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Amelioration of Ibuprofen Induced Hepato-Renal Injury: Biochemical and Histological Study in Rats

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KEYWORDS
NSAIDs,
Cyanocobalamin,
Kidney,
liver,
Ibuprofen.

ABSTRACT:

Ibuprofen is one of the Non-steroidal anti-inflammatory drugs that exert anti-inflammatory, analgesic and antipyretic effects and its chronic and overuse has been associated with hepato-renal injury. The aim of this study was to know the protective effect of cyanocobalamin supplementation in amelioration of ibuprofen induced hepatic and renal injury. Twenty-eight rats were involved in this study, Group 1 (control group): rats received normal saline IP, Group 2 (IBU group): rats received 400 mg/kg ibuprofen orally by gavage for 10 days. Group 3 (IBU-cyanocobalamin treated group): rats received cyanocobalamin 1mg/kg IP 30 min before ibuprofen administration, Group 4 (IBU-cyanocobalamin treated group): rats received cyanocobalamin 1.5mg/kg IP 30 min before ibuprofen administration.

The current results showed a significant decrease of all liver and kidney parameters after treatment with two different doses of cyanocobalamin as compared with ibuprofen group. Histopathological results showed partial improvement in histological features of liver and kidney.

In conclusion, cyanocobalamin can protect the kidney and liver tissues from injury.

Introduction

As one of the most regularly used over the counter medicines in the world, nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked to kidney damage (1). NSAIDs, such as ibuprofen, is often prescribed to children and teens for the treatment of pain and fever (2). The use of NSAIDs, particularly in children, has expanded considerably in recent years (3). NSAIDs are largely believed to be safe because to their widespread and well-accepted usage, but even at therapeutic levels, they represent a risk of renal function loss (1).

There are two separate pathophysiological entities responsible for the adverse renal effects of these medications. To begin with, NSAIDs induce acute kidney damage (AKI) by decreasing renal blood flow owing to a reduction in prostaglandins, which control the glomerular vasodilation. As a result, NSAIDs interfere with the compensatory vasodilatation response of renal prostaglandins to naturally produced vasoconstrictor hormones (4). After taking NSAID, renal prostaglandins are inhibited, resulting in an immediate decrease in renal function. Interstitial nephritis is another cause of AKI since it is characterized by an inflammatory cell infiltration inside the renal interstitium. After roughly a week of NSAID exposure, an immune response occurs (5, 6, and 7). About 15% of patients with unexplained AKI have interstitial nephritis, which is now recognized as a significant cause of drug-induced AKI (6). NSAIDs use considered to be associated with hepatic adverse effects that exist mainly as a range of conditions such as asymptomatic increase in serum ALT and AST levels and hepatitis with jaundice to fulminant hepatic failure and even death (8). In 2005, a systematic review of different NSAIDs in patients with arithritis have been conducted and the authors of this review defined liver toxicity as aminotransferase elevations of more than three times (9).

Ibuprofen is one of the most often prescribed nonsteroidal anti-inflammatory medications (NSAIDs) in the world. Osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis are among the many conditions for which it is prescribed, inhibiting cyclooxygense enzymes, which are responsible for the creation of

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prostaglandins from arachidonic acid. The toxic impact of ibuprofen on renal glomeruli and tubules cause ibuprofen-induced nephrotoxicity. Dose related reduction in renal PG in long-term ibuprofen medication leads to renal dysfunction and decreased glomerular filtration rate in the end (10-13)

Cyanocobalamin is the heaviest (MW1355) and most unusual of all vitamins, and was the last one to be defined. Cyanocobalamin may be able to protect cells from ROS-induced damage because of its antioxidant properties. Even though cyanocobalamin has been shown to be safe at large dosages and the FDA generally considers it to be safe, there have been few research examining its therapeutic application against cellular harm. When it comes to kidney ischemia/reperfusion injury IRI, ROS has been shown to play a significant role (14-16).

The aim of this study was to know the protective effect of cyanocobalamin supplementation in amelioration of ibuprofen induced hepto- renal injury.

