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The co-evaluation of ovarian epithelium edema and congestion after the erythropoietin effect on ovarian ischemia reperfusion injury

Abstract

Aim: This study co-evaluated the 2 quoted histologic variables after the erythropoietin (Epo) 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 congestion (OC) in an induced ischemia reperfusion animal experiment.

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

Results: The first preliminary study showed that Epo non singificantly recessed the ovarian epithelium edema (OE) within the "without lesions alterations" grade by 0.1272727 [-0.4530022 - +0.1984567] (p-value=0.4339).[1] However, the second preliminary study showed that Epo non significantly enhanced the ovarian congestion (OC) within the "without lesions alterations" grade by 0.1454545 [-0.1918887 - +0.4827978] (p-value=0.3882).[2] 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.

Conclusion: Epo has a hardly deteriorating potency of these histologic parameters within the "without lesions alterations" grade by 0.0090909 [-0.2586031 - +0.2767849] (p-value=0.9456) since they were co-evaluated together.

Keywords: ischemia, ovarian epithelium edema, congestion, erythropoietin, reperfusion

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Introduction

The assumption is whether erythropoietin (Epo) has antioxidant capacities. For this purpose, we tested 2 histologic variables in an ovarian ischemia reperfusion (OIR) experiment. The one variable was that of ovarian epithelium edema (OE), which was non significantly recessed within the "without lesions alterations" grade by 0.1272727 [-0.4530022 - +0.1984567] (p-value=0.4339).[1] The other variable was that of ovarian congestion (OC) but was significantly enhanced within the "without lesions alterations" grade by 0.1454545 [-0.1918887 - +0.4827978] (p-value=0.3882).[2] Epo is found in over 30,606 published biomedical experiments, however, just a 3.57% of them occupy its antioxidant capacities. This study attempted to co-evaluate these OE and OC variables together. Then its outcome was compared with each one successively, since they come from the same rat OIR experiment.

Materials and methods

Animal preparation

2 ethics committee approvals, these of 3693/12-11- 2010 & 14/10-1-2012 numbers were applied of course under the auspice of the Declaration of Helsinki. All the contributing parts, the Pathology Department, the experiment location and the granting company, are reported in preliminary references.[1,2] The human care of Albino female Wistar rats was secured. Also, all the peri-experimental stages as the pre-ones: 7 days *ad libitum* diet, the non-stop intra-ones: acidometry, anesthesiologic techniques, oxygen supply and electrocardiogram, as well the post-ones as euthanasia are also reported in preliminary references. Rats' age was that of 16–18 weeks old. Rats were randomly divided to four (4) groups consisted in ten (10) each one. A common stage of 45 min ischemia was preceded in all four groups. The next common stage was that of reperfusion; however it lasted 60 min in group A; 120min in group B; 60 min along with Epo intravenous (IV) administration in group C and 120min along with Epo intravenous (IV) administration in group D. The dose height was assessed as 10mg/Kg body mass at preliminary studies.

Induced ischemia was performed by laparotomic clamping the inferior aorta over renal arteries with forceps as mentioned for 45 min. Afterwards, the clamp retraction was carrying the inferior aorta patency and reperfusion out. Ever the blood flow was excluded, the protocol of OIR was performed, just as described above for every group. Epo administration was set through an inferior vena cava catheter at the onset of reperfusion. The OE and OC scores were assessed at the end of reperfusion–this is – at 60th min for A and C groups and at 120th min for B and D groups. Relation was rised between animals' mass with neither OE scores (p-value=0.8726); nor with OC ones (p-values=0.7816). The scale of pathology scores was kept the same as in the preliminary studies: without lesions (0-0.499), the mild lesions (0.5-1.499), the moderate lesions (1.5 -2.499) and the serious lesions damage (2.5-3).

Model of ischemia-reperfusion injury

Control groups: The preliminary studies and this one had common the 20 control rats. Reperfusion followed all the groups but its duration was varied. Certainly in:

Group A: It lasted 60 min for 10 controls rats of combined OE and OC (OE&OC) score as the mean of OE score and OC one (Table 1).

Group B: It lasted 120 min for 10 controls rats of combined OE&OC (cOE&OC) score as the mean of OE and OC one (Table 1).

Epo group: Also, the preliminary studies and this one had common the 20 Epo rats. Reperfusion followed all the groups but its duration was varied. Certainly in:

Group C: It lasted 60 min for 10 Epo rats of cOE & OC score as the mean of OE score and OC one (Table 1).

Group D: It lasted 120 min for 10L rats of cOE & OC score as the mean of OE score and OC one (Table 1).

Statistical analysis

The Wilcoxon signed-rank test was applied for every cOE & OC groups score which was compared with each one from the 3 other groups (Table 2). Along, the results were crosschecked by the generalized linear models (glm). The cOE & OC scores were occupied as dependant variable, the Epo administration or no as independent variables and their interaction as the reperfusion time in glm.

