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Original article

Effect of L-Arginine and Carvedilol on Peptic Ulcer and Hypertension in Rats

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Abstract:

Background: Adults with hypertension often suffer from peptic ulcer disease and are more likely to receive drugs for hypertension and peptic ulcer **Aim of the study:** The aim of this study was to evaluate effect of L-arginine and carvedilol as nitric oxide donors on peptic ulcer and on peptic ulcer hypertension co- morbidity regarding to these parameters: blood pressure, ulcer score, ulcer index, total antioxidant capacity(TAC),nitric oxide (NO), prostaglandinE2(PGE2)and tumor necrosis factor alpha (TNF-α) **Methods**: Rats were classified into: Group 1: control normal group. Group 2carboxy methylcelluose(CMC) group. Group 3: peptic ulcer (PU)group, Group4: hypertension -PU group, Group 5: PU L-arginine pretreated group, Group6: hypertension-PU L-arginine pretreated group, Group7: PU carvedilol pretreated group, Group8: hypertension -PU carvedilol pretreated group, Group9: hypertension- PU L-arginine treated group, Group 10: hypertension- PU carvedilol treated group **Results**: Treated groups showed significant improvement in all parameters related to PU and hypertension PU progression and improvement of the histopathology of stomach. **Conclusion:** Our study revealed that L-arginine and carvedilol showed improvement in blood pressure, ulcer score, ulcer index, TNF-α, TAC, NO and PGE2. There was no significant difference between both drugs. So our drugs have prophylactic effect against PU and hypertension PU co-morbidity and their effect appeared to be mediated, by reductions in oxidative stress and a preservation of gastro protective mechanisms as NO, PG E2 and TAC.

Key words: peptic ulcer, hypertension, L-arginine, carvedilol.

Abbreviations: PU; peptic ulcer TAC; total antioxidant capacity PGE2; prostaglandinE2, NO; nitric oxide, INDO; indomethacin, TNFα; tumor necrosis factor α.

Introduction

Peptic ulcer is one of the most common disorders considering the gastrointestinal tract; it affects 5% of the population around the world, so its prevention and management are considered very important challenges (1).

Hypertension is one of the most important factors associated with development of vascular diseases. Complications of hypertension such as coronary heart disease, stroke, myocardial infarction, heart failure are common. The etiology of hypertension has been widely accepted as responsible for endothelial dysfunction (2**).**

L-arginine is a semi-essential amino acid that is particularly rich in certain foods such as meats and nuts. L-arginine is the substrate for the enzyme nitric oxide synthase (NOS), which is responsible for the production of nitric oxide (3).

Carvedilol is a non-selective, cardiac beta-blocker with peripheral vasodilating effects, has anti-oxidant activity and is nitric oxide donor (4).

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with very effective antipyretic, analgesic, and anti-inflammatory activity(5). L-NAME is non-selective nitric oxide synthase (NOS) inhibitor (6).

Materials and method

Animals:

It is a prospective study carried out on (60) adult male albino rats obtained from (Experimental Animal Breeding Farm, Helwan-Cairo) weighing between 150- 200 g (at the beginning of the study), were used for in-vivo experiments. They were acclimatized for one week and were caged (6 rat/ cage) in fully ventilated room at room temperature in the pharmacology department, Benha Faculty of Medicine.

The study was carried out from 1st of September 2020 to 22th of September's 2020 .Rats were fed a standard chow with water.

This study was approved from ethical committee of Benha Faculty of Medicine.

Drugs

Indomethacin (**Acros, Belgium), L-NAME (Alfa Aesar, Germany), L-argnine (Alfa**

Aesar, Germany), Carvedilol (Acros, Belgium), CMC(LANXESS,Germany).

Experimental groups and procedures:

Group 1: control normal group given only standard diet. Group2: control carboxy methyl cellulose (CMC group). This group was given CMC from 5th day to 14th day.

