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The Co-evaluation of Oviductal Congestion and Salpingitis after the "U-74389G" Effect on Fallopian Ischemia Reperfusion Injury

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Abstract

Aim: This study co-evaluated the 2 quoted histologic variables after the antioxidant lazaroid agent "U-74389G" (L) administration. The calculation was based on the results of 2 preliminary studies, each one evaluating a respective histologic variable of oviductal congestion (C) or salpingitis (S) in an induced ischemia reperfusion (IR) animal experiment.

Materials and methods: The 2 main experimental endpoints at which the C and S scores were evaluated, were the reperfusion 60th min (for A & C groups) and the reperfusion 120th min (for B & D groups). Specially, 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 deteriorated the C scores, keeping them within the grade "without lesions" 0.0909091 [-0.1230462 to 0.3048644] (p-value=0.3951). The second preliminary study showed that L did not influence the S scores, also keeping them within the grade "without lesions" 0.00 (p-value=1.0000). Both studies were co-estimated since they belong to the same experimental setting. This study co-evaluated the combined diagnostic values of both variables together.

Conclusions: L hardly non-significantly deteriorated the common scores for these histologic parameters, also within the grade of "without lesions" 0.0454545 [-0.0615231 to 0.1524322] (p-value=0.3951) since they were co-evaluated together.

Keywords: Ischemia, U-74389G, Oviductal congestion, Salpingitis, Reperfusion

Introduction

U-74389G is a new antioxidant agent implicating just only 258 published studies. The ischemia reperfusion (IR) type of experiments is noted in 18.60% 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 a fallopian ischemia reperfusion (FIR) experiment were tested for this purpose. The one variable was that of oviductal congestion (C) which although was deteriorated after the process with L, it was remained within the same classification grade "without lesions" 0.0909091 [-.1230462 to 0.3048644] (p-value=0.3951) [1]. The other variable was that of salpingitis (S), but was not influenced by L treatment, remaining too within the grade "without lesions" 0.00 (p-value=1.0000) [2]. The present experimental work tried to co-evaluate these C and S variables together; out coming a common result for both variables concerning whether L can recess or deteriorate these variables.

Materials and Methods

Animal management

The Vet No 3693/12-November-2010 & 14/10-January-2012 licenses, the auspices company, and the experimental location are mentioned in preliminary [1,2]. The packaging of U-74389G is 100 mg in glass insert (5 ml), soluble in ethanol at 20 mg/ml available by CAYMAN CHEMICAL Co, [Michigan, USA]. The human animal care of female *Wistar* Albino rats, the one week pre-experimental *ad libitum* diet, 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. General anesthesia was provided by initial intramuscular (IM) administration of 0.5 cc compound, which constituted of 0.25 cc xylazine, [25 cc, 20mg/cc] and 0.25 cc ketamine hydrochloride [1000, 100mg/cc, 10cc]. Before initiation of laparotomy, 0.03 cc butorphanol [10mg/cc, 10cc] anesthetic agent was administered subcutaneously (SC). The common stage of 45 min ischemia was preceded in all 4 groups. Afterwards, 60 min reperfusion was followed in group A; 120 min in group B; immediate L intravenous (IV) administration and 60 min reperfusion in group C; and immediate L IV administration 120 min in group D. The dose height was assessed at pre-experimental phase as 10 mg/Kg body mass.

Ischemia was induced by laparotomic clamping the inferior aorta upper the renal arteries level with forceps for 45 min. The forceps removal was restoring the inferior aorta blood patency and reperfusion. L was administered at the time of reperfusion; through an inferior vena cava catheter. The C and S scores were determined at 60th min of reperfusion (for A and C groups) and at 120th min of reperfusion (for B and D groups). The pathologic score grading was maintained the same as in preliminary studies: (0-0.499) grade without lesions, (0.5-1.499) grade mild lesions, (1.5 -2.499) grade moderate lesions and (2.5-3) grade serious lesions damage. The histopathological studies are available at the Athens University 1st Pathological Department laboratory. Relation was raised between animals' mass with neither C scores (p-value= 0.6062) nor with S ones (p-values=1.0000); considering the 0.05 as significance level.

The ischemia-reperfusion injury model

Placebo groups

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

Group A

60 min reperfusion concerned 10 placebo rats of combined C and S (C&S) score as the mean of C score and S one (Table 1).

