ORIGINAL ARTICLE

The Coevaluation of Ovarian Epithelium Karyorrhexis and Ovarian Congestion after the Antioxidant Drug "U-74389G" Effect on Ovarian Ischemia-Reperfusion Injury

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ABSTRACT

Aim: This study coevaluated the two quoted histologic variables after the antioxidant lazaroid drug "U-74389G" (L) administration. The calculation was based on the results of two preliminary studies, each one evaluating a respective histologic variable of ovarian epithelium karyorrhexis (OK) or ovarian congestion (OC) in an induced ischemia reperfusion animal experiment. **Materials and Methods:** The two main experimental endpoints at which the OK and OC scores were evaluated was the 60th reperfusion min (for the Groups A and C) and the 120th reperfusion min (for the Groups B and D). Especially, the Groups A and B were processed without drugs, whereas the Groups C and D after L administration. **Results:** The first preliminary study showed that L non-significantly recessed the OK scores within the "without lesions alterations" grade 0.0818182 (−0.2159977–0.0523614) (P = 0.2246). However, the second preliminary study showed that L non-significantly recessed the OC scores within the "without lesions alterations" grade 0.2727273 (−0.6477081–0.1022535) (P = 0.1492). These two studies were coevaluated since they came from the same experimental setting. This study investigated the combined diagnostic value of both variables together. **Conclusions:** L has a hardly recessing potency of these histologic parameters within the "without lesions alterations" grade by 0.1772727 (−0.3716027–+0.0170573) (P = 0.0726) since they were coevaluated together.

Key words: Ischemia, ovarian congestion, ovarian epithelium karyorrhexis, reperfusion, U-74389G

INTRODUCTION

U-74389G is a new antioxidant agent implicating just only 259 published studies. The ischemia-reperfusion (IR) type of experiments is noted in 18.53% of these studies. A tissue protective feature of U-74389G is obvious in such IR studies. The U-74389G chemically known as 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione maleate salt is antioxidant complex, which inhibits the lipid peroxidation either iron-dependent or arachidonic acid-induced one. Animal kidney, liver, brain microvascular endothelial cells monolayers, and heart models are protected by U-74389G after IR injury. U-74389G also attenuates the leukocytes, downregulates the

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proinflammatory gene, treats the endotoxin shock, produces cytokine, enhances the mononuclear immunity, protects the endothelium, and presents antishock property. Two histologic variables in an ovarian IR (OIR) experiment were tested for this purpose. The one variable was that of ovarian epithelium karyorrhexis (OK) which was recessed within the grade "without lesions alterations" grade 0.0818182 (−0.2159977–0.0523614) (P = 0.2246).[1] The other variable was that of ovarian congestion (OC), which non-significantly recessed also within the grade "without lesions alterations" grade 0.2727273 (−0.6477081–0.1022535) (P = 0.1492).[2] The present experimental work tried to coevaluate these OK and OC variables together and to compare its outcome with each one separately, from the same rat-induced OIR protocol.

MATERIALS AND METHODS

Animal Preparation

This study received two Ethics Committee approvals under the 3693/12-11- 2010and 14/10-1-2012 numbers fully following the tenants of the Declaration of Helsinki. The granting company, the experiment location, and the pathology department are mentioned in preliminary references.[1,2] The human care of Albino female Wistar rats was kept. The 7 days pre-experimental ad libitum diet, the non-stop intra-experimental anesthesiologic techniques including the acidometry, the electrocardiogram and the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16–18 weeks old. They were randomly assigned to four groups consisted in n = 10. The stage of 45 min ischemia was common for all four groups. Afterward, reperfusion of 60 min was followed in Group A; reperfusion of 120 min in Group B; immediate L intravenous (IV) administration and reperfusion of 60 min in Group C; and immediate L IV administration and reperfusion of 120 min in Group D. The dose height assessment was described at preliminary studies as 10 mg/Kg body mass.

Ischemia was caused by laparotomic clamping the inferior aorta over renal arteries with forceps for 45 min. The clamp removal was restoring the inferior aorta patency and reperfusion. After exclusion of the blood flow, the protocol of OIR was applied, as described above for each experimental group. L was administered at the time of reperfusion; through inferior vena cava catheter. The OK and OC scores were determined at 60th min of reperfusion (for A and C groups) and 120th min of reperfusion (for B and D groups). Relation was raised between animals' mass neither with OK scores (P = 0.9572) nor with OC ones (P = 0.0953). Thus, no need for predicted variables calculations was raised. The pathologic score grading was maintained the same as in preliminary studies: (0–0.499) without lesions, (0.5–1.499) the mild lesions, (1.5–2.499) the moderate lesions, and (2.5–3) the serious lesions damage.

