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Effects of ukrain in rats with intestinal ischemia and reperfusion



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ABSTRACT

Background: The purpose of this study is to investigate the potential protective effect of the ukrain on ischemia–reperfusion (IR) injury in rat intestine, which has not previously been studied.

Methods: Thirty-one male Sprague–Dawley rats were randomly assigned to four groups, each consisting of eight rats as follows: (1) a sham group (S) (laparotomy, but no IR injury); (2) ukrain group (U) (no IR, and ukrain was administered intraperitoneally 1 h before laparotomy); (3) intestinal ischemia–reperfusion (II/R) group (30-min occlusion of the superior mesenteric artery then 2-h reperfusion); and (4) ukrain + II/R group (U + II/R) (30-min occlusion of the superior mesenteric artery then 2-h reperfusion; ukrain was administered intraperitoneally 1 h before IR).

Results: Serum total oxidant status (TOS) and total antioxidant status (TAS) were measured using Erel method. Oxidative stress index was calculated using the TOS/TAS ratio. TAS levels increased and TOS serum levels were also significantly decreased in the ukrain + IR group compared with the IR group ($P = 0.000$ and $P = 0.015$).

Conclusions: In this study, we demonstrated for the first time in literature that ukrain helps to prevent intestinal tissue breakdown against II/R injury and that this effect can be achieved by antioxidant activities.

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1. Introduction

Mesenteric ischemia is a severe disease of the gastrointestinal tract that can result in varying degrees of tissue damage, which results in intestinal necrosis. Ischemia–reperfusion (IR) injury is often observed in abdominal organ transplantations, arterial and venous occlusive diseases of the digestive tract, and circulatory shock [1]. When therapeutic measures are performed to restore blood flow, the paradoxical worsening of ischemic

damage by the action of cytokines, interleukins, and especially of reactive oxygen species (ROS) can occur [2,3]. Toxic oxygen metabolites have emerged as a major common pathway of tissue injury in a wide variety of diseases including IR injury because many constituents of the cell are potentially subjected to a free-radical attack [4].

Ukrain (NSC 631570) contains alkaloids of greater celandine (*Chelidonium majus*, a member of the Papaveraceae family) [5], made water soluble by derivatization with thiotepa,

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Table 1 – Criteria of intestinal tissue injury evaluation according to Chiu et al. [15].

Level	Microscopic findings
0	Mucosa without changes
1	Well-constituted villusities, no cellular lysis, or inflammatory process, although there is formation of Grunhagen subepithelial space
2	Presence of cellular lysis, formation of Grunhagen subepithelial space, and increased spacing among the villusities
3	Destruction of the free villusities section, presence of dilated capillaries, and inflamed cells
4	Structural destruction of the villusities, only traces of some villusities, formed by inflamed cells and necrotic material, with hemorrhage and basal glandular ulceration
5	Destruction of all the mucosa, no glandular structure can be seen, only the amorphous material laying on the submucosa tissue

displaying a putative proapoptotic effect. This drug has previously been reported to be an effective anti-cancer agent with minimal side-effects because of its selective toxicity toward malignant cells as demonstrated *in vitro* [6]. The molecular mechanisms of ukrain-induced antineoplastic effects, however, are not yet completely understood, although an immunostimulating and immunomodulating [7] antiangiogenic on human endothelial cells *in vitro*, and antiapoptotic actions [8,9] of Ukrain have been reported.

Because of the antioxidative properties of ukrain, it seems possible that using ukrain before IR may protect the intestinal tissue against oxidative intestinal IR injury. To the best of our knowledge, there has not been such a report in the literature. The mechanism of action of ukrain is as yet unknown. The purpose of this study was to determine the mechanism of action of ukrain and whether ukrain could prevent intestinal tissue injury induced by IR by measuring oxidant parameters, such as total oxidative status (TOS), oxidative stress index (OSI), and antioxidative parameters, such as total antioxidant status (TAS) in the serum samples of rats.

2. Materials and methods

2.1. Animals

Sprague–Dawley, 10–12-wk-old male rats (250–300 g), were obtained from the Experimental Research Unit of the

University of Dumlupinar (Kütahya, Turkey). They were maintained on a 12/12 h light–dark cycle under controlled temperature and humidity. The animals were fed standard rat chow and given water *ad libitum*. All protocols used in this study were approved by the Dumlupinar University Ethics Committee on animal research.

2.2. Experimental protocol and model of intestinal IR

A rat's small-intestinal IR model was created, as described previously, by some investigators [10]. All rats were fasted for 18 h before the experiments, but were allowed free access to water until 20–30 min before starting the experiment. All experiments were started between 10 and 11 AM. The rats were anesthetized with an intraperitoneal injection of ketamine/xylozine HCl (75 mg/kg/10 mg/kg). The rats were placed on a heating mat, to keep the body temperature at $36 \pm 1^\circ\text{C}$. They were placed in the supine position and secured in the dissection tray. The abdominal region was shaved, cleaned with povidone–iodine 10% antiseptic solution, and 2–3 cm abdominal mid-line incision was applied. Laparotomy was performed. This procedure was sufficient to keep the animals under anesthesia until the end of the experiment. In the intestinal IR injury model, the superior mesenteric artery (SMA) was exposed with care and occluded with a nontraumatic microvascular clamp, for 30 min. At the end of this period, the clamp was removed, mesenteric artery pulsation was observed, and the intestine reperused for 120 min [10]. During the IR period, the area of operation was covered with a warm moist dressing to prevent hypothermia.

Rats were allocated to four experimental groups as follows: (1) a sham group (S; $n = 7$) that underwent sham surgery with isolation of the SMA without occlusion were treated in an identical fashion with 0.5-mL sterile, pyrogen-free saline; (2) ukrain group (U, $n = 8$) (no ischemia–reperfusion [IR] and ukrain [7 mg/kg in a volume of 0.5 mL/100 g] was administered intraperitoneally 1 h before laparotomy); (3) an intestinal ischemia–reperfusion group (II/R; $n = 8$) that was subjected to intestinal ischemia and reperfusion after the SMA had been isolated and occluded; (4) ukrain treatment plus ischemia–reperfusion group (U + II/R, $n = 8$) subjected to intraperitoneal injection of ukrain (7 mg/kg in a volume of 0.5 mL/100g) 1 h before intestinal IR.

Ukrain ampoules were donated by Nowicky Pharmaceuticals (Margaretenstrasse 7, 1040 Vienna, Austria). The ampoules were consistently protected from light and stored at 7°C until use.

Table 2 – The levels of TOS, TAS, and OSI in sham (S), ukrain (U), II/R, and Ukrain + II/R (U + II/R) groups (mean $\pm$ SE).

Gruplar	S ($n = 7$)	U ($n = 8$)	II/R ($n = 8$)	U + II/R ($n = 8$)	P
TOS ($\mu\text{mol/L}$)	12.2 ± 2.40^a	10.0 ± 1.15^b	51.1 ± 12.8^{ab}	22.4 ± 8.36^b	0.002
TAS (mmol/L)	1.61 ± 0.03^a	1.79 ± 0.04^{ab}	1.60 ± 0.02^{bc}	2.49 ± 0.18^{ac}	0.000
OSI (TOS/TAS)	7.57 ± 1.41^a	5.63 ± 0.67^b	31.5 ± 7.79^{abc}	10.3 ± 3.30^c	0.001

SE = standard error.

P values show the differences between all groups (Kruskal–Wallis test).

^{a,b,c} In each line, the difference between the means with same letters are significant, $P \leq 0.05$ (Mann–Whitney U-test).

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