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Protective Effect of Vitamin E Against Renal Dysfunction in Rats Treated with ibuprofen.

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ABSTRACT

Ibuprofen is an important commonly used analgesic for many chronic disorders as rheumatoid arthritis. One of the probable adverse effects is renal impairment especially with long term use. Vitamin E is an antioxidant which may decrease oxidative stress and improve renal function therefore this sudy evaluates protective effects of vit. E on rats treated with Ibuprofen. The study groups included three groups, normal control, Ibuprofen treated group, Vit. E +Ibuprofen treated group, each group consists of 10 rats. Several investigations were done at the start and after one and two weeks including: blood urea, creatinine, urinary albumin/creatinine ratio, systolic blood pressure. After sacrifice hisopathological study of the renal tissue was done. The results of this study showed significant increase in all parameters measured in Ibuprofen treated group when compared to normal group$p < 0.05$. Treatment with vit.E resulted in improvement of all parameters measured$p < 0.05$.Concluding that vitamin E. has protective effect against renal damage caused by Ibuprofen.

Keywords: Ibuprofen, Vitamin E., creatinine, urea, albumin, antioxidant.

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INTRODUCTION

Ibuprofen is one of the most important prescribed NSAID and widely used in osteo-arthritis and rheumatoid arthritis and other medical conditions requiring analgesic drug[1]. It is one of the commonly prescribed drug in different situations requiring analgesia and antipyretic drug as fever, mild to moderate pain and primary dysmenorrhea and its toxicity and adverse effects are also common. The side effects are widespread, includeing gastrointestinal manifestions as gastric dyspesia, peptic ulcer, renal dysfunction, dermal lesion, central nervous system manifectaion as change of mood, hallucination. However, spectrum of nephrotoxicity is the most frequently encountered side-effect associated with different types of analgesic abuse [2]. Spuhler and Zollinger were the first to report analgesic induced chronic interstitial nephritis [3]. The urinary system has an important and main role in termination of toxic products in most situations. It has a main role in filtration, metabolism and excretion of xenobiotic and its metabolic end products [4]. Chemical materials or their active metabolic products may transfer from plasma to kidney tubules and if we compare its concentration in kidney to other tissues we can find a manifold concentration. Kidneys nearly receive 25% of heart output in order to have a good extraction of

Chemical materials and filtration of toxic products [4]. Various biochemical abnormalities produced in the kidney as a result of administration of NSAIDs including oxidative damage and impairment of structure and function of mitochondria caused by production of free radicals[5]

Vitamin E has many beneficial effects and can protect body organs such as the kidneys [6]. It has been reported that vitamin E limits and suppress the harmful effects of free radicals in cell membranes [7] and increase antioxidant enzyme activity in kidney tissues [8].

Thus this study evaluated the effect of vitamin E as a strong antioxidant on the kidney dysfunction caused by one important member of NSAIDs , ibuprofen.

MATERIAL AND METHODS

The present study is an experimental study . It was undertaken in the Department of pharmacology, Suez Canal University, with 30 male albino rats. They were purchased from the Egyptian Organization for Biological Products and Vaccines (Egypt), and allowed free access to food and water ad libitum. They were kept under constant conditions with 12/12 h light/dark cycles and left for acclimatization for one week before the start of thestudy. The care and handling of the animals were approvedby the Animal Care and Use Committee at the Suez Canal University and were in accordance with the National Institutes of Health guide for the care and use of laboratory animals (Maryland, USA).

All efforts were made to minimize animal suffering and toreduce the number of animals used.All rats were approximately of same weight (150-200gm), kept in similar environmental and dietary conditions.

Study groups:

The rats were divided into the following groups (10 rats per group):

- Normal Control Group received 2 ml of distilled water in two divided doses
- Ibuprofen treated group, The ibuprofen treated group was given (50mg/kg) which is the therapeutic dose of Ibuprofen, dissolved in 2 ml of distilled water per day[9]
- Ibuprofen + vitamin E group AS Ibuprofen + oily solution of vitamin E intraperitoneally in a dose of100 mg/kg BW/24h vitamin E for two weeks [10]

At the end of the experiments and 24 hours after receiving the last dose of vitamin E , rats were sacrificed by cervical dislocation.