Materials and methods:

Twenty-eight rats were involved in this study, their weight was between 200-250 gm, before beginning this study, and the animals were allowed for acclimatization for 7 days and were kept on controlled temperature and environment with 12h light\dark cycle. Rats were divided into 3 groups randomly; each group contain 8 animals. The groups were divided as follow: **Group 1** (control group): rats received normal saline IP, **Group 2** (IBU group): rats received 400 mg/kg orally by gavage ibuprofen for 10 days (17). **Group 3** (IBU-cyanocobalamin treated group): rats received cyanocobalamin 1mg/kg IP 30 min before ibuprofen administration, **Group 4** (IBU-cyanocobalamin treated group): rats received cyanocobalamin 1.5mg/kg IP 30 min before ibuprofen administration (18)

At the end of the experiment 24 hr. after last adminstrtion, the animals were anesthetized with ketamine and xylazine then after opening the abdominal cavity, liver and right kidney were washed with D.W. then keep in 10 % formalin for progressive histopathological examination.

Direct heart puncture to collect blood samples which were centrifuged for 5 min. at 3000 pm to prepare the serum. ALT, AST, ALP, creatinine and urea were measured.

Results and discussions:

The current results showed a significant increase of all liver and kidney parameters after administration of ibuprofen as compared with control group while there is a significant decrease of all liver and kidney parameters after administration of cyanocoblmin in two different doses as compared with ibuprofen group (Table 1).

Table 1. Liver and kidney functions tests in study groups**.**

Treatments	Parameters				
	ALT U/L	**AST U/L**	**ALP U/L**	**Creatinine mg/dl**	**Urea mg/dl**
Group 1	81.83±7.32c	20.03±5.11c	227.5±28.04c	0.83±0.13c	38.01±6.51c
Group 2	110.63±13.05a	36.53±6.07a	256.03±31.44a	0.98±0.11a	52.56±4.21a
Group 3	90.56±2.6b	27.7±1.02b	235.01±5.1b	0.91±0.11b	43.1±1.5b
Group 4	89.3±1.65b	27.1±1.07b	237.01±2.6b	0.93±0.2b	45.3±1.1b
L.S.D$_{0.05}$	9.172	5.842	9.033	0.239	4.048

Histopathological results showed deterioration of kidney and liver tissues in ibuprofen group as compared with control group while there is partial improvement in histological features of liver and kidney after administration of cyanocobalamine in group 3 and 4 as compared with ibuprofen group as shown in (Figure 1,2,3 and 4) for kidney tissue and (Figure 5,6,7 and 8) for liver tissue.

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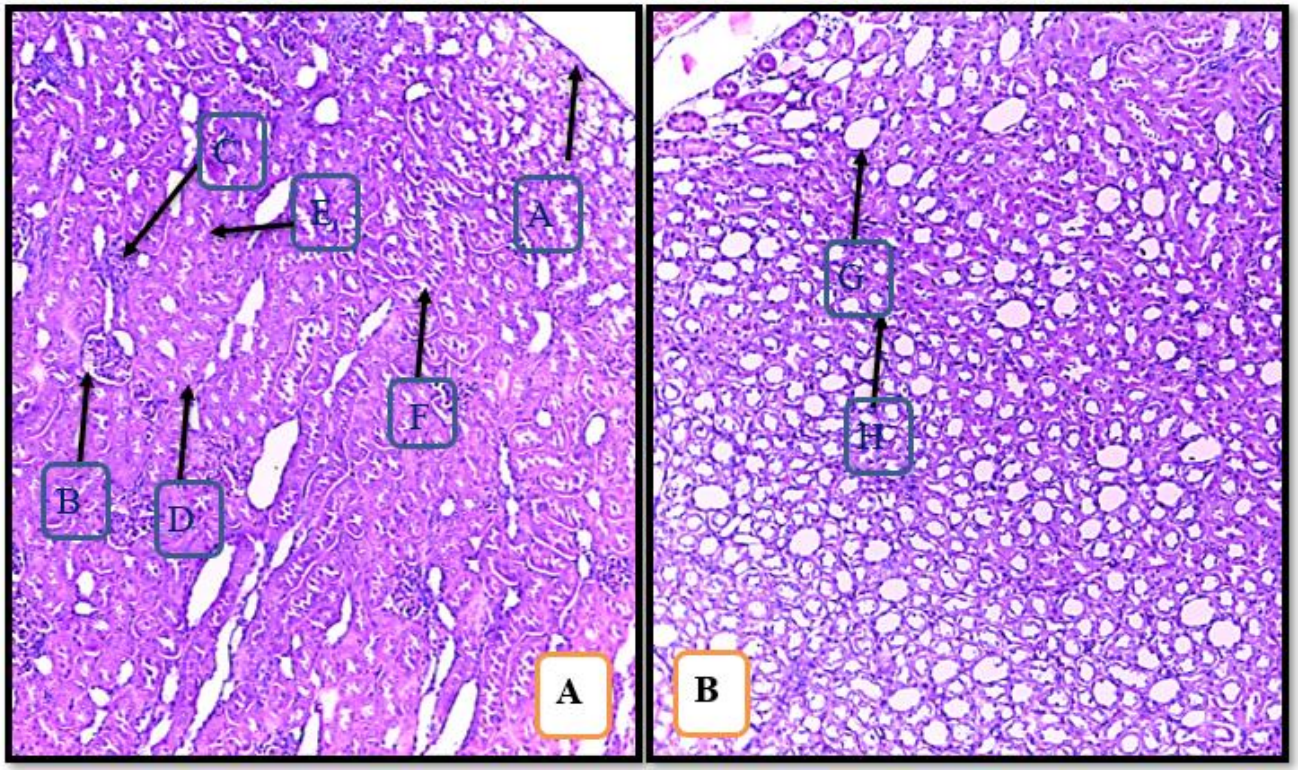