Group 3: peptic ulcer group (PU group). In this group PU was induced by single oral dose of indomethacin (INDO) in dose of 100 mg/kg (7). Indomethacin was dissolved in 0.5% CMC (8). Group 4: hypertension -PU group (L-NAME +PU group). Rats were given L-NAME oral in dose 40mg/kg per day (9) for 2 weeks and INDO PU was done at 14th day. Group 5: PU L-arginine pretreated group (L-arginine +PU group). L-arginine was given at dose 200mg/kg per day (10) oral to rats in this group from 5th day till 14th day and INDO induced PU was done at 14th day. Group6: hypertension PU L-arginine pretreated group (L-arginine +L-NAME+PU group). In this group rats were given L-NAME from 1st day to 14th day, L-arginine from 5th day to 14th day and INDO induced PU was done at 14th day. Group 7: PU carvedilol pretreated group (carvedilol +PU group). In this group rats were given carvedilol oral in dose (30 mg/kg) (11) from 5th day to 14th day and INDO induced PU was done at 14th day. Carvedilol were suspended in 0.25% carboxy methyl cellulose (CMC) (12) given orally by gavage. Group 8: hypertension PU carvedilol pretreated group (carvedilol +L-NAME+PU group). In this group rats were given L-NAME from 1st day to 14th day, carvedilol from 5th day to 14th day and INDO induced PU was done at 14th day, Group 9: hypertension PU L-arginine treated group (L-arginine SD+L-NAME+PU). This group was given L-NAME for 2 weeks and single dose of L-arginine at 14th day one hour before INDO induced PU group 10: hypertension PU carvedilol treated group (carvedilol SD+L-NAME+PU). This group was given L-NAME for 2 weeks and single dose of carvedilol at 14th day one hour before INDO induced PU.

Systolic blood pressure measurement:

Blood pressure was measured at the start of experiment and in last day of working. SBP in conscious non-anaesthetized rats was measured by noninvasive tail cuff plethysmography. Briefly tails of rats were placed in plastic restrainer. Cuff with a

pneumatic pulse sensor was attached to the tail (13).

Determination of the ulcer score

The gastric lesions were evaluated according to the method of (14) and scored according to ulcerated area between 1 and 5 as following: score (1): 1-6 $mm^{2,}$ (2): 7-12mm^2 ,(3): 13-18 mm^2 ,(4): 19-24 mm^2 ,(5): Above 24mm^2 **.**

Determination of the ulcer index

The ulcer index was determined using the formula described by (15)

Ulcer index = $\frac{10}{X}$ (X = total mucosal area/total ulcerated area).

Serum TAC assays:

TAC was determined colorimetrically (16)

Serum NO assay:

Serum NO was measured by Total Nitric Oxide and Nitrate/Nitrite Assay, R&D system (USA) (17)

Measurement of serum PGE2:

PGE2 was measured by rat PGE2 ELISA test, Fine test (China) **(**18**).**

Measurement of serum TNF-α:

Serum TNF-α was measured by Rat TNF-α Immunoassay, R&D system (USA) (19).

Histological examination of stomach:

The stomachs were dissected out, washed and fixed in 10% para formaldehyde. Tissue samples were cut into 5 mm thick sections using a HistoRange microtome and stained with hematoxylin & eosin (H&E).

Stomach tissue sections were examined under light microscope.

Statistical analysis:

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical Package for social science) version 26.0. Descriptive statistics were calculated in the form of Mean ±SD standard deviation (SD). In the statistical comparison between the different groups, the significance of difference was tested using the following test: AVONA (analysis of variance): used to compare between more than two different groups of numerical data followed by post-hoc Tukey. P value <0.05 was considered statistically significant

Results

Effect of L-arginine and carvedilol on blood pressure, ulcer score, ulcer index in rats' groups showed in table (1).

Effect of L-arginine and carvedilol on TAC, NO, PGE2, TNF-α in rats' groups showed in table (2).

