-inflammatory drugs (NSAIDs), and toxic substances like alcohol use, it is the most common gastrointestinal disorder ever reported (2,3). Gastric ulcers occur due to the difference between potentially destructive and defensive factors of the gastric mucosa (4). One of the keys contributing reasons to this stomach ulcer disorder is an NSAID (5), and complications are increasing risk factors, with a prior history of ulcer disease are more likely to experience problems (6). The pathological changes are characterized by erosion, bleeding, and exfoliation of the mucosa due to an imbalance between aggressive (Helicobacter pylori, acid pepsin, prostaglandin, mucus, defensive factors, nitric oxide, growth factors, bicarbonate, and mucosal blood flow (7). NSAIDs consisting of Aspirin and Indomethacin are most used as an analgesic and anti-inflammatory drug and are commonly set by doctors, which act with other potent luminal factors such as *Helicobacter pylori* and acid to cause mucosal damage. An indomethacin-induced peptic ulcer in the glandular pattern is also accompanied by depletion of mucus and thiol-defense, increased protein oxidation and lipid peroxidation, prostaglandin (PG) synthesis, and depletion of mucus and

thiol-defense in the gastric tissues and reducing expressions of cyclooxygenases (7,8). Aspirin is an analgesic, antipyretic, and anti-inflammatory drug for inflammation and preventing cardiovascular system thrombotic diseases (9). Aspirin is known to induce peptic ulcers. Aspirin has a vital role in contributing to *Helicobacter pylori* in the occurring gastric ulcer due to an acid-driven mechanism (10). Ethanol is a standard model for acute gastric ulcer induction in experimental animals, causing mucosal permeability disorders, hemorrhage, and mucosal barrier damage with cell exfoliation (11). Products of lipid peroxidation and reactive oxygen species ROS play a vital role in the pathogenesis of gastric ulcer induction by ethanol (12). Typical histological changes shown by Ethanol administration include exfoliation of gastric mucosa, submucosal edema, congestion of blood vessels, necrosis of epithelium, and infiltrations of neutrophil and eosinophil (10,13). The oral administration of 1 ml Ethanol to cause gastric mucosal injury was induced in mice (14). Ethanol enhances gastric damage by invading immune cells that trigger inflammation corresponding with HCl causing gastric mucosa erosive damage and oxidative stress (15).

Although many studies used Indomethacin, Aspirin, and Ethanol in gastric ulcer induction and investigated their roles alone, this study aimed to compare the gastric ulcer induced by all of them on the level of pathological changes, ulcers surface area, ulcer index, mucous production, and COX-2 expression.

Materials and methods

Ethical approve

This study was carried out at the College of Veterinary Medicine, University of Mosul, Iraq in the animal house with the IACUC ethical approve number UM.VET.2021.28 at 4/11/2021.

Animals

Forty rats from both sex variants (3 months ago) weighing 200-250 g were used in the experiments housed at 24°C and deprived for the night of diet and water.

Reagents and chemicals

We used Indomethacin 25 mg conc. as an active ingredient from Medochemie LTD (Cyprus) at a dose of 40 mg/kg. Aspirin from Samarra drug Industry (Iraq) at dose 100 mg/kg. Absolute Ethanol from Scharlau Brand (Spain) at dose 5 ml/kg of 80%. Antibodies for COX-2 and DAB staining detection kit from Dako Brand, Denmark.

Experimental design

40 rats in total were divided into 4 groups (10 animals in each group). Group I: Control group rats received normal saline orally by gavage needle. Group II: rats received Indomethacin dissolved in distilled water, 1 dose orally of 40 mg/kg before 3 and 24 hours of euthanizing by ether. Group III: rats were administered aspirin dissolved in distilled water, 1 dose orally of 100 mg/kg before 3 and 24 hours of euthanizing by ether. Group IV: rats were administered diluted Ethanol 80% 1 dose orally of 5ml/kg of absolute ethanol before 3 and 24 hours of euthanizing by ether.

Gross appearance, fixation, and tissue processing

After euthanizing the animals, stomachs were examined grossly for gastric ulcers or erosions. The stomachs were extensively cleansed with saline for twenty minutes after being opened along the bigger curvature, dried with filter paper, and noted gastric ulcers were counted for each group and photographed. Samples of the stomach were fixed in neutral buffered formalin 10% for 72 h, followed by treatments with various alcohol concentrations for dehydration and xylene clearances, which were then embedded in hot paraffin wax and sectioned at a thickness of 6 microns. The tissue sections were stained using the Hematoxylin and Eosin stain (16), Periodic Acid Stain/Alsian Blue PAS/AB histochemical stain (17), and immunohistochemical staining of COX-2 expression using Rabbit monoclonal antibody against COX-2. The streptavidin-biotin enhanced system is the primary antibody, with a dilution of 1:20. (Dako, Denmark's Glostrup). Streptavidin that was peroxidase-labeled was applied after sections. Sections were followed by peroxidase-labeled streptavidin complex and DAB stain (DAB; DAKOpatts), then counter-stained with hematoxylin (18).

Assessment of ulcer index and ulcer score

These parameters were measured in all animal groups after induction of ulcer by Indomethacin, Aspirin, and Ethanol to calculate the ulcer index. The stomachs were dissected from the cardiac orifice and washed with tap water to clean the stomach from its content. Ulcer index (Ui) was calculated by applying the below formula (19). Ui= (Uno+Uss+Uperc)/100, where Ui: ulcer index; Uno: average number of ulcers per animal; Uss: average severity score; Upere: percentage of animals with an ulcer.