Figure.1. Cross section of the normal kidney in rat (**Group 1**) show : A: Capsule B- glomerula. C-Visceral layer. D-Distal tubule. E-Proximal tubule. F. Collect tubule. G. Megar papilla. H. Miner papilla. H&E (A) Cortex (B) Medulla X (100)

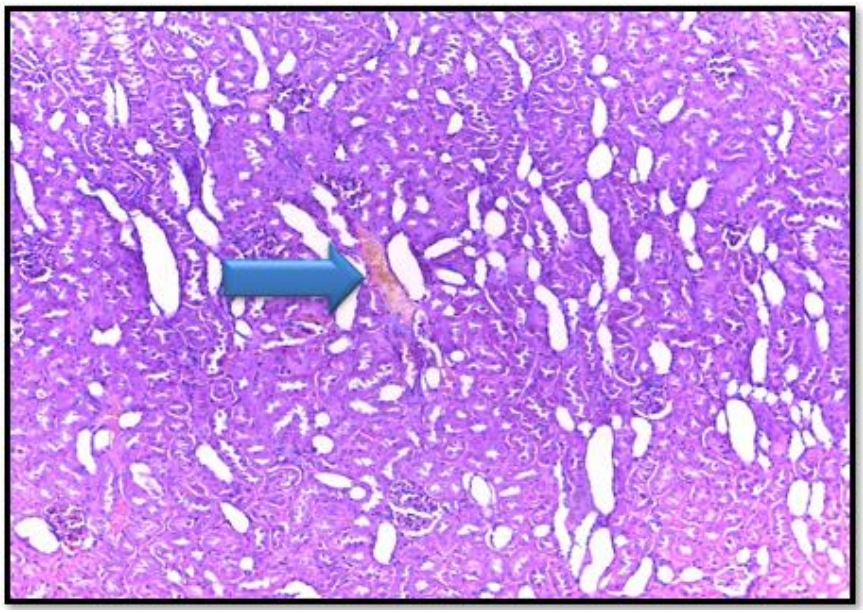

Figure.2. Cross section of the kidney in rat (Group 2) show hemorrhage (arrow) and cystic dilation of renal tubules (arrowhead)H&E X (100)