Effect of L-arginine and carvedilol on histological examination of gastric mucosa showed in fig. (1,2,3,4,5,6,7,8,9,10)

Table (1) Effect of L-arginine and carvedilol on blood pressure, ulcer score, ulcer index in rats' groups

	control	**CMC**	**PU**	**L-NAME+ PU**	**L-arginine + PU**	**L-arginine +L-NAME +PU**	**Carvedilol +PU**	**carvedilol +L-NAME +PU**	**L-arginine SD +L-NAME +PU**	**carvedilol SD +LNAME +PU**
Blood pressure mm Hg	119.50 (±5.21)	118.83 (±4.79)	122.50 (±9.05)	162.33 abc ±(11.22)	120.83 d (±10.93)	134.83 d (±7.65)	107.50 df (±9.46)	123.67 d (±6.31)	154.17 abcefgh (±12.92)	146.33 abcegh (±8.80)
Ulcer score	0(±0)	0(±0)	3.50ab (±.84)	4.83abc (±.41)	1.67 abcd (±.52)	2.17 abcd (±.41)	1.50 abcd (±.55)	1.83 abcd (±.75)	4.67 abcdefgh (±.52)	4.50 abcdefgh (±.55)
Ulcer Index	0(±0)	0(±0)	0.326ab (±0.032)	0.501 abc (±0.07)	0.143 abcd (±0.055)	0.194 abcd (±0.057)	0.124 abcd (±0.046)	0.173 abcd (±0.043)	0.459 abcefgh (±0.06)	0.462 abcefgh (±0.037)

Data expressed as mean±SD

SD: standard deviation P: Probability *: significance <0.05

Test used: One-way ANOVA followed by post-hoc tukey

a: significance relative to control group b: significance relative to CMC group

c: significance relative to PU group d: significance relative to L-NAME + PU group

e: significance relative to L-arginine+ PU group f: significance relative to L-arginine +L-NAME +PU group

g: significance relative to carvedilol +PU group h: significance relative to carvedilol +L-NAME+PU group

i: significance relative to L- arginine SD+L-NAME+PU group.

Table (2) Effect of L-arginine and carvedilol on TAC, NO, PGE2, TNF-α in rats' groups

	control	CMC	PU	L-NAME +PU	l-arginine +PU	L-arginine +L-NAME +PU	Carvedilol +PU	Carvedilol +L-NAME +PU	L-arginine SD +L-NAME +PU	carvedilol SD +LNAME +PU
Total antioxidant mM/L	**0.334 (±0.030)**	**0.341 (±0.072)**	**0.173ab (±0.021)**	**0.049 abc (±0.011)**	**0.299 cd (±0.045)**	**0.266 cd (±0.057)**	**0.306 cd (±0.069)**	**0.282 cd (±0.073)**	**0.059 abcefgh (±0.019)**	**0.068 abcefgh (±0.023)**
NO µmol/L	**113.25(±15.40)**	**112.67(±4.76)**	**67.23ab(±6.88)**	**32.53 abc (±5.41)**	**100.72 cd (±4.59)**	**96.41 cd (±18.75)**	**105.25 cd (±6.45)**	**98.55 cd (±7.06)**	**48.19 abcefgh (±5.92)**	**46.81 abcefgh (±3.79)**
PGE2 Pg/ml	**84.96(±5.66)**	**82.62(±5.41)**	**62.65ab(±8.83)**	**36.53 abc (±8.81)**	**92.34 cd (±5.90)**	**80.5 cd (±2.07)**	**94.50 cd (±6.12)**	**83.66 cd (±5.18)**	**45.28 abcefgh (±6.63)**	**47.40 abcefgh (±4.98)**
TNF-α Pg/ml	**98.56 (±2.06)**	**99.49 (±7.54)**	**262.71ab (±13.62)**	**308.83 abc (±7.65)**	**117.04 abcd (±7.37)**	**131.22 abcd (±5.25)**	**119.43 abcd (±13.08)**	**134.73 abcd (±6.89)**	**293.95 abcefgh (±8.55)**	**295.51 abcefgh (±6.77)**

Data expressed as mean±SD

SD: standard deviation P: Probability *: significance <0.05

Test used: One-way ANOVA followed by post-hoc tukey

a: significance relative to control group b: significance relative to CMC group

c: significance relative to PU group d: significance relative to L-NAME + PU group

e: significance relative to L-arginine+ PU group f: significance relative to L-arginine +L-NAME +PU group

g: significance relative to carvedilol +PU group h: significance relative to carvedilol +L-NAME+PU group

i: significance relative to L- arginine SD+L-NAME+PU group.