All drugs and chemicals were purchased from Sigma Chemical Co., Egypt.

Investigations done at the beginningof the study,after one week and after two weeks:

- Systolic blood pressuse was measured by using tailcuff plethysmograph in conscious prewarmed rats [11].
- Then, blood samples were collected via the tail veins after overnight fasting rats for 16 h to determine serum levels of blood urea nitrogen and creatinine by standard urease assaysand picric acid reactions by colorimetric methods [12], using Bioclin kit (Santa Coloma, Spain).
- Urine samples were evaluated for proteinuria using albumin/creatinine ratio. These urine samples were obtained by palpation and gentle pressing on urinary bladder [13]. The urinary albumin concentration was measured by using microalbumin kits strip [14].

Histopathological examination

Severity of glomerular lesions was graded on scale based on Gellman criteria: D0, all glomeruli normal;D1, focal lesions on glomeruli; D2, mesangial thickening presents diffusely throughout the kidney; D3, capillary lumina narrowed and obliterated; D4, glomerulus appear hylanized [14].

Tubulointerstitial damage was graded as follows:

0 – no lesions showing cell infiltration and fibrosis;1 – minimal injury (single focus of lesion); 2 – mildinjury (more than two isolated foci); 3 – moderate injury(more than five isolated foci); and 4 – severe injury(more than ten isolated foci or diffuse infiltrationand fibrosis) [14].

Vascular lesions were graded as follows: 0 – normal;1 – focal thickening of the walls; 2 – diffusethickening of the walls; 3 – obliterated lumen ,Interstitial inflammation was graded as follows: 0 –no cell infiltration; 1 – minimal cell infiltration; 2 –mild to moderate cell infiltration; and 3 – severe diffuseinfiltration [14].

Statistical analysis

Results were collected and expressed as the mean± SD. Results were analyzed using The StatisticalPackage for the Social Sciences, version 15 (SPSSSoftware, SPSS Inc., Chicago, USA). One-way analysisof variance (ANOVA) followed by Duncan'spost-hoc test were used to test the significance of thedifference between quantitative variables; p value <0.05 was considered to be statistically significant.

No conflict of interest or funding agency for this work

RESULTS

Ibuprofen treated group showed gradual significant ($p < 0.05$) increase inblood urea levels(fig1), serum creatinine(fig.2), compared with normal control group, suggesting a significantdegree of glomerular dysfunction. These functionalchanges were associated with a significant elevationin Urinary albumin/creatinine ratio (table 1) and systolic arterial blood pressure (table2) ($p < 0.05$) in comparison with the normal control group .

In the group treated with vitamin E , there was a significant improvement of all parameters measured ($p < 0.05$) fig. 1,2, table 1,2.

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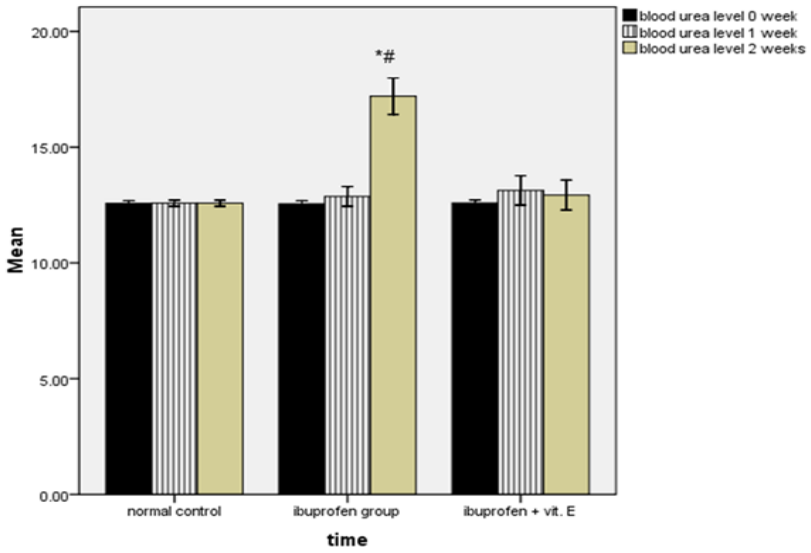

