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Research Article

The Rat Uterus after U-74389G Process

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Abstract

Aim: This study co-evaluated the 4 quoted histologic variables after the lazaroid U-74389G (L) drug administration. The calculation was based on the results of 2 preliminary studies, each one evaluating two respective histologic variables of Endometrial Edema (EE) and Uterus Inflammation (UI) or Endometrial Karyorrhexis (EK) and Uterus Congestion (UC); in an induced ischemia reperfusion animal experiment.

Materials and methods: The 2 main experimental endpoints at which the EE, UI and EK, UC 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 L administration.

Results: The first preliminary study showed that L has a non-significant recessing potency for EE and UI histologic parameters at the "without lesions" grade 0.2636364 ± 0.14594051 (p-values=0.0698). The second preliminary study showed that L has a non-significant recessing potency for EK and UC histologic parameters at the "without lesions" grade 0.1253529 ± 0.08529668 (p-values=0.1373) since they were co-evaluated together. These 2 studies were co-evaluated since they came from the same experimental setting. This study co-evaluated the combined diagnostic values of the four variables together.

Conclusion: L administration and reperfusion time together non-significantly accentuated the 4 histologic variables within the "without lesions alterations" score 0.0758471 [$-0.1464624 - +0.2981566$] (p-value=0.4940).

Keywords: Ischemia, U-74389g, Endometrial edema, Endometrial karyorrhexis, Uterus congestion, Uterus inflammation, Reperfusion.

Abbreviations: EK-Endometrial Karyorrhexis, UC-Uterus Congestion, EE-Endometrial Edema, UI-Uterus Inflammation, IR-Ischemia Reperfusion, GLM-Generalized Linear Models, CS-Cesarean Scar, RUPP-Reducing Uterine Perfusion Pressure, IMA-Inferior Mesenteric Artery, PPH-Post-Partum Hemorrhage, MIUH-Mild Intrauterine Hypoperfusion, MMP-Matrix Metallo Proteinase, CI-Cold Ischemia.

Introduction

U-74389G is a novel Lazaroid (L) antioxidant factor implicating just only 261 published studies. The Ischemia Reperfusion (IR) type of experiments is noted in 19.15% of these studies. A tissue protective feature of U-74389G is obvious in these 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 an antioxidant complex, which prevents 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. 4 histologic variables in a Uterine Ischemia Reperfusion (UIR) experiment were tested for this purpose. The two variables were those of Endometrial Edema (EE) and Uterus Inflammation (UI) which had a non-significant recessing potency at the "without lesions" grade 0.2636364 ± 0.14594051 (p-values=0.0698) since they were co-evaluated together [1]. The other variables were those of Endometrial Karyorrhexis (EK) and Uterus Congestion (UC) which had a non-significant recessing potency at the "without lesions" grade 0.1253529 ± 0.08529668 (p-values=0.1373) since they were co-evaluated together [2]. The present experimental work tried to co-evaluate these EE, EK, UC and UI variables together and to end up to their outcome totally, from the same rat induced UIR protocol. The

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paradox of this study is that, taking into account two recessing studies, it yielded an accentuating one concerning the histologic variables.

Materials and methods

Animal preparation

The 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 electrocardiograms, the oxygen supply and the 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 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 the blood flow interruption, the protocol of UIR were applied, as described above for each experimental group. L was administered at the time of reperfusion; through inferior vena cava catheter.

The EE, EK, UC and UI 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 raised between animals' mass with neither EE scores (p-value=0.7779) nor with UI ones (p-values=0.0576), nor with EK scores (p-value=0.8683) but only with UC ones (p-values=0.0047); hence the predicted UC scores were used. The pathologic score grading was maintained the same as in preliminary studies: (0-0.499) without lesions, (0.5-1.499) for mild lesions, (1.5-2.499) for moderate lesions and (2.5-3) for serious lesions damage. The paradox of this study is that, taking into account two recessing studies, it yielded an accentuating one concerning the histologic variables.

Model of ischemia-reperfusion injury

Control groups: The 20 control rats were the same for preliminaries and this study **(Table 1)**.
Group A: Reperfusion which lasted 60 min concerned 10 controls rats of combined EE, UI, EK and UC Uterine Score (cUS) as the mean of EE & UI scores and the EK & predicted UC ones.
Group B: Reperfusion which lasted 120 min concerned 10 controls rats of combined EE, UI, EK and UC Uterine Score (cUS) as the mean of EE & UI scores and the EK & predicted UC ones.
L group: The 20 Epo rats were the same for preliminaries and this study.
Group C: Reperfusion which lasted 60 min concerned 10 L rats of combined EE, UI, EK and UC Uterine Score (cUS) as the mean of EE&UI scores and the EK & predicted UC ones.
Group D: Reperfusion which lasted 120 min concerned 10 L rats of combined EE, UI, EK and UC Uterine Score (cUS) as the mean of EE & UI scores and the EK & predicted UC ones.

Statistical Analysis

Every cUS 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 dependent variable the cUS scores, and independent variables the L administration or no, the reperfusion time and their interaction.