Histopathological changes:

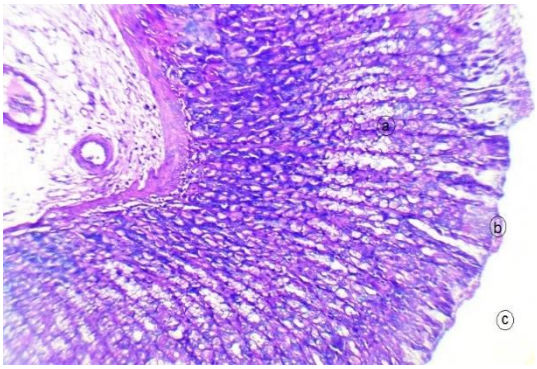

Fig1: photomicrograph of stomach of G1 showing typical histologic layers of stomach mucosa, including the glandular tissue, submucosa, muscular coat, and covering serosa.

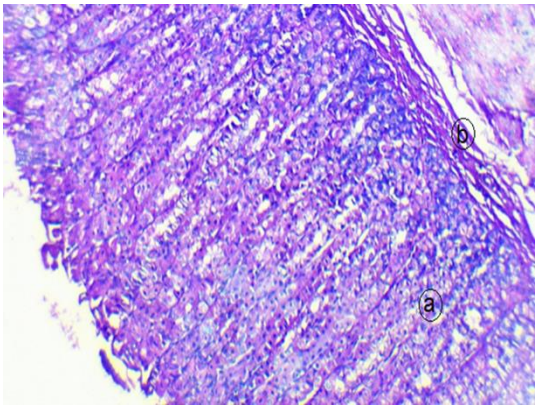

fig.2: photomicrograph of stomach of G2showing intact gastric mucosa without ulceration and regular glands in the lamina

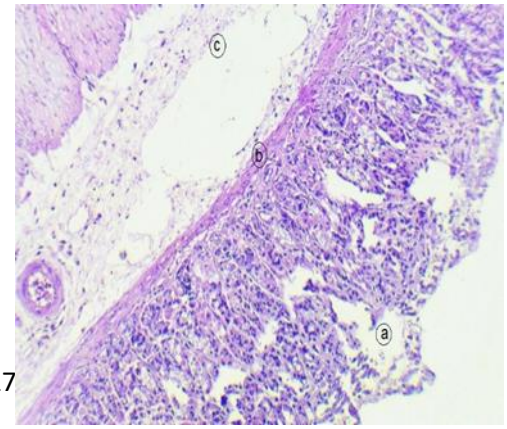

fig.3: photomicrograph of stomach of G3 showing severe mucosal injury, complete multiple erosions mixed with inflammatory cells and cellular debris.

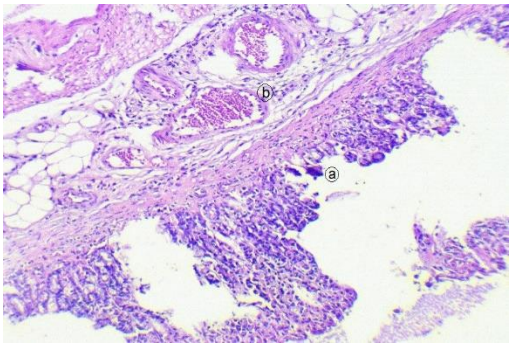

fig 4: photomicrograph of stomach of G4 showing severe gastric ulcer formation with loss of the epithelium over the area of ulceration reaching severely congested submucosa.

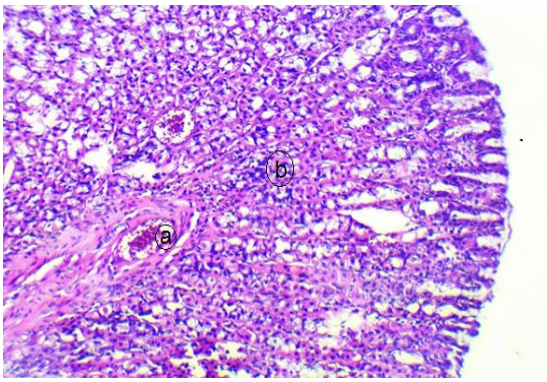

fig.5: photomicrograph of stomach of G5 showing mucosal damage mild disruption of gastric mucosa, mild inflammatory cell infiltration, and mucosal and sub-mucosal congestion with no apparent ulceration.