The surface area in mm of each lesion was measured (20). The percentage of ulcerated surface area was calculated as equal to the total area covered by all lesions. The gastric injury was graded from the histological slides based on the severity of lesions (of hyperemia and hemorrhagic erosions). Ulcer index has also been considered by ulcer score and using the following scoring method (21). Score 0=almost normal mucosa. Score 1=vascular congestion. Score 2=one or two lesions. Score 3=severe lesions

Score 4=very severe lesions. Score 5= full lesions of the mucosa. Mean ulcer score (calculated by dividing the total number of ulcers in each group by the number of rats in that group).

Statistical analysis

The data for 5 rats of each group analyzed statistically by the One-Way Analysis of Variance test was used to compare groups with Duncan's multiple comparisons in the Sigma Plot software program for statistical analysis.

Results

The histomorphometric measurements of ulcer surface area/mm^2 and ulcer index after 3 hours of ulcer induction revealed that the highest ulcer surface area was in the Ethanol group and differed significantly with Indomethacin and Aspirin groups, as well as the significantly lower ulcer index was in the Indomethacin group than Aspirin and Ethanol group (Table 1).

Results of the assessment of ulcer surface area/mm^2 and ulcer index after 24 hours of ulcer induction showed no significant differences among the study groups (Table 2).

The gross appearance of rats' stomachs of the Indomethacin and Ethanol groups revealed severe mucosa redness after 3 hours of ulcer induction with the site of erosions or gastric ulcers were obvious and more in number in number the Ethanol group. The site of erosions or gastric ulcers was more prominent than other sites, and high numbers in all three groups after 24 hours of gastric ulcer induction (Figure 1).

Table 1: Measurements of ulcer surface area (mm^2) and ulcer index after 3 hours in the groups of the study

Criteria	Control group	Indomethacin group	Aspirin group	Ethanol group	P value
Ulcer surface area (mm^2)	0.0±0.00	0.0302±0.0135*B	0.0219±0.0098*B	0.138±0.0617*A	0.011
Ulcer index	0.0±0.00	0.82±0.0139*B	1.034±0.001*A	1.08±0.014*A	0.002

Data expressed as Mean±Stander error (N = 5rats/group). * Means a significant difference between groups and control group at P≤0.05. The different letters in rows mean there is a significant difference at P≤0.05.

Table 2: Measurements of ulcer surface area (mm^2) and ulcer index after 24 hours in the groups of the study

Criteria	Control group	Indomethacin group	Aspirin group	Ethanol group	P value
Ulcer surface area (mm^2)	0.0±0.00	0.107±0.0193*A	0.141±0.0636*A	0.171±0.0554*A	0.05
Ulcer index	0.0±0.00	1.052±0.002*A	1.05±0.003*A	1.048±0.013*A	0.011

Data expressed as Mean±Stander error (N = 5rats/group). * Means a significant difference between groups and control group at P≤0.05. The different letters in rows mean there is a significant difference at P≤0.05.

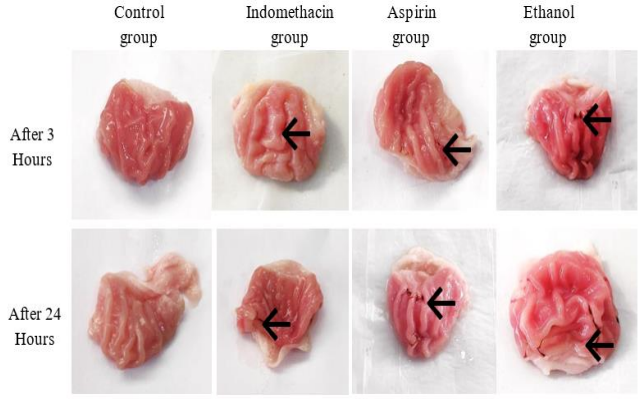

Figure 1: Gross appearance of rat's stomach of the four groups of the study after 3 and 24 hours of peptic ulcer induction showing the site of erosions or peptic ulcers (arrow).

The results of histopathological changes after 3 hours of gastric ulcer induction in the indomethacin, aspirin, and ethanol groups revealed the site of erosions or gastric ulcers with exfoliation and necrotic cells, hemorrhage, and inflammatory cells infiltration compared with the control group without gastric ulcer induction with a total thickness of mucosa and normal glandular pattern (Figure 2). The same lesions appeared after 24 hours of gastric ulcer induction and observed complete ulcer exfoliation of mucosa reaching the musculari in the Indomethacin and Ethanol groups in addition to decreasing mucosal thickness in the Aspirin group (Figure 3).

The tissue sections stained by PAS/AB histochemical stain after 3 hours of gastric ulcer induction showed the site of erosions or gastric ulcers with intense magenta color (indication of mucus) in the Indomethacin group, a very slight magenta color in the Aspirin group and moderate magenta color in the Ethanol group. While after 24 hours of gastric ulcer induction revealed the site of erosions or gastric ulcers with moderate magenta color in the Indomethacin and Ethanol groups and without magenta color in the Aspirin group compared with the control group, which was without gastric ulcer induction showing total thickness of mucosa with the apparent magenta color of mucus (Figure 4).

The results of immunohistochemical evaluations of COX-2 expression of the rat stomach tissue sections appeared the site of erosions or gastric ulcers with moderate expression in the Indomethacin group, strong expression in the Aspirin group, and mild expression in the Ethanol group compared with the control group which was without gastric ulcer induction with a mild expression of COX-2 (Figures 5 and 6).