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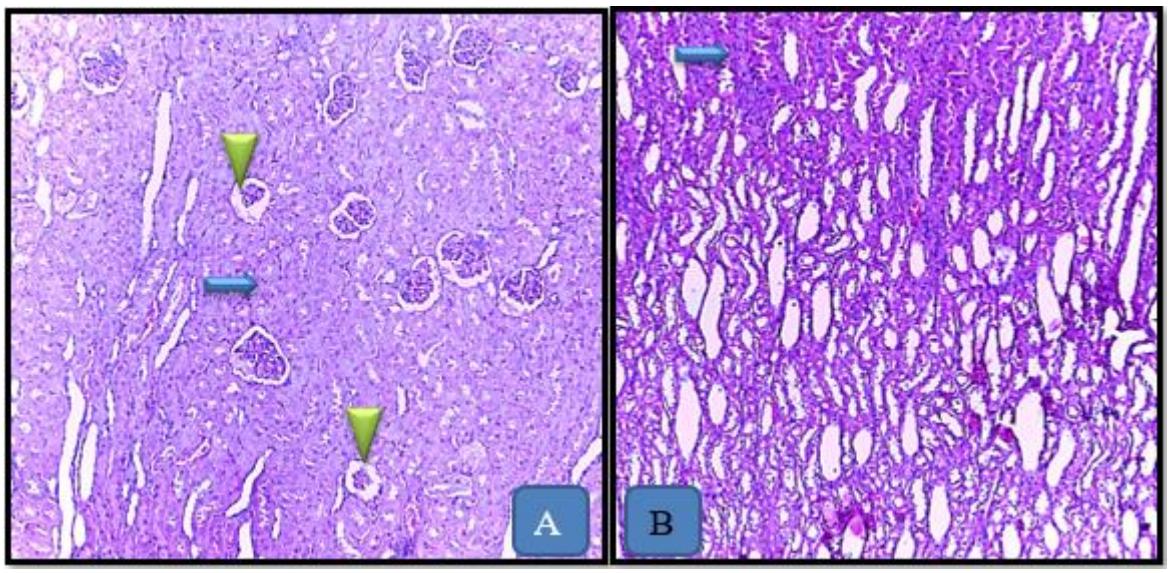

Figure 3. Cross section of the kidney in rat (Group 3) show acute cellular swelling of renal tubular epithelium (arrow) and glomerular tuft atrophy H&E (A) Cortex, (B) Medulla X100. H&E (A) Cortex (B) Medulla X (100)

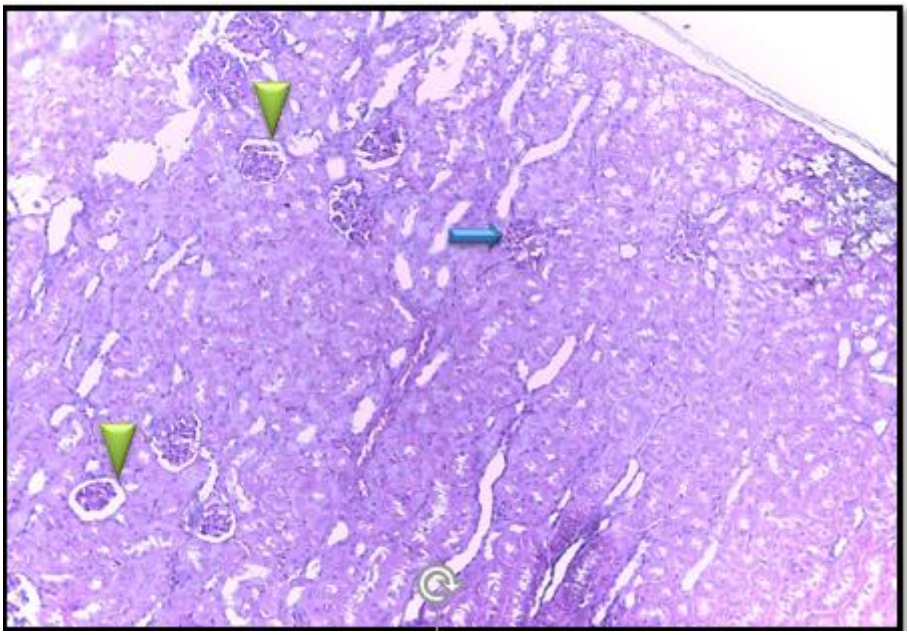

Figure.4. Cross section of the kidney in rat (**Group 4**) show mesangial cell proliferation (arrow) Hydropic degeneration(arrow head). H&E X (100*)*