	Mean EE&UI score ± SD	Mean EK&UC score ± SD	Mean EE&EK&UC&UI score ± SD
Group A	mild lesions 1.35 ± 0.6687468	mild lesions 0.943129 ± 0.5121834	mild lesions 1.146564 ± 0.5479395
Group B	moderate lesions 1.55 ± 0.831665	mild lesions 1.066787 ± 0.3325432	mild lesions 1.308393 ± 0.5542169
Group C	mild lesions 0.8 ± 0.6324555	mild lesions 0.5748878±0.2454082	mild lesions 0.6874439 ± 0.4251255
Group D	mild lesions 1 ± 0.781736	mild lesions 0.8151959 ± 0.509367	mild lesions 0.9075979 ± 0.618711

Table 1: EE, EK, UC and UI their mean and SD scores.

DG	Difference	p-value
A-B	-0.161829	0.6465
A-C	0.4591206	0.0745
A-D	0.2389665	0.3863
B-C	0.6209495	0.0125
B-D	0.4007955	0.0593
C-D	-0.220154	0.1258

Table 2: The values difference for groups (DG) after Wilcoxon signed-rank test for all histologic variables mean scores.

Results

L administration non-significantly recessed the 4 histologic variables within the "without lesions alterations" score 0.24361355 [-0.57263045- -0.227816] (p-value=0.3830), after co-calculation by both Wilcoxon signed-rank test and glm methods. Contrary, reperfusion time non-significantly accentuated the 4 histologic variables within the "without lesions alterations" score 0.19002235 [-0.1554684 - +0.5355131] (p-value=0.2707), after co-calculation by the same methods. Totally, L administration and reperfusion time together non-significantly accentuated the 4 histologic variables within the "without lesions alterations" score 0.0758471 [-0.1464624 - +0.2981566] (p-value=0.4940) (**Tables 3 and 4**).

Restore	95% c. in.	Reperfusion time	Wilcoxon	Glm
Without lesions alterations - 0.4591206	-0.996066	1h	0.0745	
Without lesions alterations 0.1337227	-1.0123978	1h		0.5857
Without lesions alterations - 0.0572691	-0.7409768	1.5h		0.756
Without lesions alterations -0.429958	-0.8599161	1.5h	0.01	
Without lesions alterations - 0.4007955	-0.7969931	2h	0.0593	
Without lesions alterations 0.1909915	-0.1342568 0.5162398	2h		0.2395
Without lesions alterations 0.1890532	-0.7314664	reperfusion		0.302
Without lesions alterations 0.1909915	-0.1342568 0.5162398	reperfusion	0.2395	
Without lesions alterations 0.0758471	-0.444619	interaction		0.494

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

Restore	95% c. in.	Reperfusion time	p-value
without lesions alterations -0.16269895	-0.6648149 -0.339417	1h	0.3301
without lesions alterations -0.24361355	-0.80044645	1.5h	0.383
without lesions alterations -0.104902	-0.46677445	2h	0.1494
without lesions alterations 0.19002235	-0.1554684	reperfusion	0.2707
without lesions alterations 0.0758471	-0.444619	interaction	0.494

Table 4: Concise form of the table 3.

Discussion

Tsuji M, et al., consider UIR as one of the major causes of intrauterine/fetal growth restriction, preterm birth, and low birth weight [3]. The offspring of their Mild Intrauterine Hypo-perfusion (MIUH) model clearly demonstrates long-lasting alterations in neurological, neuroanatomical and behavioral test results. Ugurlu T, et al., showed that antioxidant acetyl L-carnitine that added to the organ preservation solution (Post-Partum Hemorrhage) HTK, has prevented the formation of free radicals and mitochondrial damage, thus protects the uterus that was stored in short and long cold storage periods in female rats [4].

UIR is a complex pathophysiological process involved in hypoxia and/or reoxygenation (UHR), ionic imbalance-induced edema and acidosis, oxidative stress, mitochondrial uncoupling, coagulation and endothelium activation. VEGFR-2 plays an important role in angiogenesis, chemotaxis, proliferation and migration of endothelial cells. Sholapurkar SL, et al., proposed an "ischemia and mal-apposition hypothesis for Cesarean Scar (CS) niche", stating that the surgical technique of uterine incision closure is the most important determinant of CS defect formation [5]. Single-layer technique may be best reserved for thin myometrial edges especially during repeat cesareans. Alotaibi M suggested that a mechanism of uterine tolerance (preconditioning) is confined to uterine tissues very close to labour and it is a protective phenomenon to improve the uterine activity despite the long-lasting paradoxical metabolic challenges that occur during the repeated strong labour contractions in rat uterine term-pregnant tissues [6]. Ren Z, et al., showed that correcting soluble fms-like tyrosine kinase-1 (sFlt-1)/Placental Growth Factor (PlGF) imbalance by infusing PlGF reverses the decreases in vascular and uteroplacental Matrix Metallo Proteinase (MMP)-2 and MMP-9 and the increases in MMP-1, MMP-7, and collagen types I and IV induced by placental ischemia and antiangiogenic sFlt-1 in hypertension of pregnancy [7].