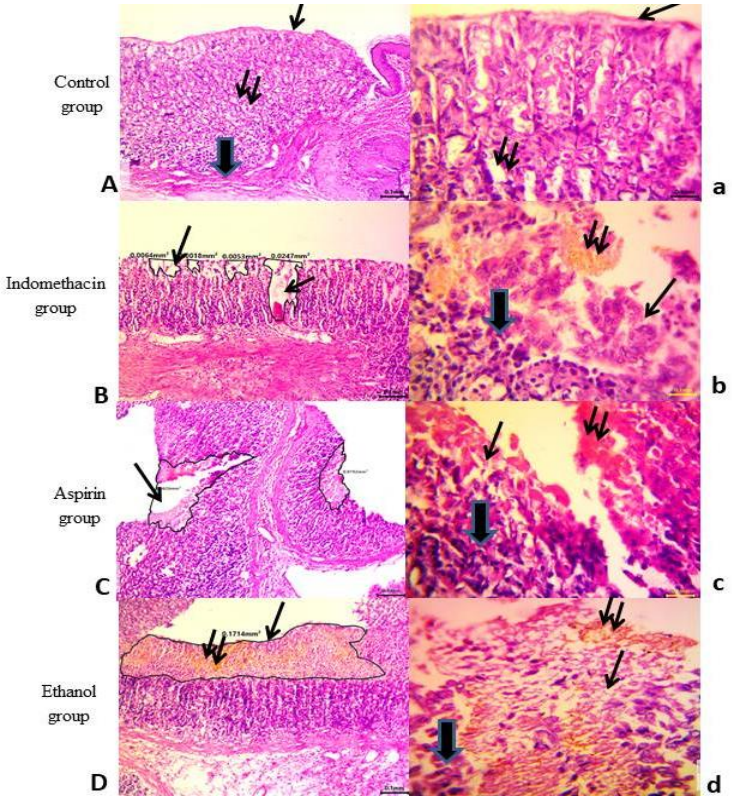

Figure 2: A photomicrograph of rat's stomach after 3 hours of peptic ulcer induction. (A, a) is the control group without peptic ulcer induction showing full thickness of mucosa (arrow) with normal glandular pattern (double arrow) and musculari (bold arrow). The other sections, Indomethacin (B, b), Aspirin (C, c), and Ethanol (D, d) groups show the site of erosions or peptic ulcers with exfoliation and necrotic cells (arrow), hemorrhage (double arrow) and inflammatory cells infiltration (bold arrow). H&E stain, (A, B, C & D 100X), (a, b. c & d 400X).

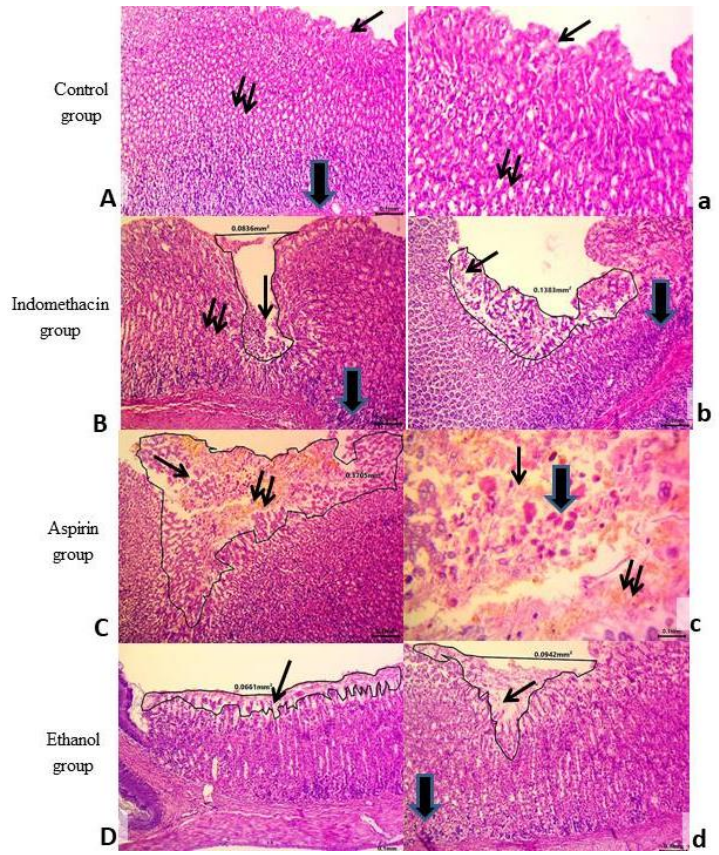

Figure 3: A photomicrograph of rats' stomachs after 24 hours of peptic ulcer induction. (A, a) is the control group without peptic ulcer induction showing full thickness of mucosa (arrow), normal glandular pattern (double arrow), and muscularii (bold arrow). The other sections, Indomethacin (B, b), Aspirin (C, c), and Ethanol (D, d) groups show the site of erosions or peptic ulcers with exfoliation and necrotic cells (arrow), hemorrhage (double arrow) and inflammatory cells infiltration and edema (bold arrow). H&E stain, (A, B, C & D 100X), (a, b. c & d 400X).

