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The Co-Evaluation of Ovarian Epithelium Edema and Oophoritis After the Antioxidant Drug "U-74389G" Effect on Ovarian Ischemia Reperfusion Injury

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Abstract

***Aim:** This study co-evaluated the 2 quoted histologic variables after the antioxidant lazaroid drug "U-74389G" (L) administration. The calculation was based on the results of 2 preliminary studies, each one evaluating a respective histologic variable of ovarian epithelium edema (OE) or oophoritis (OI) in an induced ischemia reperfusion animal experiment.*

***Materials and methods:** The 2 main experimental endpoints at which the OE and OI 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). Specially, the groups A and B were processed without drugs, whereas the groups C andD after L administration.*

Results: *The first preliminary study showed that L non significantly recessed the OE scores within the "without lesions alterations" grade-0.0634052 [-0.160525 - 0.0337146] (p-value=0.1942). However, the second preliminary study showed that L non significantly increased the OI scores within the "without lesions alterations" grade 0.0454545 [-0.0145524 - 0.1054615] (p-value=0.1334). These 2 studies were co-evaluated 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 -0.0089753 [-0.0629372 - 0.0449866] (p-value=0.7382) since they were co-evaluated together.*

Keywords: *ischemia, ovarian epithelium edema, oophoritis, U-74389G, reperfusion*

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; down-regulates the proinflammatory gene; treats the endotoxin shock; produces cytokine; enhances the

mononuclear immunity; protects the endothelium and presents antishock property. 2 histologic variables in anovarian ischemia reperfusion (OIR) experiment was tested for this purpose. The one variable was that ofovarian epithelium edema(OE) which was recessed within the grade "without lesions" by 0.0634052 [-0.160525 - 0.0337146] (p-value=0.1942).[1]The other variable was that ofoophoritis (OI), which hardly non significantly was deteriorated also within the grade "without lesions" by 0.0454545 [-0.0145524 - 0.1054615] (p-value=0.1334). [2]The present experimental work tried to co-evaluate these OE and OI 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 2 ethics committee approvals under the 3693/12-11- 2010 & 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 animal care of Albino female Wistar rats, the 7 days pre-experimental *ad libitum* diet, the non-stop intra-experimental anesthesiologic techniques, 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 (4) groups consisted in N=10. The stage of 45 min ischemia was common for all 4 groups. Afterwards, 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; immediate LIV 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. TheOE and OI scores were determined at 60th min of reperfusion (for A and C groups) and at 120th min of reperfusion (for B and D groups). Relation was rised between animals' mass with OE scores (p-value=0.0416); but nowith OI ones (p-values=0.3137). Thus, the predicted OE scores (pOE) were used for the further calculation. 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 OE and OI (OE&OI) score as the mean of OE score and OI one (Table 1).

Group B

Reperfusion which lasted 120 min concerned 10 controls rats of combined OE&OI (cOE&OI) score as the mean of OE and OI 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 cOE & OI score as the mean of OE score and OI one (Table 1).

Group D

Reperfusion which lasted 120 min concerned 10 L rats of cOE & OI score as the mean of OE score and OI one (Table 1).

Table1. *Ovarian epithelium edema (OE), Oophoritis (OI) and their mean and SD scores*

	Mean pOE score ±SD	Mean OI score ±SD	Mean pOE&OI score ±SD
Group A	mild lesions 0.5772061±0.3176882	without lesions 0±0	without lesions 0.288603±0.1588441
Group B	mild lesions 0.7090637±0.2158934	without lesions 0±0	without lesions 0.3545319±0.1079467
Group C	without lesions 0.3655399±0.1237665	without lesions 0±0	without lesions 0.1827699±0.0618832
Group D	without lesions 0.3481902±0.1256439	without lesions 0.1±0.3162278	without lesions0.2240951±0.1521952

Statistical analysis

Every cOE & OI groups score was compared with each other from 3 remained groups applying Wilcoxon signed-rank test (Table 2). Then, the generalized linear models (glm) were applied with dependant variable the cOE & OI scores, and independent variables the L administration or no, the reperfusion time and their interaction.

Table2. *The values difference for groups (DG) after Wilcoxon signed-rank test for mean pOE&OI scores.*

DG	Difference	p-value
A-B	+0.0659288	0.4142
A-C	-0.1058331	0.0926
A-D	-0.0645079	0.2023
B-C	-0.1717619	0.0125
B-D	-0.1304367	0.0367
C-D	+0.0413252	0.7974

Results

L administration non-significantly recessed the cOE & OI scores within the "without lesions alterations" 0.1181349 [-0.1932065- -0.0430634] (p=0.0053) after co-calculation by both Wilcoxon signed-rank test and glm methods. Similarly, reperfusion time hardly enhanced the cOE & OI scores within the "without lesions alterations" + 0.04835035 [-0.0209897 -+0.11769045] (p=0.3857) after co-calculation by the same methods. However, L administration and reperfusion time together also hardly recessed the cEE & UI scores within the "without lesions alterations" 0.0089753 [-0.0629372 -+0.0449866] (p=0.7382). A concise form of the above findings is depicted at table 4.