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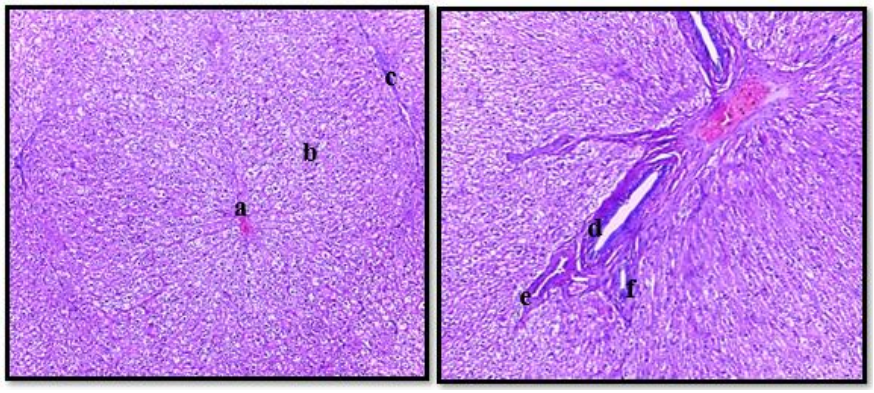

Figure 5. Cross section of the normal liver in rat (Group 1) show : a. Central vein, b. Hepatocytes, c. C.T. Septa, d. Hepatic artery, e. Portal vein, f. bile duct. H&E X (100)

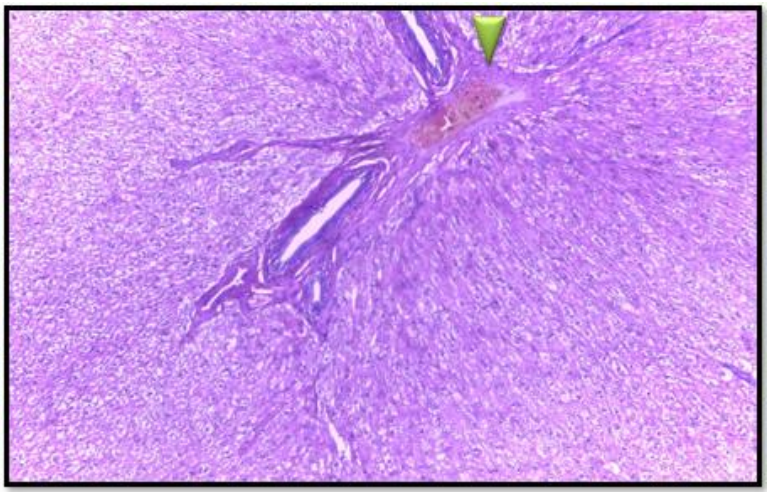

Figure 6. Cross section of the liver in rat (**Group 2**) showed Dilation of bile duct (arrow), and blood vessels congestion (arrow head) , fibroplasia H&E X(100)

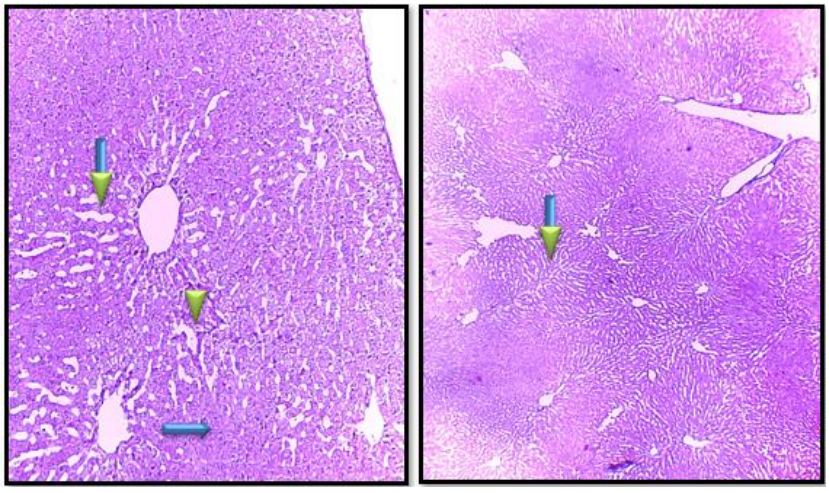

Figure 7. Cross section of the liver in rat (Group 3) showed vacuolar degeneration (arrow) and atrophy hepatocyte (arrow head) with widening of sinusoid (double arrow) H&E X(100)