Fig 1: Urea level in study groups at different time interval.Values are expressed as the mean ± SD (n = 10), analyzed by one-way ANOVA followed by Duncan's multiple comparisons test. *, #, p < 0.05; * compared with normal control group, # compared with ibuprofen+vit.E group

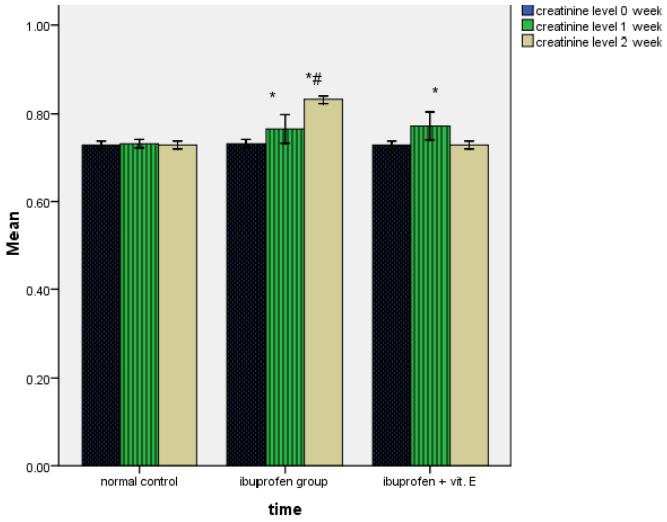

Fig 2: creatinine level in study groups at different time interval. Values are expressed as the mean ± SD (n = 10), analyzed by one-way ANOVA followed by Duncan's multiple comparisons test. *, #, p < 0.05; * compared with normal control group, # compared with ibuprofen+vit.E group

Additiinally , there was a significant increase in urinary albumin/ creatinine ratio in Ibuprofen treated group as compared with normal control $p < 0.05$, treatment with vit. E resulted in significant decrease in this ratio $p < 0.05$. as shown in table 1.

Table 1: Urinary albumin/creatinine ratio (µg/mg) in study groups at different time intervals

Study group	0 week	1 week	2 weeks
Normal control	33.0 ± 1.38	34.0 ± 1.58	33.0 ± 1.33
Ibuprofen group	34.0 ± 1.37	45 ± 2.33*	63.0 ± 1.38*#
Ibuprofen +vitamin E	33.0 ± 1.32	40.0 ± 1.22*	35.0 ± 1.58

Values are expressed as the mean ± SD (n = 10), analyzed by one-way ANOVA followed by Duncan's multiple comparisons test. *, #, $p < 0.05$; * compared with normal control group, # compared with ibuprofen+vit.E group

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Systolyic blood pressure was significantly higher in Ibuprofen treated group $p < 0.05$, also treatment with vit.E resulted in significant decrease in systolic blood presusure $p < 0.05$ as shown in table 2.

Table2: Systolic blood pressure in study groups

Study group	0 week	1 week	2 weeks
Normal control	100 ± 5	100± 5	100 ± 3
Ibuprofen group	100± 7	110 ± 3*	115± 8*#
Ibuprofen +vitamin E	100± 3	105 ± 2	102 ± 5

Values are expressed as the mean ± SD (n = 10), analyzed by one-way ANOVA followed by Duncan's multiple comparisons test. *, #, $p < 0.05$; * compared with normal control group, # compared with ibuprofen+vit.E group