Table3. *The recessing influence of U-74389G in connection with reperfusion time.*

p-values

Increase	95% c. in.	Reperfusion time	Wilcoxon	Glm
without lesions alterations -0.1058331	-0.2209969 +0.0093307	1h	0.0926	
without lesions alterations -0.1353275	-0.2487083 -0.0219468	1h		0.0220
without lesionsalterations -0.1181349	-0.1932065 -0.0430634	1.5h	0.0057	0.0053
without lesions alterations +.0274454	-0.0827743 +0.1376652	2h		0.6073
without lesions alterations -0.1304367	-0.2502768 -0.0105967	2h	0.0367	
without lesionsalterations -0.0089753	-0.0629372 0.0449866	reperfusion		0.7382
without lesionsalterations +0.105676	+0.0209578 +0.1903943	reperfusion	0.0333	
without lesionsalterations -0.0089753	-0.0629372 0.0449866	interaction		0.7382

Table4. *Concise form of the table 3.*

Increase	95% c. in.	Reperfusion time	p-value
without lesions alterations -0.1205803	-0.2348526 -0.00630805	1h	0.0573
without lesionsalterations -0.1181349	-0.1932065 -0.0430634	1.5h	0.0053
without lesions alterations -0.05149565	-0.16652555 +0.06353425	2h	0.3220
without lesions alterations +0.04835035	-0.0209897 +0.11769045	reperfusion	0.3857
without lesionsalterations -0.0089753	-0.0629372 0.0449866	interaction	0.7382

Discussion

Kolusari A 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 M 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 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 YS et al found the number of apoptosis cells decreased in 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 YS et al found[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 MI et al evaluated[7] the tissue and serum TOS levels and OSI levels markedly decreased. The ovarian protective effect of 2-APB appears to be mediated through its antiapopitotic and antioxidative effects in experimental I/R injury in rat ovaries. Stanley JA et al have shown[8] that edaravone mitigated or inhibited the effects of CrVI on follicle atresia, pubertal onset retardation, steroidogenesis hormone levels and AOX 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 OE et al found[9] that etoricoxib [a selective cyclooxygenase (COX)-2 inhibitor] prevented oxidative damage induced with I/R that may arise with reperfusion by detorsion in rat ovarian tissue. Yapca OE et al[10] suggested that thiamine pyrophosphate may be useful in the prevention of IR-related infertility in diabetic rats. Celik M et al ameliorated[11] I/R injury by sildenafil treatment in an ovarian tissue rat model. Gungor AN et al observed that omegaven improved[12] the detrimental effects of ovarian I/R in torsioned - detorsioned ovaries. Kurt RK et al revealed[13] that colchicine significantly reduced catalase activities and thus ovarian ischemia-reperfusion injury in experimental rat ovarian torsion model up to 5 days. Dokuyucu R et al found[14] the numbers of primordial follicles ($p=0.006$) and primary follicles ($p=0.036$) increased whereas the mean levels of (Total Oxidant Status) 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 ovarian IR torsion model injury. Keskin Kurt R et al revealed that zofenopril attenuated injury in an experimental model of ovarian IR torsion in rats. Guven S et al observed[16] that the elevated serum ischemia-modified albumin IMA levels with high sensitivity-specificity values in women with ovarian torsion seem to have a potential role as a serum marker in the preoperative diagnosis of ovarian torsion in emergency settings and significantly distinguished patients with or without ovarian torsion. Yurtcu E 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 E 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 Ş et al reduced[19] hemorrhage, edema and vascular dilatation after proanthocyanidin administration known as free radical scavenger, antioxidant and protective against tissue damage induced by IR in rat ovaries. Mete Ural Ü 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. AksakKaramese S et al normalized[21] values after beta-carotene treatment which is a potent antioxidant in an experimental ischemia-reperfusion groups model. Sayar I et al suggested[22] that ozone (O) and ellagic acid (EA) are effective against an ovarian torsion-detorsion I/R injury. Eser A 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 Y et al concluded[24] that aliskiren [a direct renin inhibitor] treatment is effective in reversing IR induced ovary damage via

the improvement of cytokine and oxidative stress, reduction of inflammation and suppression of the renin-angiotensin aldosterone system in rat ovaries. Esteban-Zubero E 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 D et al described carthamus tinctorius[26] in prescriptions and composite to promote blood circulation, remove blood stasis, regulate menstruation, alleviate pain, significantly promote ovarian granulosa cell proliferation with the effects of antioxidation. Tuncer AA et al evaluated[27] the combination of alpha-lipoic acid and coenzyme Q10 having beneficial effects on oxidative stress induced by ischemia-reperfusion injury related with rat model of ovarian torsion. Nayki UA 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 V et al significantly retained[29] severe acute inflammation, polynuclear leukocytes, macrophages, stromal edema, hemorrhage, degenerative changes in the ovary PCNA (+) cell numbers; decreasing lipid peroxidation products and leukocytes aggregation after treatment with erdosteine in adnexal torsion of ovarian IR injury in rats. Pınar N 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 ovarian I/R injury in female Wistar albino rats. GüleçBaşer B et al found vascular congestion, hemorrhage, polymorphonuclear neutrophils interstitial edema and the number of apoptotic cells lower[31] in PG group. Preoperative PG treatment might exert protective effects in ovarian IR injury through its anti-apoptotic and antioxidative properties. Melekoglu R 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 35seric variables of complete blood count and blood chemistry tests versus reperfusion time coming from the same experimental setting (table 5).

Table5. *The L influence (±SD) on the levels of 35seric variables of complete blood count and blood chemistry tests versus reperfusion (rep) time*

35 Variables	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of Epo and rep	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

Conclusion

L has a slight recessing potency for ovarian epithelium edema and oophoritis together (p-values=0.7382) encouraging for beneficial usage in situations such asthe 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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