Model of Ischemia-Reperfusion Injury

Control groups

The 20 control rats were the same for preliminaries and this study.

- Group A - Reperfusion which lasted 60 min concerned 10 controls rats of combined OK and OC score as the mean of the OK score and OC one [Table 1].
- Group B - Reperfusion which lasted 120 min concerned 10 controls rats of combined OK and OC score as the mean of OK and OC one [Table 1].
- U-74389G Group - The 20 L rats were the same for preliminaries and this study.
- Group C - Reperfusion which lasted 60 min concerned 10 L rats of cOK and OC score as the mean of OK score and OC one [Table 1].
- Group D - Reperfusion which lasted 120 min concerned 10 L rats of cOK and OC score as the mean of OK score and OC one [Table 1].

Statistical Analysis

Every cOK and OC groups score was compared with each other from three remained groups applying the Wilcoxon signed-rank test [Table 2]. Then, the generalized linear models (GLM) were applied with dependent variable the cOK and OC scores, and independent variables the L administration or no, the reperfusion time and their interaction.

RESULTS

L administration non-significantly recessed the cOK and OC scores within the "without lesions alterations" by without lesions alterations 0.225 (−0.5298931–+0.0798931) (P = 0.3328) after cocalculation by both Wilcoxon signed-rank test and GLM methods. Similarly, reperfusion time hardly enhanced the cOK and OC scores within the "without

Table 1: OK and OC and their mean and SD scores

Groups	Mean OK score±SD	Mean OC score±SD	Mean OK and OC score±SD
Group A	Without lesions 0.1±0.3162278	Moderate lesions 1.6±1.074968	Mild lesions 0.85±0.5797509
Group B	Without lesions 0.2±0.6324555	Moderate lesions 1.9±0.9944289	Mild lesions 1.05±0.4972145
Group C	Without lesions 0±0	Mild lesions 1±0.8164966	Mild lesions 0.5±0.4082483
Group D	Without lesions 0±0	Mild lesions 1.3±0.9486833	Mild lesions 0.65±0.4743416

OK: Ovarian epithelium karyorrhexis, OC: Ovarian congestion, SD: Standard deviation

lesions alterations" by 0.3 (−0.0188755–+0.6188755) (P = 0.1526) after cocalculation by the same methods. However, L administration and reperfusion time together also hardly recessed the cOK and OC scores within the "without lesions alterations" by 0.1772727 (−0.3716027–+0.0170573) (P = 0.0726). An analytical form of the above findings is depicted in Table 3 and a concise one is depicted in Table 4

DISCUSSION

Kolusari *et al*. improved[3] the survival of follicles, determined significantly higher levels of E_2 in ovarian grafts most likely by reducing ischemic injury, by improving neoangiogenesis, and by its antioxidant effects. Follicle counts in the EPO group were significantly higher than those in the untreated group ($P \leq 0.05$) after condensated EPO administration in autotransplanted rat ovaries. Mahmoodi *et al*. found the mean total volume of ovary, cortex, medulla, the number of follicles, the follicle survival and function, and the concentration of E_2 increased[4] whereas, apoptosis rate and the concentration of malondialdehyde (MDA) decreased significantly in the autografted EPO-treated group than in the autografted placebo one ($P < 0.01$) reducing the IR injury in grafted ovaries of Naval Medical Research Institute mice. Ma *et al*. found the number of apoptosis cells decreased in the rhEPO treated group ($P < 0.01$) than I/R group. rhEPO showed effects to inhibit the apoptosis of fetal neural cells and the expression of Caspase-3 protein due to intrauterine hypoxic-ischemic brain tissue injury. Ma *et al*. found[5,6] the expression of caspase-3, the death rate of fetal rats and the number of fetal rat brain cells apoptosis decreased in rhEPO treated groups ($P < 0.05$) than the I/R group in an intrauterine hypoxic-ischemic injury. Taskin *et al.* evaluated[7] the tissue and serum total oxidant status (TOS) levels, and OSI levels markedly decreased. The ovarian protective effect of 2-aminoethoxydiphenyl borate appears to be mediated through its antiapoptotic and antioxidative effects in experimental I/R injury in rat ovaries. Stanley *et al*. have shown[8] that edaravone mitigated or inhibited the effects of CrVI on follicle atresia, pubertal onset retardation, steroidogenesis hormone levels, and alternative oxidase enzyme activity, as well as the expression of Bcl2 and Bcl2l1 in the ovary; whereas increased E_2 restored CrVI-induced depletion of glutathione peroxidase 1, catalase, thioredoxin 2, and peroxiredoxin 3 in the ovary of female Sprague Dawley rats. Yapca *et al*. found[9] that etoricoxib (a selective cyclooxygenase-2 inhibitor) prevented oxidative damage induced with I/R that may arise with reperfusion by