Group B

120 min reperfusion concerned 10 placebo rats of combined C&S (cE&K) score as the mean of C and S one (Table 1).

L group

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

Table 1: Oviductal congestion (C), salpingitis (S), and their mean and SD scores

	Mean C score ±SD	Mean S score ±SD	Mean C&S score ±SD
Group A	mild lesions 0.5±0.5270463	without lesions 0	without lesions 0.25±.2635231
Group B	without lesions 0.4±0.6992059	without lesions 0	without lesions 0.2±0.3496029
Group C	without lesions 0.2±0.421637	without lesions 0	without lesions 0.1±0.2108185
Group D	mild lesions 0.7±0.4830459	without lesions 0	Without lesions 0.35±0.2415229

Group C

60 min reperfusion concerned 10 L rats of cC&S score as the mean of C score and S one (Table 1).

Group D

120 min reperfusion concerned 10 L rats of cC&S score as the mean of C score and S one (Table 1).

Statistical Analysis

Successive comparisons among the 4 cC&S groups were performed applying Wilcoxon signed-rank test (Table 2). Then, the generalized linear models (glm) were applied with

Table 2: The values difference for groups (DG) after Wilcoxon signed-rank test for mean C&S scores.

DG	Difference	p-value
A-B	-0.05	0.7055
A-C	-0.15	0.2568
A-D	+0.1	0.4142
B-C	-0.1	0.5225
B-D	+0.15	0.2864
C-D	+0.25	0.0588

dependant variable the cC&S scores. L administration or no, the reperfusion time and their interaction were used as independent variables.

Results

The following results were crosschecked by both Wilcoxon signed-rank test and glm methods. So, L administration did not influenced the cC&S scores than control ones; they remained uninfluenced within "without alterations" grade 0.00 [-0.2034435 to 0.2034435] (p=1.0000). Contrary, reperfusion time non-significantly deteriorated the cC&S scores; however, remaining them within the "without alterations" grade 0.1 [-0.185566 to 0.185566] (p=0.2771). Finally, L administration and reperfusion time together also hardly non-significantly deteriorated the cE&K scores; remaining them again within the "without alterations" grade +0.0454545 [-0.0615231 to 0.1524322] (p-value=0.3951). A concise form of the above findings is depicted at table 4 (Table 3, Table 4).

Table 3: The alteration influence of L in connection with reperfusion time.

Alteration	95% c. in.	Reperfusion time	p-values	
			wilkoxon	glm
without alterations -0.15	-0.4444669 to 0.1444669	1h	0.2568	
without alterations -0.15	-0.3742077 to 0.0742077	1h		0.1769
without alterations -0.00	-0.1791211 to 0.1791211	1.5h		1.0000
without alterations -0.00	-0.2277659 to 0.2277659	1.5h	1.0000	
without alterations +0.15	-0.2289066 to 0.5289066	2h	0.2864	
without alterations +0.15	-0.1323029 to 0.4323029	2h		0.2790
without alterations +0.1	-0.0760849 to 0.2760849	reperfusion		0.2575
without alterations +0.1	-0.2950471 to 0.0950471	reperfusion	0.2967	
without alterations +0.0454545	-0.0615231 to 0.1524322	interaction		0.3951

Table 4: Concise form of the table 3.

Increase	95% c. in.	Reperfusion time	p-value
without alterations -0.15	-0.4093373 to 0.1093373	1h	0.2168
without alterations 0.00	-0.2034435 to 0.2034435	1.5h	1.0000
without alterations +0.15	-0.18060475 to 0.48060475	2h	0.2827
without alterations +0.1	-0.185566 to 0.185566	reperfusion	0.2771
without alterations +0.0454545	-0.0615231 to 0.1524322	interaction	0.3951