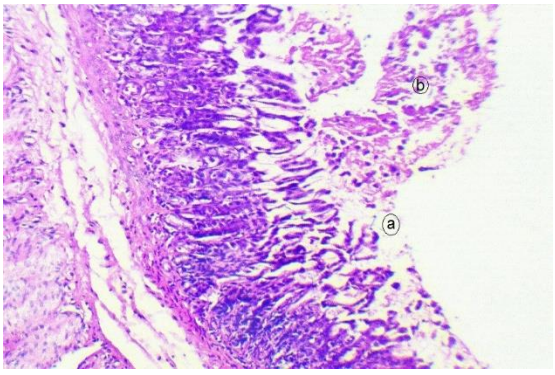

fig.6 photomicrograph of stomach of G6 showing partial erosions, epithelial damage and glandular disruption.

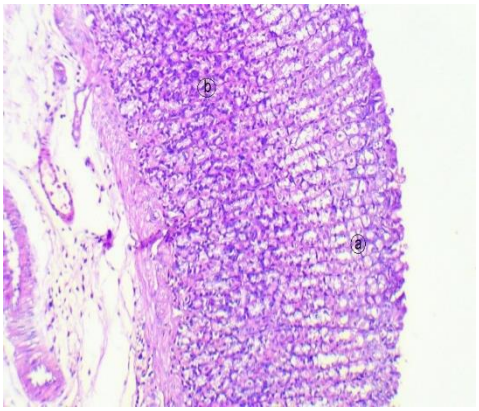

fig.7: photomicrograph of stomach of G7 showing no observable ulceration of gastric mucosa, mild inflammatory cell infiltration, very mild partial necrosis of the surface epithelium, glandular cells appear enlarged and ballooned, goblet cells are few and there is mild submucosal edema.

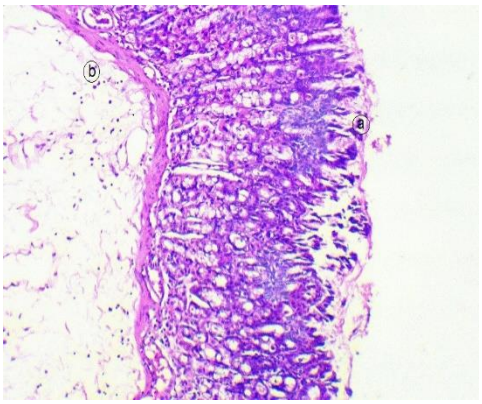

fig.8: photomicrograph of stomach of G8 showing mild mucosal damage with injured epithelium and mild inflammatory cell infiltration

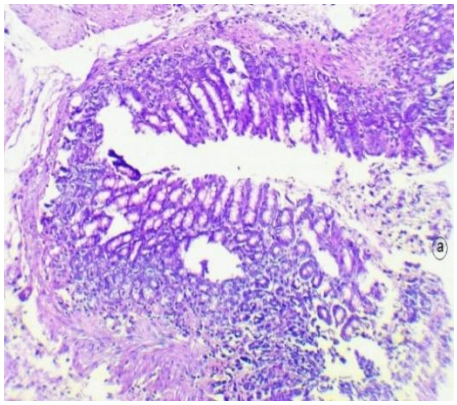

fig.9 photomicrograph of stomach of G9 showing prominent gastric ulcer formation that extended and involved the gastric glands and submucosa.

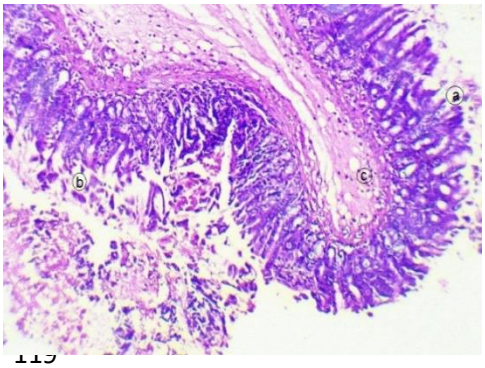

fig.10 photomicrograph of stomach of G10 showing mucosal injury, multiple erosions and gastric ulcer formation with infiltration of mixed inflammatory cells.