Table 2: The values DG after Wilcoxon signed-rank test for mean OK and OC scores

DG	Difference	*P* value
A-B	+0.2	0.3941
A-C	−0.35	0.2562
A-D	−0.2	0.4352
B-C	−0.55	0.0289
B-D	−0.4	0.0960
C-D	+0.15	0.5294

OK: Ovarian epithelium karyorrhexis, OC: Ovarian congestion, SD: Standard deviation, DG: Difference for groups

Table 3: The recessing influence of U-74389G in connection with reperfusion time (*P* value)

Recession	95% c. in.	Reperfusion time	Wilcoxon	GLM
Without lesions alterations−0.35	−0.9820111+0.2820111	1 h	0.2562	
Without lesions alterations−0.1	−0.5775459 0.3775459	1 h		0.6652
Without lesions alterations−0.375	−0.6880585−0.0619415	1.5 h		0.0202
Without lesions alterations−0.075	−0.3717277+0.2217277	1.5 h	0.6454	
Without lesions alterations−0.05	−0.57987870.4798787	2 h		0.8451
Without lesions alterations−0.04	−0.8709056+0.0709056	2 h	0.0960	
Without lesions alterations+0.175	−0.1564645+0.5064645	Reperfusion		0.2919
Without lesions alterations+0.425	+0.1187135+0.7312865	Reperfusion	0.0133	
Without lesions alterations−0.1772727	−0.3716027+0.0170573	Interaction		0.0726

Table 4: Concise form of the Table 3

Recession	95% c. In.	Reperfusion time	*P* value
Without lesions alterations−0.225	−0.7797785+0.3297785	1 h	0.4607
Without lesions alterations−0.225	−0.5298931+0.0798931	1.5 h	0.3328
Without lesions alterations−0.045	−0.72539215+0.27539215	2 h	0.4705
Without lesions alterations+0.3	−0.0188755+0.6188755	Reperfusion	0.1526
Without lesions alterations−0.1772727	−0.3716027+0.0170573	Interaction	0.0726