Discussion

Adamyan LV et al reduced the surgical trauma and disappeared tissue ischemia in oviduct stumps using fibrin glue anastomoses than microsurgical anastomoses resulting in reparative regeneration, adhesion formation decline and complete recanalization of fallopian tubes [3]. Castadot RG protected against salpingitis, other pelvic infections and tubal pregnancies after combined oral contraceptives administration [4]. Guennoun A et al reported the rare case of a pregnant presenting with acute lateropelvic pain due to adnexal torsion [5]. Çılgın H et al indicated that plasma heat shock protein 70 level could be used as a serum marker in the early detection of adnexal torsion when found over 1.47-fold (P = 0.001) than control groups after 12 h adnexal torsion [6]. Ayachi A et al reported two cases of adnexal torsion during the second trimester of pregnancy;

presenting with appendix syndrome the one and acute left iliac fossa pain the other [7]. Laparotomy revealed the torsion of a hydatid of Morgagni whose necrotic appearance due to twisting required hydatid ablation. Sukkong K et al evaluated that adnexal torsion results in ischemia of structures distal to twisted pedicle and acute onset of pain is responsible for about 3% of all gynecologic emergencies especially in young nulliparous women [8]. Lee MH et al reviewed all computed tomography signs of adnexal torsion with the exception of deviation of the uterus to the twisted vascular pedicle side and moderately agreed only in patients with a mass [9]. Damasceno RW et al concluded a decrease in elastic fibers with ultrastructural abnormalities and an overexpression of elastin-degrading enzymes as the consequence of local ischemia, inflammation, and/or chronic mechanical stress [10]. Furthermore, aging results in progressive loss of tone and laxity. Spinelli C et al described the conservative treatment for adnexal torsion, consisting of detorsion, to keep the future reproductive capacity [11]. Tunc SY et al observed degeneration of epithelium, loss of cilia, dilation of blood vessels, and hemorrhages in sections of the ischemic group in the fallopian tube structure following ovarian torsion [12]. The studied fallopian section revealed a significant decrease in density of desmin in the torsion group with strong positive cytoplasmic CD68 expression. Türk E et al found that adnexal torsion and detorsion significantly increased [13].

The tissue level of malondialdehyde, superoxide dismutase and reduced glutathione, whereas hypothermia inhibited their production as well the histopathological changes in rats. Calis P et al found only the loss of cohesion to be significantly different by 1.28-fold than control sides (p=0.017) in terms of the means of total tissue damage [14]. Significantly lower proliferating cell nuclear antigen counts were revealed in the 16-hour torsion rat group demonstrating the functional status. Navve D et al associated the lateral whirlpool sign with enlarged masses; the mean volume of which was significantly greater by 2.81-fold than those with the medial whirlpool sign (P = 0.035) [15]. Sanez HA et al described that adnexal torsion over its pedicle produces lymphatic and venous stasis, later it develops into ischemia and necrosis, when left untreated [16]. Hirth D et al identified cell necrosis by high mobility group box 1 protein and apoptosis by caspase 3a staining of tissue samples taken at 3 endpoints post burn [17]. Endothelial cell necrosis at 1 hour divided the zone of injury progression (Jackson's zone of stasis) into an upper subzone with necrotic endothelial cells initially viable adnexal and interstitial cells that progressed to necrosis by 24 hours. The other was a lower zone initially with viable endothelial cells but necrosis and apoptosis of all cell types by 24 hours came in a validated porcine model of vertical burn injury progression. Ozler A et al found the mean number of preantral and small antral follicles lower and only anti-Müllerian hormone (AMH) levels significantly decreased after 3-hour IR (P < .05) in detorsion group than sham one (P < .01) [18]. After torsion, AMH, estradiol, and inhibin B levels were decreased significantly than whole perioperative period (P = 0.032). A numeric evaluation 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) [19].

Table 5: The U-74389G 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 U-74389G 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 hardly non-significantly deteriorated the common cE&K scores. However, this deterioration kept the scores within the "without alterations" grade (p-value=0.3951). This non-significant alteration created a suspicion for beneficial usage in situations such as tubal pregnancies, fertility, elastic and desmin ultrastructure, aging, tone, laxity and cohesion, regeneration of epithelium, conservation of cilia, blood vessel diameter regulation and lymphatic and venous stasis, cytoplasmic CD68, antioxidant markers, PCNA counts, mobility group box 1 protein, caspase 3a staining, anti-Mullerian hormone, estradiol and inhibin B presence or absence, ischemia, cell necrosis and apoptosis.