Table 1 Ovarian epithelium edema (OE), ovarian congestion (OC) and their mean and SD scores

	Mean OE score ±SD	Mean OC score ±SD	Mean OE&OC score ±SD
Group A	mild lesions 0.7±0.8232726	moderate lesions 1.6±1.074968	mild lesions 1.15±0.7835106
Group B	mild lesions 1.1±0.9944289	moderate lesions 1.9±0.9944289	moderate lesions 1.5±0.8164966
Group C	mild lesions 0.5±0.7071068	moderate lesions 2.1±0.5676462	mild lesions 1.3±0.5868939
Group D	mild lesions 0.7±0.8232726	moderate lesions 2±0.8164966	mild lesions 1.35±0.5797509

Table 2 The values difference for groups (DG) after Wilcoxon signed-rank test for mean OE&OC scores

DG	Difference	p-value
A-B	+0.35	0.3513
A-C	+0.15	0.6787
A-D	+0.2	0.5009
B-C	-0.2	0.4914
B-D	-0.15	0.6009
C-D	+0.05	0.5994

Results

Epo administration hardly non significantly deteriorated the cOE&OC scores within the "without lesions alterations" by 0.025 [-0.42442325 - +0.47442325] (p=0.8958) after co-calculation by both Wilcoxon signed-rank test and glm methods. Furthermore, reperfusion time hardly enhanced the cOE & OC scores within the "without lesions alterations" by 0.02 [-0.63224825 - +0.23224825] (p=0.3034) after co-calculation by the same methods (Table 3). However, Epo administration and reperfusion time together also hardly deteriorated the cOE&OC scores within the "without lesions alterations" grade by 0.0090909 [-0.2586031 - +0.2767849] (p-value=0.9456) since they were co-evaluated together. A concise form of the above findings is depicted at Table 4.

Table 3 The alteration influence of erythropoietin in connection with reperfusion time

			p-values	
Recession	**95% c. in.**	**Reperfusion time**	**Wilcoxon**	**Glm**
without lesions alterations +0.15	-0.676883+0.976883	1h	0.6787	
without lesions alterations +0.45	-0.1812485+1.081249	1h		0.1515
without lesions alterations 0	-0.4439479+0.4439479	1.5h		1.0000
without lesions alterations +0.05	-0.4048986+0.5048986	1.5h	0.7916	
without lesions alterations +0.05	-0.604141+0.704141	2h		0.8742
without lesions alterations -0.15	-0.7591045+0.4591045	2h	0.6009	
without lesions alterations +0.2	-0.63224825+0.23224825	reperfusion	0.3623	0.3034
without lesions alterations +0.0090909	-0.2586031+0.2767849	interaction		0.9456

Table 4 Concise form of the table 3

Recession	95% c. in.	Reperfusion time	p-value
without lesions alterations +0.3	-0.42906575+1.029066	1h	0.4151
without lesions alterations +0.025	-0.42442325+0.47442325	1.5h	0.8958
without lesions alterations -0.05	-0.68162275+0.58162275	2h	0.7375
without lesions alterations +0.02	-0.63224825+0.23224825	reperfusion	0.3034
without lesions alterations+0.0090909	-0.2586031+0.2767849	interaction	0.9456

Citation: Tsompos C, Panoulis C, Toutouzas K, et al. The co-evaluation of ovarian epithelium edema and congestion after the erythropoietin effect on ovarian ischemia reperfusion injury. *J Anal Pharm Res.* 2019;8(2):45–49. DOI: 10.15406/japlr.2019.08.00310

Discussion

Kolusari A et al.,[3] improved 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.,[6] found 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.,[7] evaluated 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.,[8] have shown 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.,[9] found 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.,[11] ameliorated I/R injury by sildenafil treatment in an ovarian tissue rat model. Gungor AN et al.,[12] observed that omegaven improved the detrimental effects of ovarian I/R in torsioned - detorsioned ovaries. Kurt RK et al.,[13] revealed 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.,[14] found 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.,[15] revealed that zofenopril attenuated injury in an experimental model of ovarian IR torsion in rats. Guven S et al.,[16] observed 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.,[17] found 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.,[18] considered 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.,[19] reduced hemorrhage, edema and vascular dilatation after proanthocyanidin administration known as free radical oxygen scavenger, antioxidant and protective versus tissue injury induced by IR in rat ovaries. Mete Ural Ü et al.,[20] 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 S et al.,[21] normalized values after beta-carotene treatment which is a potent antioxidant in an experimental ischemia-reperfusion groups model. Sayar I et al.,[22] suggested that ozone (O) and ellagic acid (EA) are effective against an ovarian torsion-detorsion I/R injury. Eser A et al.,[23] showed that curcumin exerted no major significant protective effect on ischemia-reperfusion injury in the rat ovary female Wistar albino rats. Bayir Y et al.,[24] concluded 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.,[25] proved 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.,[26] promoted blood circulation, regulated menstruation, removed blood stasis, alleviated pain and significantly promoted ovarian granulosa cell proliferation with the effects of antioxidation after carthamus tinctorius administration. Tuncer AA et al.,[27] evaluated 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.,[28] significantly decreased 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.,[29] significantly retained 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. Güleç Başer B et al.,[31] 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.,[32] evaluated 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 meta-analysis of 35 seric variables of complete blood count and blood chemistry tests vs reperfusion time provided a numeric evaluation[33] of the erythropoietin efficacies from the same experimental setting (Table 5).

Table 5 The erythropoietin influence (+SD) on the levels of 35 seric 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	3.39%+12.15%	0.5636	4.44%+14.50%	0.3711	0.2404	0.3496	0.0996	0.4045

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Conclusion

Epo has a slight deteriorating potency for ovarian epithelium edema and congestion together (p-values=0.9456). This finding was discouraging for treating 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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Conflicts of interest

The author declares that there is no conflicts of interest.

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