detorsion in rat ovarian tissue. Yapca *et al*.[10] suggested that thiamine pyrophosphate may be useful in the prevention of IR-related infertility in diabetic rats. Celik *et al*. ameliorated[11] I/R injury by sildenafil treatment in an ovarian tissue rat model. Gungor *et al*. observed that omegaven improved[12] the detrimental effects of OIR in torsioned - detorsioned ovaries. Kurt *et al*. revealed[13] that colchicine significantly reduced catalase activities and thus OIR injury in experimental rat ovarian torsion model up to 5 days. Dokuyucu *et al*. found[14] the numbers of primordial follicles ($P = 0.006$) and primary follicles ($P = 0.036$) increased whereas the mean levels of TOS and (oxidative stress index) decreased in groups that received erdosteine and/or alpha lipoic acid (ALA) than the detorsion group in an experimental rat OIR torsion model injury. Keskin Kurt *et al*.[15] revealed that zofenopril attenuated injury in an experimental model of OIR torsion in rats. Guven *et al*. observed[16] that the elevated serum ischemia-modified albumin levels with high sensitivity-specificity values in women with ovarian torsion seem to have a potential role as a serum marker in the pre-operative diagnosis of ovarian torsion in emergency settings and significantly distinguished patients with or without ovarian torsion. Yurtcu *et al*. found[17] statistically significant dose-dependent decreased edema and follicle degeneration, with vascular congestion, hemorrhage, and follicle degeneration in vardenafil treatment groups attenuating ischemia-reperfusion induced ovary injury in a rat model. Türk *et al*. considered[18] hypothermia as effective in inhibiting inflammatory responses and also ischemia/reperfusion injury perhaps by inhibiting the production of oxidative stress in ovaries subjected to torsion/detorsion injury. Yıldırım *et al*. reduced[19] hemorrhage, edema, and vascular dilatation after proanthocyanidin administration known as a free radical scavenger, antioxidant, and protective against tissue damage induced by IR in rat ovaries. Mete Ural *et al*. reversed[20] the biochemical, histopathological, and immunohistochemical alterations, alleviated the injury and attenuated ovarian ischemia and ischemia/reperfusion injury after thymoquinone administration in rats. Aksak Karamese *et al*. normalized[21] values after beta-carotene treatment which is a potent antioxidant in an experimental ischemia-reperfusion groups model. Sayar *et al*. suggested[22] that ozone (O) and ellagic acid are effective against an ovarian torsion-detorsion I/R injury. Eser *et al*. showed[23] that curcumin exerted no major significant protective effect on ischemia-reperfusion injury in the rat ovary female Wistar albino rats. Bayir *et al*. concluded[24] that aliskiren (a direct renin inhibitor) treatment is effective in reversing IR induced ovary damage through the improvement of cytokine and oxidative stress, reduction of inflammation, and suppression of the renin-angiotensin-aldosterone system in rat ovaries. Esteban-Zubero *et al*. proved[25] melatonin as a potentially useful therapeutic tool in the reduction of graft rejection. Its benefits are based on its direct actions as a free radical scavenger as well as its indirect antioxidative actions in the stimulation of the cellular antioxidant defense system. Moreover, it has significant anti-inflammatory activity. Melatonin has been found to improve the beneficial effects of preservation fluids when they are enriched with the indoleamine. Yao *et al*. described *Carthamus tinctorius*[26] in prescriptions and composite to promote blood circulation, remove blood stasis, regulate menstruation, alleviate pain, and significantly promote ovarian granulosa cell proliferation with the effects of antioxidation. Tuncer *et al*. evaluated[27] the combination of ALA and coenzyme Q10 having beneficial effects on oxidative stress induced by ischemia-reperfusion injury related with a rat model of ovarian torsion. Nayki *et al*. significantly decreased[28] severe hemorrhage, degeneration, inflammatory signs in the follicular cells, and markedly ameliorated increased apoptosis, caused by IR in rats ovarian tissue. Ugurel *et al*. significantly retained[29] severe acute inflammation, polynuclear leukocytes, macrophages, stromal edema, hemorrhage, and degenerative changes in the ovary proliferating cell nuclear antigen (+) cell numbers; decreasing lipid peroxidation products and leukocytes aggregation after treatment with erdosteine in adnexal torsion of OIR injury in rats. Pınar *et al*. found catalase levels significantly increased[30] whereas MDA levels significantly lower in the I/R + tempol i.p. group. Tempol can be used for reducing OIR injury in female Wistar albino rats. Güleç Başer *et al*. found vascular congestion, hemorrhage, polymorphonuclear neutrophils interstitial edema, and the number of apoptotic cells lower[31] in PG group. Pre-operative PG treatment might exert protective effects in OIR injury through its anti-apoptotic and antioxidative properties. Melekoglu *et al*. evaluated[32] the serum follicle-stimulating hormone levels significantly reduced, the serum anti-Müllerian hormone levels significantly increased and the histopathological scores ameliorated in rats treated with chrysin and glycyrrhetinic acid preventing I/R injury in rat adnexal torsion detorsion procedure.

A numeric evaluation[33] of the L efficacies was provided by a meta-analysis of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion time coming from the same experimental setting [Table 5].

Table 5: The L influence (±SD) on the levels of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion time

35 Variables	1 h Reperfusion (%)	*P* value	1.5 h Reperfusion (%)	*P* value	2 h Reperfusion (%)	*P* value	Interaction of EPO and reperfusion (%)	*P* value
Mean	2.03±27.26	0.2168	0.19±29.41	0.1836	−1.63±33.15	0.2389	−0.33±16.23	0.2016

CONCLUSIONS

L has a slight recessing potency for OK and OC together ($P = 0.0726$) encouraging for beneficial usage in situations such as the survival of follicles in ovarian grafts, the follicle atresia, the pubertal onset retardation, the steroidogenesis hormone levels, the follicle degeneration and inflammatory responses inhibition, and the adnexal torsion detorsion procedure.

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