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References

1. Tsompos C, Panoulis C, Toutouzas K, Zografos G, Papalois A. The Effect of the Antioxidant Drug "U-74389G" On Oviductal Congestion during Ischemia Reperfusion Injury in Rats. AJBPS. 2016;6(52):15-18.
2. Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G, Papalois A. The effect of the antioxidant drug "U-74389G" on salpingitis during ischemia-reperfusion injury in rats. J Curr Res Sci Med. 2016;2(1):24-28.
3. Adamyan LV, Myinbayev OA, Kulakov VI. Use of fibrin glue in obstetrics and gynecology: a review of the literature. Int J Fertil. 1991;36(2):76-7, 81-88.
4. Castadot RG. Oral contraception in 1983 (author's transl). Contracept Fertil Sex (Paris). 1982;10(11):753-757.
5. Guennoun A, Krimou Y, Mamouni N, Errarhay S, Bouchikhi C, Banani A. Normal adnexal torsion and pregnancy: about a case. Pan Afr Med J. 2017;14(27):197.
6. Çılgın H, Şimşek M, Bal R. Can adnexal torsion be predicted by measuring plasma heat shock protein 70 level? An experimental study. Arch Gynecol Obstet. 2017;296(5):941-

946.

7. Ayachi A, Blel Z, Khelifa N, Mkaouer L, Bouchahda R, Mourali M. Adnexal torsion during the second trimester of pregnancy: about two cases. Pan Afr Med J. 2016;25(25):113.
8. Sukkong K, Sananpanichkul P, Teerakidpisan P, Bhamarapravatana K, Suwannarurk K. High Rate of Gangrenous Adnexal Torsion: Dilemma of a Missing Silent Cancer. Asian Pac J Cancer Prev. 2016;1;17(11):4981-4984.
9. Lee MH, Meyers N, Raptis CA, Mellnick VM. Interobserver reliability for computed tomography findings of adnexal torsion. Emerg Radiol. 2017;24(1):21-24.
10. Damasceno RW, Avgitidou G, Belfort R Jr, Dantas PE, Holbach LM, Heindl LM. Eyelid aging: pathophysiology and clinical management. Arq Bras Oftalmol. 2015;78(5):328-331.
11. Spinelli C, Piscioneri J, Strambi S. Adnexal torsion in adolescents: update and review of the literature. Curr Opin Obstet Gynecol. 2015;27(5):320-325.
12. Tunç SY, Ağaçayak E, Yaman NS, Deveci E, Kalkanlı S, Özler A. Effects of adnexal torsion on the Fallopian tube in rats: a histologic and immunohistochemical study. Anal Quant Cytopathol Histpathol. 2014;36(5):285-289.
13. Türk E, Karaca İ, Ozcinar E, Celebiler A, Aybek H, Ortac R, Güven A. The effect of hypothermia on adnexal torsion/detorsion injury in a rat ovary model. J Pediatr Surg. 2015;50(8):1378-1381.
14. Calis P, Bozdag G, Karakoc Sokmensuer L, Kender N. Does ischemia-reperfusion injury affect ovarian reserve and follicle viability in a rat model with adnexal torsion?. Eur J Obstet Gynecol Reprod Biol. 2015;185:126-130.
15. Navve D, Hershkovitz R, Zetounie E, Klein Z, Tepper R. Medial or lateral location of the whirlpool sign in adnexal torsion: clinical importance. J Ultrasound Med. 2013;32(9):1631-1634.
16. Sánez HA, Taboada-Pérez GC, Hernández-Arroyo L, Mateo-Madrigal M, Mateo-Madrigal V. Adnexal torsion: three cases. Ginecol Obstet Mex. 2013;81(5):272-278.
17. Hirth D, McClain SA, Singer AJ, Clark RA. Endothelial necrosis at 1 hour postburn predicts progression of tissue injury. Wound Repair Regen. 2013;21(4):563-570.
18. Ozler A, Turgut A, Soydinç HE, Sak ME, Evsen MS, Alabalik U, Basarali MK, Deveci E. The biochemical and histologic effects of adnexal torsion and early surgical intervention to unwind detorsion on ovarian reserve: an experimental study. Reprod Sci. 2013;20(11):1349-1355.
19. Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G, Papalois A. The Antioxidant Drug "U-74389g" Effect on Alanine Aminotransferase Levels. J Anal Pharm Res. 2017;4(2):95