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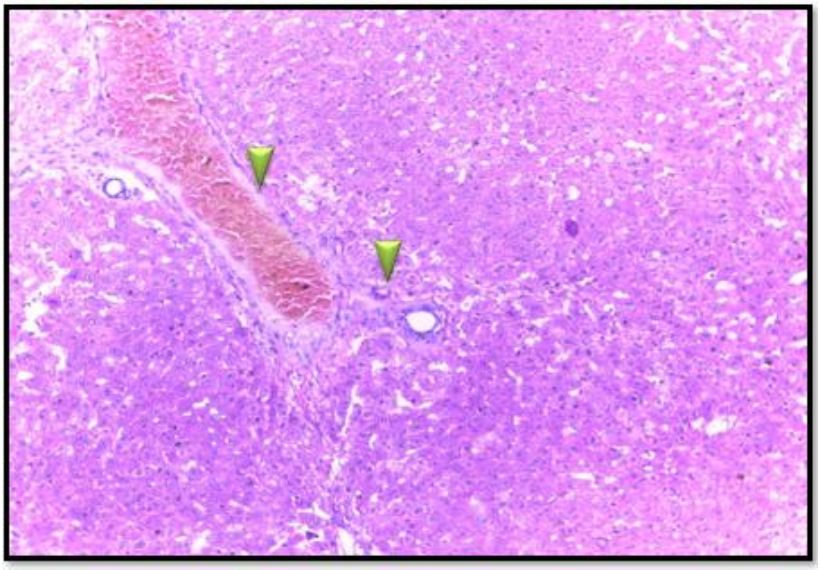

Figure 8 Cross section of the liver in rat (Group 4) showed widening and congested portal vein(arrow) and bile duct

Because ibuprofen is an analgesic and anti-inflammatory medicine, it's often prescribed to patients with aches and pains. However widespread ibuprofen use, renal problems have been reported as a result of its use (19). There were substantial differences in plasma creatinine, urea, ALT, AST and ALP levels between the ibuprofen group and the control group, suggesting impaired renal and hepatic function (17,20). ROS (reactive oxygen species) production and elevated oxidative stress were side effects of ibuprofen therapy (21). As a result, antioxidants may help to reduce ROS-induced cellular damage. As a result, it may be used therapeutically to avoid the cytotoxic effects of ibuprofen (22).

Current results showed partial repair in liver and kidney histology in group 2 and group 3 (B12 Treated group) in addition to liver and kidney function tests these may be due to the theory that various systems are activated by B vitamins in order to deliver the health benefits that they provide (23). The analgesic effects of B vitamins have been linked to an increase in inhibitory regulation of afferent nociceptive neurons in the spinal cord and a reduction in thalamic neurons' sensitivity to nociceptive stimulation (24). In addition, research suggests that the nitric oxide-cGMP pathway is involved in the effects caused by the combination of B vitamins (25).

Renal and hepatic effects of ibuprofen treatment in this investigation, is in agreement with (17,26). Restored tubules and glomeruli with dilated Bowmann's space were seen after treatment with cyanocobalamin. When tested on rats suffering from gentamycin-induced nephrotoxicity, antioxidant and anti-inflammatory actions of cyanocobalamin are believed to be responsible for the protection it provided (27). Another author (28) has studied the effects of high B12 doses on kidney function and morphology in I/R-injured animals. Inflammation, fibrosis, and apoptosis are all linked to ROS formation, and B12 substantially inhibited them. Human AKI mediated by IRI may be prevented or treated with B12, which is usually considered safe in humans. Abdulwahhab et al (14) and Abdulkhaleq et al (22) confirmed that cyanocobalamin has hepatoprotective effect.

Conclusion:

Cyanocobalamin can protect the kidney and liver tissues from injury induced by ibuprofen.

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