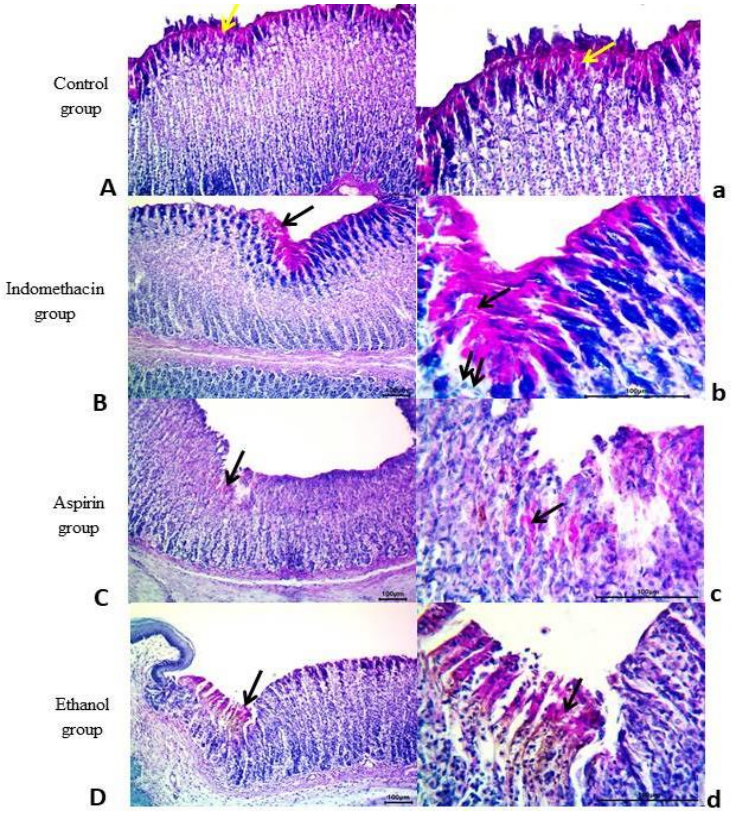

Figure 4: A photomicrograph of rat's stomach after 3 hours of peptic ulcer induction. (A, a) The control group without peptic ulcer induction shows total mucosa thickness with the obvious magenta color of mucin (arrow). The other sections show the Indomethacin group (B, b): the site of erosions or peptic ulcers with intense magenta color (arrow). Aspirin group (C, c): the site of erosions or peptic ulcers with a very slight magenta color. Ethanol group (D, d): the site of erosions or peptic ulcers with slight magenta color. PAS/Alsian blue stain, (A, B, C & D 100X), (a, b. c & d 400X).

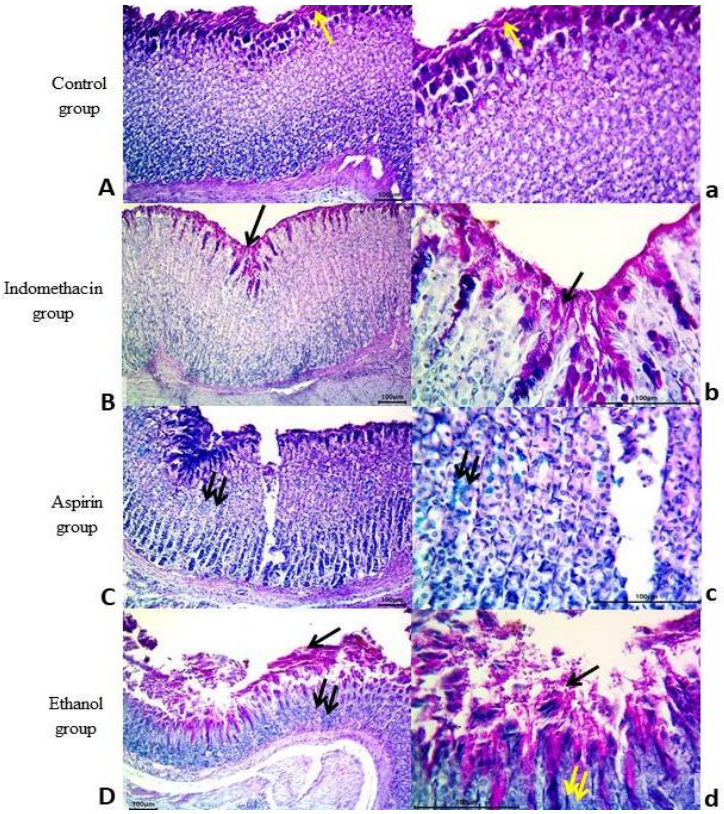

Figure 5: A photomicrograph of rats' stomachs after 24 hours of peptic ulcer induction. (A, a) is the control group without peptic ulcer induction showing total thickness of mucosa with the obvious magenta color of mucin (arrow). The other sections show the Indomethacin group (B, b): the site of erosions or peptic ulcers with intense magenta color (arrow). Aspirin group (C, c): the site of erosions or peptic ulcers without magenta color but blue color of mucopolysaccharides. Ethanol group (D, d): the site of erosions or peptic ulcers with a magenta color. PAS/Alsian blue stain, (A, B, C & D 100X), (a, b. c & d 400X).