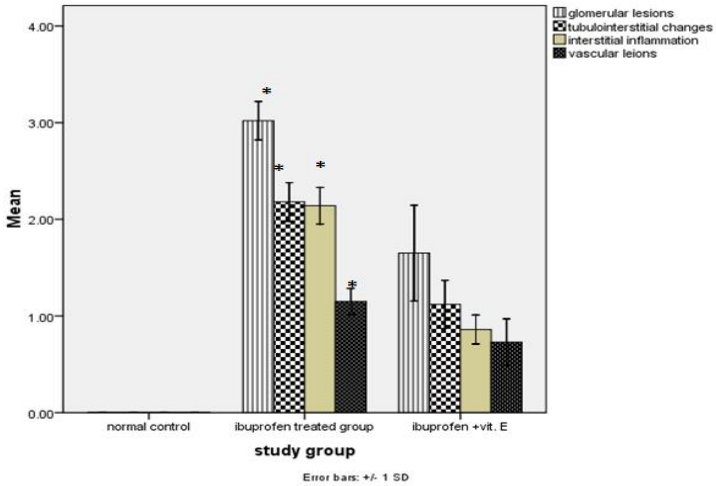
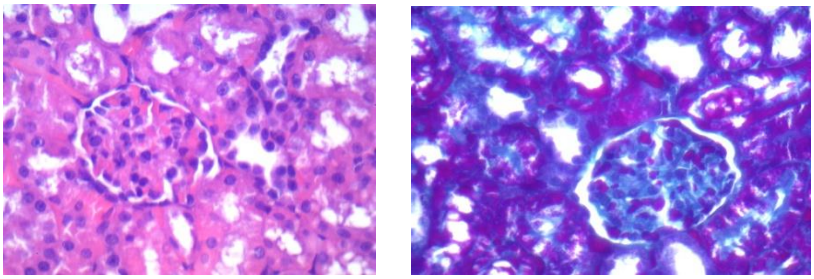


Fig 3: the histopathological score in study groups at different time interval. Values are expressed as the mean ± SD (n = 10), analyzed by one-way ANOVA followed by Duncan's multiple comparisons test. *, #, $p < 0.05$; * compared with normal control group, # compared with ibuprofen+vit.E group

Hisopathologically, Ibuprofen treated group showed hylanosis,hypertrophy and distortion of glomeruli, dilatedtubules and thick basement membranes, withsignificant ($p < 0.05$) elevation in mean histopathological score when compared to normal control group, These deleterious effects associated with Ibuprofen were significantly ameliorated by treatment withvit. E ($p < 0.05$) as shown in fig. 3,4.



A normal control

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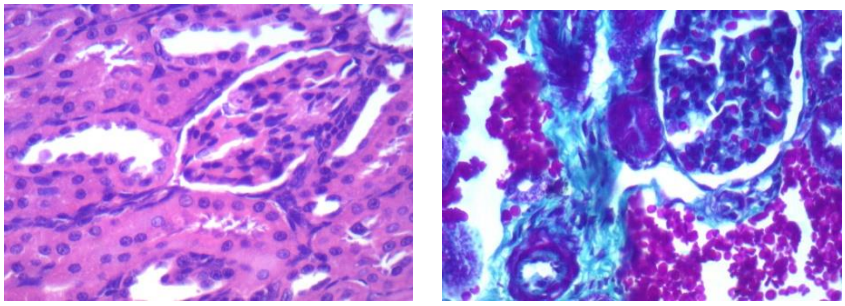
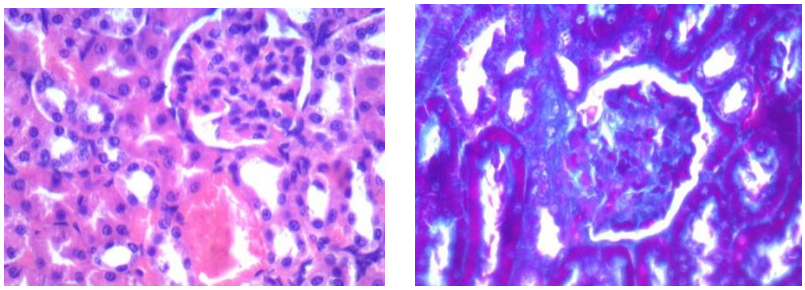