Discussion

The present study was done to evaluate the effect of carvedilol and L-arginine on PU rats and hypertension -PU rats regarding to their effect on blood pressure, ulcer score and index, NO, PGE2 TAC and TNF-α.

In the current work PU was achieved by administration of INDO (100mg/kg) SD (7). Hypertension was achieved by administration of L-NAME (40mg/kg/d) for 2 weeks (8). L-NAME and INDO were given by oral gavage.

Induction of PU in rats by INDO resulted in significant increases in ulcer score, ulcer index and TNF-α levels and significant decrease in NO, PGE2 and TAC levels. These finding are in agreement with several studies [20, 21, 22, 23 & 24] which reported that INDO induced PU resulted in significant increases in ulcer score, ulcer index and TNF-α levels and significant decrease in NO, PGE2 and TAC levels.

Induction of hypertension by L-NAME and PU by INDO resulted in significant increases in blood pressure, ulcer score, ulcer index and TNF-α levels and significant decrease in NO, PGE2 TAC levels. These finding are in agreement with several studies [25, 26, 27, 28 & 29] who reported that L-NAME induced hypertension and INDO induced PU resulted in significant increases in blood pressure, ulcer score, ulcer index and TNF-α levels and significant decrease in NO, PGE2 and TAC levels.

Treatment with L-arginine200 mg/kg/day and carvedilol 30mg/kg/day for 10 days in PU rats resulted in non-significant change in blood pressure but showed significant decrease in ulcer score, ulcer index and TNF-α levels. This is in line with several studiers (30,31,32,33,34) which reported that treatment with L-arginine and carvedilol protected against PU and significantly decrease ulcer score, ulcer index and TNF-α levels.

. They also showed significant increase in NO, PGE2 TAC levels. This is in consistence with several studies (35, 36, 37 & 38) which concluded that L-arginine and carvedilol had strong anti-oxidant effect through increasing NO/ PGE2 path way.

Regarding treatment with L-arginine200 mg/kg/day and carvedilol 30mg/kg/day for 10 days in hypertensive PU rats resulted in significant decrease in high blood pressure

caused by L-NAME. this is in line with several studiers (29 & 39) which reported that L-arginine and carvedilol significantly decrease high blood pressure. They also showed significant decrease in ulcer score, ulcer index and TNF-α level. This is in line with several studiers (39 & 40) which reported that treatment with L-arginine and carvedilol protected against hypertension and PU and significantly decrease ulcer score, ulcer index and TNF-α levels. They also showed significant increase in NO, PGE2 and TAC levels. This is in consistence with several studies (29 & 41) which concluded that L-arginine and carvedilol had strong anti-oxidant effect through increasing NO/ PGE2 path way.

Treatment with L-arginine200 mg/kg/day and carvedilol 30mg/kg/day for 10 days PU rats and in hypertension -PU rats showed significant improvement in histological examination of gastric tissue. This is in agreement with several studies (31& 42) which found that protective activity of L-arginine and carvedilol result in less mucosal injury and limited or absent edema of submucosa

SD of L-arginine or carvedilol failed to lower blood pressure. This is in line with study (43) which reported that L-arginine reduce blood pressure in dose dependent manner and (44) which reported that SD carvedilol failed to lower L-NAME induced hypertension. Also SD of both drugs failed to decrease in ulcer score, ulcer index and TNF-α levels or increase in NO, PGE2 TAC levels. This is in agreement with the study (45) which concluded that effect of L-arginine and carvedilol blocked by long administration of L-NAME.

SD of L-arginine or carvedilol failed to improve histological damage cause by L-NAME and INDO.

Conclusion

In conclusion the results of this study showed that L-Arginine and carvedilol displayed gastro protective activity in indomethacin-induced peptic ulceration and in L-NAME induced hyper tension + indomethacin-induced peptic ulceration. It can be maintained by chronic use of these drugs, the effect appeared to be mediated, by reductions in oxidative stress and a preservation of gastro protective mechanisms as NO, PG E2 and TAC.

Also L-arginine and carvedilol significantly decrease blood pressure and that this decrease can be maintained by chronic use

of these drugs. Effect of L- arginine and carvedilol is directly associated with an increase of plasma levels of NO. There was non-significant difference between L-arginine and carvedilol on hypertension and peptic ulcer healing.

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