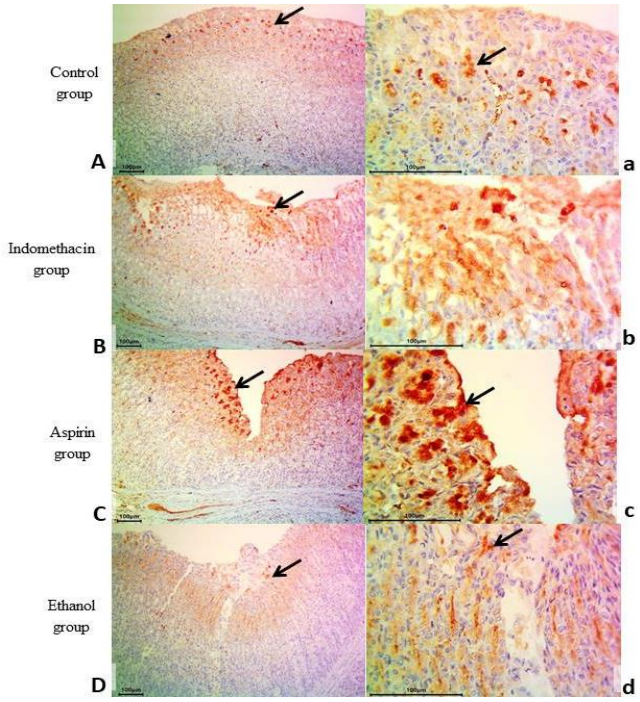

Figure 6: A photomicrograph of rats' stomachs of immunohistochemical expression of COX-2 after 24 hours of peptic ulcer induction. (A, a) is the control group without peptic ulcer induction showing mild expression (arrow). The other sections show the Indomethacin group (B, b): the site of erosions or peptic ulcers with moderate expression (arrow). Aspirin group (C, c): the site of erosions or peptic ulcers with strong expression. Ethanol group (D, d): the site of erosions or peptic ulcers with a mild expression. hematoxylin stain, (A, B, C & D 100X), (a, b. c & d 400X).

Discussion

Many models have induced gastric ulcers in animals, such as those induced by using HCL ethanol or acetic acid and NSAID. In the president study, indomethacin, aspirin, and ethanol-induced gastric ulcers in rats. The ulcer surface area was significantly the largest in the ethanol group. In contrast, the indomethacin group had the lowest ulcer index after 3 hrs of gastric ulcer induction, which may be attributed to ethanol as a potent and rapid injurious noxious to the gastric mucosa epithelium (18,22). However, there were no significant differences among the groups after 24 hrs. may be due to the attenuation of the mechanism of ethanol after 24 hrs and the escalating action of the NSAID indomethacin and aspirin. NSAID-induced damage to the gastric mucosa may occur due to several causes: inflammatory cell infiltration, mucosal blood flow, cytokines, free radicals, and gastric acid production (23). The role of reactive oxygen species ROS is vital when it is present in high concentrations. It overwhelms the antioxidant defense mechanism by disrupting cell proteins, most notably DNA and lipids (22). The occurrence of ROS in physiological amounts has a prominent role in many cellular functions, notably fighting against infection regulation of some intercellular signaling pathways and facilitating normal maturation (24).

The gross appearance of rats' stomachs of the indomethacin and ethanol groups revealed severe mucosa redness after 3 hrs of ulcer induction with the site of erosions or gastric ulcers were obvious and more in number in the ethanol group. The gastric ulcers were more evident and had high numbers in all three groups after 24 hrs of gastric ulcer induction, which agrees and corresponds with the many studies that animal studies frequently use the ethanol and Indomethacin-induced gastric ulcer model (3,25-27). The administration of ethanol reduces the release of bicarbonate, nitric oxide, and gastric mucus, with subsequent necrosis and damage of gastric mucosa and infiltration of inflammatory cells. Additionally, ethanol causes oxidative stress by increasing malondialdehyde formation and lowering glutathione synthesis (25). Both COX-dependent and -independent pathways are thought to be implicated. Additionally, numerous mechanisms, such as infiltration of inflammatory cells, cytokines, gastric acid production induction, free radicals, and mucosal blood flow, are known to contribute to NSAID-induced injury to the gastric mucosa. It hypothesized that the activation of early gross response-1 (Egr-1), phosphatase, and tension homolog lost on chromosome 10 caused impairments in angiogenesis, apoptosis, and sensory neuron function and could increase the stomach mucosa more vulnerable to damage (28).

The histopathological changes of gastric ulcer induction in the indomethacin, aspirin, and ethanol groups revealed the site of erosions or gastric ulcers with exfoliation and necrotic cells, hemorrhage, and inflammatory cell infiltration. This result agrees with most studies that used the same medicines for induction gastric ulcers, also acute ulceration by blocking COX and lowering circulating prostaglandin levels (29-32). NSAID prolongs its therapeutic efficacy and increases the risk of stomach ulcers by reducing bicarbonate and mucus secretions and blood flow, which has been connected to stomach injury and ulcer etiology in lab animals (33). Additionally, linked gastrointestinal damage to eroding mucus content, oxidants, and pepsin generated in the gastric lumen, in addition to extrinsic noxious agents and drugs acting on the epithelium of mucosa, both contributing to this erosion (34). This corresponds with our result of mucus production evaluation by PAS/AB histochemical stain, which revealed decreasing in the mucus secretions in all three groups of gastric ulcer induction after 24 hrs. but disagreed with others by the result of intense magenta color (indication of mucus) in the Indomethacin group after 3 hrs. Also, there was a reduction in the reactivity of goblet cells in gastric mucosa in the treated groups compared with the control group (35).