B Ibuprofen group



c-Ibuprofen +vit. E group

Fig 4: A photomicrograph of renal sections stained with hematoxylin and eosin (H & E) on the left and PAS stain on the right showed:

a- no histopathological changes in control group
b- hypertrophied distorted glomeruli and dilated tubules with interstitial fibrosis and inflammation in Ibuprofen treated group
c- slightly hypertrophied glomeruli in Ibuprofen+vit.E treated group

DISCUSSION

Nonsteroidal anti-inflammatory drugs (NSAIDS) are most commonly prescribed medication for pain management [15]. Most NSAIDS act as non-selective inhibitor of the enzyme cyclo-oxygenase inhibiting both COX - 1 and COX - 2 isoenzymes. This enzyme catalyzes the formation of prostaglandins from the precursor of arachidonic acid. Prostaglandins maintain renal blood flow (RBF) and glomerular filtration rate (GFR) especially in fluid depleted states. Locally synthesized prostaglandins PGI2 (Prostacyclin), PGE2 and PGD2 cause vasodilation, diminish vascular resistance and enhance renal perfusion with redistribution of blood flow from the renal cortex to nephrons in the Juxtamedullary region, PGE2 and to a linear extent PGF2α cause diuresis and natriuresis by inhibiting the transport of sodium and chloride in thick ascending limb of loop of Henle and the collecting ducts. PGE-1 tends to antagonise the action of antidiuretic hormone (Vasopressin)[15].

Lastly prostacyclin in concert with PGE2 serves to maintain the glomerular filtration rate. In volume depleted states, renin-angiotensin - aldosterone axis is stimulated with increased renin, angiotensin and aldosterone production resulting in renal vasoconstriction and increased sodium & chloride reabsorption. There is increased sympathetic outflow which increases vascular tone. In this setting prostaglandins provide compensatory vasodilation of renal vasular bed and ensure adequate renal blood supply precluding acute renal functional deterioration[16].

PGE2, PGD2 and to lesser degree prostacyclin causes vasodilation by depressing norepinephrine release. PGE2 antagonizes the vasoconstrictive action of angiotensin II on afferent arterioles. NSAIDs by inhibiting prostaglandin synthesis promotes unopposed vasoconstrictive action of leukotrienes, angiotensin II, vasopresin, endothelin and Catecholamines. This produces different nephrotoxic effects of NSAIDS [17].

In the present study, effects of Ibuprofen were observed on renal functions manifested by significantly increased serum urea , creatinine , urinary albumin/ creatinine ratio and systolic blood pressure($p < 0.05$). Histomorphology of renal parenchyma of albino rats. Showed dilated hypertrophied glomeruli, increase in the capsular space , unlike work by Yasmeen et al. and Ejaz et al. , which describes tubulo-intestitial lesion without glomerular involvement [18,19]. The results of this study also revealed that administration of vitamins E can reduce the harmful effects of ibuprofen and improve the adverse changes on rat renal tissue in the treated group compared to the Ibuprofen group.

Vitamin E as a powerful antioxidant and is the first line of defense against the peroxidation of fatty acids in phospholipids of cell membranes [20]. In addition, lipid peroxidation index decreases in the presence of vitamin E[21]. Vitamin E is also a powerful antioxidant that maintains the permeability of fluidity of biological membranes and prevents them from demolition [22] Vitamin E may improve renal tubular basal membrane degradation [22].

Factors such as carboxyethyl hydroxychromans (CEHC) are water-soluble metabolites of vitamin E that have anti-inflammatory and antioxidant properties. These metabolites increase in progressive renal diseases and improve renal function [23] Given the protective role of vitamin E against oxidative damage in the kidney[23] and other study results, it has been accepted that vitamin E has antioxidant properties and elevates the levels of catalases in kidney tissue[24].

Considering that these enzymes are responsible for the body's defense against free radicals[23]. vitamin E has greatly improved the harmful effects of oxidative stress created by ibuprofen in the kidney tissue. The results of this study indicate that vitamin E may largely improve the adverse effects of Ibuprofen on rat kidney tissue.

CONCLUSION

Considering that Ibuprofen is one of the commonly used analgesic, a greater consumption of vitamin E is recommended, and vit. E should be prescribed along with Ibuprofen to protect kidneys from probable toxic effect.

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