According to the current investigation, either the generation of free radicals or the suppression of prostaglandin synthesis is responsible for the ulcer index, and stomach volume significantly increased after oral indomethacin administration in the ulcerated rats. The significant events in the pathogenesis of mucosal ulcers impair gastroprotection and increase gastric acid output, which has been linked to decreased prostaglandin levels (36).

In our investigations, the production of ulcers was linked to an increase in PGE_2 levels, most likely due to increased COX-2 expression (37). Immunohistochemical IHC staining revealed the increased expression of COX-2 in the Indomethacin and Aspirin but not in the Ethanol groups. This increase is attributed to COX-2 expression increasing in inflammatory conditions with gastric ulcer rising COX-2 expression in different types of gastric tissue of cells like surface epithelial cells, endothelial cells, parietal cells, and inflammatory cells that many research revealed that NSAIDs inhibits both of COX isoforms (COX-1 and COX-2) this explain the increasing of COX-2 expression with NSDIAs (38-40).

Conclusion

This study conclude that gastric ulcer surface area was severer in the Ethanol group after 3 hrs., whereas severe gastric ulcers and a decline in mucus production after 24 hrs. The indomethacin group had a modest rise in COX-2 expression, which was stronger in the aspirin and weak in the ethanol groups.

Acknowledgment

We appreciate the help from the University of Mosul, College of Veterinary Medicine for the hands-on this work.

Conflict of interest

There were no conflicts of interest regarding this research.

References

1- Sabiu S, Garuba T, Sunmonu T, Ajani E, Sulyman A, Nurain I, Balogun A. Indomethacin-induced gastric ulceration in rats: Protective roles of *Spondias mombin* and *Ficus exasperata*. Toxic Rep. 2015;2:261-7. DOI: 10.1016/j.toxrep.2015.01.002
2- Adhikary B, Yadav SK, Roy K, Bandyopadhyay SK, Chattopadhyay S. Black tea and theaflavins assist healing of indomethacin-induced gastric ulceration in mice by antioxidative action. Evid Based Complement Alternat Med. 2011;1-11. DOI: 10.1155/2011/546560
3- Falsoni RMP, Moraes F de SA, Rezende MS de, Silva CL da, Andrade TU de, Brasil GA, et al. Pretreatment with water kefir reduces the development of acidified ethanol-induced gastric ulcers. Brazil J Pharmaceut Sci. 2022;58. DOI: 10.1590/s2175-97902022e191046
4- Aldossary SA. Ameliorative effect of cannabidiol against gastric ulcer induced by diclofenac in rats. J Pharm Res Int Sci. 2021;23:836-44. DOI: 10.9734/jpri/2021/v33i60b34686
5- Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: Why does not the stomach digest itself?. Physiol Rev. 2008;88:1547-1565. DOI: 10.1152/physrev.00004.2008
6- Sabiu S, Garuba T, Sunmonu T, Ajani E, Sulyman A, Nurain I, Balogun A. Indomethacin-induced gastric ulceration in rats: Protective roles of *Spondias mombin* and *Ficus exasperata*. Toxicol Rep. 2015;2:261-7. DOI: 10.1016/j.toxrep.2015.01.002
7- Karampour NS, Arzi A, RezaieA, Pashmforoosh M, Kordi F. Gastroprotective effect of zingerone on ethanol-induced gastric ulcers in rats. Med. 2019;(55):64. DOI: 10.3390/medicina55030064
8- Matsui H, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. J Clin Biochem Nutr. 2011;48(2):107-11. DOI: 10.3164/jcbn.10-79
9- Cryer B, BhattD L, Lanza FL, Dong J, Lichtenberger LM, Marathi UK. Low-dose aspirin-induced ulceration is attenuated by aspirin-phosphatidylcholine: A randomized clinical trial. Am J Gastroenterol. 2011;106:272-277. DOI: 10.1038/ajg.2010.436
10- Goldstein JL, Lowry SC, Lanza FL, Schwartz HI, Dodge WE. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. Aliment Pharmacol Ther. 2006;23(10):1489-1498. DOI: 10.1111/j.1365-2036.2006.02912.x
11- Guzman-Gomez O, Garc´ıa-Rodr´ıguez R, Quevedo- Corona L. Amelioration of ethanol-induced gastric ulcers in rats pretreated with phycobiliprotein of *Arthrospira (Spirulina) maxima*. Nutrients. 2018;10(6):763. DOI: 10.3390/nu10060763
12- Mittal N, Kanwar SS, Sanyal SN. Effect of nonsteroidal anti-inflammatory drugs and the procarcinogen 1,2-dimethylhydrazine on the antioxidant defense system. Int J Toxicol. 2008;27(2):169-74. DOI: 10.1080/10915810801977880
13- Shin JK, Park JH, Kim KS, Kang TH, Kim HS. Antiulcer activity of steamed ginger extract against ethanol/HCl-induced gastric mucosal injury in rats. Molecules. 2020;25(20):4663. DOI: 10.3390/molecules25204663
14- Dokmeci D, Akpolat M, Aydogdu N, Doganay L, Nesrin T. L-carnitine inhibits ethanol-induced gastric mucosal injury in rats. Pharmacol Rep. 2005;57:481-488. [available at]
15- Li CY, Xu HD, Zhao BT, Chang HI, Rhee HI. Gastroprotective effect of cyanidin 3-glucoside on ethanol-induced gastric lesions in rats. Alcohol. 2008;42:683-687. DOI: 10.1016/j.alcohol.2008.08.009
16- Al-Abdaly YZ, Saeed MG, Al-Hashemi HM. Effect of methotrexate and aspirin interaction and its relationship to oxidative stress in rats. Iraqi J Vet Sci. 2021;35(1):151-156. DOI: 10.33899/ijvs.2020.126490.1335
17- Al-Sabawi B, Sadoon H, Saeed M. Histochemical study of the hepatic metacestodes in infected sheep with hydatidosis. Iraqi J Vet Sci. 2022;37(1):45-51. DOI: 10.33899/ijvs.2022.133402.2222
18- Fornai M, Blandizzi C, Antonioli L, Colucci R, Bernardini N, Segnani C, De Ponti F, Del Tacca M. Differential role of cyclooxygenase 1 and 2 isoforms in the modulation of colonic neuromusculari function in experimental inflammation. J Pharmacol Exp Ther. 2006;317(3):938-45. DOI: 10.1124/jpet.105.098350.
19- Hajrezaie M, Salehen N, Karimian H, Zahedifard M, Shams K, Batran RA, Majid NA, Khalifa SA, Ali HM, El-Seedi H, Abdulla MA. Biochanin a gastroprotective effects in ethanol-induced gastric mucosal ulceration in rats. PloS One. 2015;10(3):e0121529. DOI: 10.1371/journal.pone.0121529
20- Murakami S, Kijima H, Isobe Y, Muramatsu M, Aihara H, Otomo S, Liang-niang L, Chun-bo A. Effect of salvianolic acid A, a depside from roots of *Salvia miltiorrhiza*, on gastric H+, K+-ATPase. Planta Medica. 1990;56(04):360-3. DOI: 10.1055/s-2006-960982
21- Kanter M, Demir H, Karakaya C, Ozbek H. Gastroprotective activity of *Nigella sativa* L oil and its constituent, thymoquinone against acute alcohol-induced gastric mucosal injury in rats. World J Gastroenterol. 2005;11(42):6662. DOI: 10.3748/wjg.v11.i42.6662
22- Mohammed IA, Shaban KA, Albadrany YM. Hepato-renal and hematological effects of flunixin and silymarin coadministration in rats.

Iraqi J Vet Sci. 2022;36(2):367-373. DOI: 10.33899/ijvs.2021.130323.1800
23- Brzozowski T, Konturek PC, Konturek SJ, Sliwowski Z, Pajdo R, Drozdowicz D, Ptak A, Hahn EG. Classic NSAID and selective cyclooxygenase (COX)-1 and COX-2 inhibitors in healing of chronic gastric ulcers. Microsc Res Tech. 2001;43:343-353. DOI: 10.1002/jemt.1102
24- Ahmed I, Elkablawy MA, El-Agamy DS, Bazarbay AA, Ahmed N. Carvedilol safeguards against aspirin-induced gastric damage in rats. Hum Exp Toxicol. 2020;39(9):1257-1267. DOI: 10.1177/0960327120918306
25- Utsumi H, Yasukawa K, Soeda T. Noninvasive mapping of reactive oxygen species by in vivo electron spin resonance spectroscopy in indomethacin-induced gastric ulcers in rats. Pharmacol Exp Ther. 2006;317(1):228-235. DOI: 10.1124/jpet.105.095166
26- Martindale JL, Holbrook NJ. Cellular response to oxidative stress: Signaling for suicide and survival. J Cell Physiol. 2002;192(1):1-15. DOI: 10.1002/jcp.10119
27- Arab HH, Salama SA, Omar HA, Arafa EA, Maghrabi IA. Diosmin protects against ethanol-induced gastric injury in rats: Novel anti-ulcer actions. PLoS One. 2015;10:E0122417. DOI: 10.1371/journal.pone.0122417
28- El-Maraghy SA, Rizk SM, Shahin NN. Gastroprotective effect of crocin in ethanol-induced gastric injury in rats. Chem Biol Interact. 2015;229:26-35. DOI: 10.1016/j.cbi.2015.01.015
29- Seo PJ, Kim N, Kim JH, Lee BH, Nam RH, Lee HS, Park JH, Lee MK, Chang H, Jung HC, Song IS. Comparison of Indomethacin, diclofenac and aspirin-induced gastric damage according to age in rats. Gut Liver. 2012;6(2):210-7. DOI: 10.5009/gnl.2012.6.2.210
30- Raish M, Shahid M, Bin Jardan YA, Ansari MA, Alkharfy KM, Ahad A, Abdelrahman IA, Ahmad A, Al-Jenoobi FI. Gastroprotective effect of sinapic acid on ethanol-induced gastric ulcers in rats: Involvement of Nrf2/HO-1 and NF-κB signaling and antiapoptotic role. Front Pharmacol. 2021;١٢:٦٢٢٨١٥. DOI: 10.3389/fphar.2021.622815
31- Mahmoud YI, Abd El-Ghffar EA. Spirulina ameliorates aspirin-induced gastric ulcers in albino mice by alleviating oxidative stress and inflammation. Biomed Pharmacother. 2019;109:314-21. DOI: 10.1016/j.biopha.2018.10.118
32- Byeon S, Oh J, Lim J, Lee J, Kim JS, "Protective effects of *Dioscorea batatas* flesh and peel extracts against ethanol-induced gastric ulcer in mice. Nutrients. 2018;(10)11:1680. DOI: 10.1177/0960327120918306
33- Lüllmann H, Mohr K, Ziegler A, Bieger D. Color atlas of pharmacology. 2nd ed. New York: Thieme; 2000. 166 p.
34- Olaniyi O, Salami A, Oluwole F. Gastroprotective mechanisms of *Entandrophragma angolense* extract against indomethacin-induced gastric ulceration in rats. J Complement Altern Med Res. 2017;3(3):1-12. DOI: 10.9734/jocamr/2017/3444
35- Rahman Z, Dwivedi D, Jena G. Ethanol-induced gastric ulcer in rats and intervention of tert-butylhydroquinone: Involvement of Nrf2/HO-1 signaling pathway. Hum Exp Toxicol. 2019;39(4):547-62. DOI: 10.1177/0960327119895559
36- Beck PL, Xavier R, Lu N, Nanda NN, Dinauer M, Podolsky DK, Seed B. Mechanisms of NSAID-induced gastrointestinal injury defined using mutant mice. Gastroenterol. 2000;119(3):699-705. DOI: 10.1053/gast.2000.16497
37- Colucci R, Antonioli L, Bernardini N, Ippolito C, Segnani C, Awwad O, Tuccori M, Blandizzi C, Scarpignato C, Fornai M. Nonsteroidal anti-inflammatory drug-activated gene-1 Plays a role in the impairing effects of cyclooxygenase inhibitors on gastric ulcer healing. J Pharmacol Exp Ther. 2012;342(1):140-9. DOI: 10.1124/jpet.111.190116
38- Halter F, Tarnawski AS, Schmassmann A. Cyclooxygenase 2—implications on maintenance of gastric mucosal integrity and ulcer healing: Controversial issues and perspectives. Gut. 2001;49:443-453. DOI: 10.1136/gut.49.3.443
39- Araújo Júnior RF, Souza TO, Medeiros CA, Souza LB, Freitas MD, de Lucena HF, do Socorro Costa Feitosa Alves M, de Araújo AA. Carvedilol decrease IL-1β and TNF-α, inhibits MMP-2, MMP-9, COX-2, and RANKL expression, and Up-regulates OPG in a rat model of periodontitis. PLoS One. 2013;8(7):e66391. DOI: 10.1371/journal.pone.0066391
40- Tawfeek FK, Ahmed SM. Effect of COX-2 inhibitor, rofecoxib, on epididymal sperm characters and accessory sex glands. Iraqi J Vet Sci. 2006;20(2):107-115. DOI: 10.33899/ijvs.2006.62488

دراسة مرضية وقياسية نسيجية مقارنة لقرح المعدة المحدثة بواسطة الاندوميثاسين والأسبرين والإيثانول في الجرذان

محمد غسان سعيد، انتصار خزعل الحمداني و هناء خليل إسماعيل

فرع الأمراض وأمراض الدواجن، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

هدفت هذه الدراسة إلى مقارنة قرحة المعدة التي يسببها الإندوميثاسين والأسبرين والإيثانول على مستوى التغيرات المرضية والمساحة السطحية ومؤشر القرحة. وزع ٤٠ جرذا إلى ٤ مجموعات على النحو التالي: مجموعة السيطرة تلقت محلول الملح الفسلجي أما المجاميع الأخرى لإستحداث قرحة المعدة كانت مجموعة إندوميثاسين ٤٠ ملغم/كغم ومجموعة الأسبرين ١٠٠ ملغم/كغم ومجموعة الإيثانول ٨٠% ٥ مل/ كغم وكانت جميع الجرع عن طريق الفم. تمت التضحية بعد ٣ و ٢٤ ساعة بخمسة جرذان لكل فترة بكل مجموعة. أظهرت النتائج أن أكبر مساحة سطحية للقرحة كانت في مجموعة الإيثانول مقارنة بمجموعتي الإندوميثاسين والأسبرين بعد ٣ ساعات من استحداث القرحة وكان مؤشر القرحة أقل معنويا في مجموعة الإندوميثاسين بينما لم توجد فروق معنوية بين المجموعات بعد ٢٤ ساعة. أظهرت التغيرات العيانية تقرحات معدية أكثر وضوحًا في مجموعة الإيثانول بعد ٣ ساعات، بينما كانت القرحة المعدية أكثر وضوحًا وعددا في المجموعات الثلاث بعد ٢٤ ساعة. أظهرت التغيرات النسيجية المرضية في كل المجاميع تآكلات أو تقرحات مع نخر ونزف والتهاب بعد ٢٤ ساعة. أظهرت صبغة باس الاليشيان الأزرق تفاعل شديد (وجود المخاط) في مجموعة الإندوميثاسين وخفيف جدا في الأسبرين ومتوسط في الإيثانول في موقع القرحة المعدية بعد ٣ ساعات بينما كانت كمية المخاط أقل بعد ٢٤ ساعة. ظهر ارتفاع تعبير إنزيمات الأكسدة الحلقية الثانية في مجموعتي الإندوميثاسين والأسبرين ماعدا مجموعة الإيثانول. نستنتج أن القرحة المعدية كانت شديدة في مجموعة الإيثانول مقارنة بمجموعات الإندوميثاسين والأسبرين بعد ٣ ساعات مع زيادة القرحة المعدية في جميع المجموعات بعد ٢٤ ساعة وظهر انخفاض إنتاج المخاط بعد ٢٤ ساعة في المجموعات المعاملة الثلاثة وزاد تعبير إنزيمات الأكسدة الحلقية الثانية في مجموعتي الإندوميثاسين والأسبرين وكان اقل في مجموعة الإيثانول.