Angiogenic factors and MMP modulators could rectify changes in vascular and uteroplacental MMPs and collagen content and ameliorate hypertension and intrauterine growth restriction in preeclampsia. Clayton AM, et al., claims that placental ischemia, induced by Reducing Uterine Perfusion Pressure (RUPP), leads to cerebral edema and increased blood-brain barrier permeability and thus increased mortality risk from Alzheimer's disease, stroke, and cerebrovascular complications in women with a history of preeclampsia in pregnancy [8]. Astrocyte number was increased in both regions but area covered by astrocytes increased only in posterior cortex following RUPP. Posterior cortical occludin was decreased. These results suggest that 2 months postpartum, neuroinflammation, along with decreased occludin expression, may partly explain posterior cortical edema in rats with history of placental ischemia. Simoni M, et al., considered insufficient stem cell recruitment to adequately repair the uterus resulting in conditions such as Asherman syndrome, endometriosis and other endometrial receptivity defects [9].

In contrast, excessive recruitment of stem cells underlies endometriosis. Further, the normal endometrium is a rich source of multipotent stem cells that can be used for numerous applications in regenerative medicine beyond reproduction. Stem-cell mobilization inhibiting may also be helpful in endometriosis therapy. Almohanna AM, et al., suggestedwhat may be general mechanisms of conditioning occurring in all smooth muscles and tabulated tissue-specific mechanistic findings [10]. Kisu I, et al., achieved the first delivery after autologous uterus transplantation (UTx) in primates and the first periodic recovery of menstruation after allogeneic UTx in nonhuman primate models [11]. In addition, more validation in nonhuman primate models is needed for resolution of medical issues and further development of UTx in humans, despite clinical application of UTx in several countries. Vaka VR, et al., found mitochondrial ROS significantly elevated in endothelial cells incubated with RUPP serum compared with normal ones [12].

Impaired mitochondrial function and vascular, placental, and renal mitochondrial ROS play an important role in hypertension and reduced fetal weight in response to placental ischemia during pregnancy in female pregnant Sprague Dawley rats. Koizumi N, et al., submitted a 41-year-old woman [13]. In an elective needlescopic operation using 2- and 3-mm instruments after bowel decompression out of right broad ligament hernia. The defect in the right broad ligament was closed with sutures and she was discharged 2 days after the operation. In the treatment of broad ligament hernia without bowel ischemia, neither an abdominal incision nor any energy devices are required. Needle scopic operation seems to be a promising approach among minimally invasive operations. Kopko J, et al., found intra-operatively acute appendicitis and levorotation of the pregnant uterus at 19th week of gestation by about 100 degrees [14].

As the signs of ischemia were absent, the uterus was returned into its normal position. The patient underwent cesarean section at 36 weeks of pregnancy due to early leakage of amniotic fluid and failure to progress during first stage of labor. Padma AM, et al., distinguished reperfusion injury-related differences associated with organ preservation; that may lead to improved human uterus transplantation protocols curing women with uterine factor infertility. A much faster and severe reperfusion damage of all uterine layers during the reperfusion experiment was got evident following 48 hours of cold ischemia [15]. This was indicated by major accumulation of extracellular fluid, presence of apoptotic-labeled glandular epithelial layer and vascular endothelium. A significant accumulation of lactate was measured in the perfusate with a subsequent decrease in pH in a novel ex vivo sheep uterus model. Chen C, et al., assessed the safety and efficacy of Transcatheter Arterial Embolization (TAE) of the Inferior Mesenteric Artery (IMA) for the management of Post-Partum Hemorrhage (PPH) [16].

Bleeding from the IMA should be suspected when there is persistent vaginal bleeding after sufficient embolization of bleeders from the bilateral iliac arteries. Saat N, et al., indicated that melatonin improved fertility and reduced uterine torsion related tissue damage and that its application during torsion was more effective than application following removal of torsion in pregnant rats [17]. Tardieu A, et al., demonstrated hypoxia-associated degradation of the organ by the significantly higher lactate levels, accompanied by cell lysis and significantly higher levels of creatine kinase activity ($p < 0.05$) [18]. The metabolic results indicate a significant degradation of the uterus during 24 h of Cold Ischemia (CI) before transplantation in explanted ewes uteri. Tardieu A, et al., calculated the mean CI time in studies of births from uteri obtained from live donors between 2 h 47 min and 6 h 20 min from a deceased donor; with only one birth in this case in women [19].

Muscle contractions have also been demonstrated in myometrial samples from women, after six or more hours of CI. The uterus seems to be able to tolerate a prolonged period of CI, of at least six hours; for

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the development of UTx, particularly for procedures using grafts from deceased donors. Along with other authors, we believe that the initial step resulting in uterine damage is an acute increase in lipid peroxidation following ischemia, which damages endometrium and other myometrial cells that ultimately induce their own apoptosis. In theory, high levels of lipid peroxidation are decreased over the course of reperfusion. During this time, either the cells may be destroyed via apoptosis or they remain alive but show signs of damage such as the 4 Mentioned histologic features if oxidative damage is not intense

enough. We hypothesize that lipid peroxidation may decrease following an oxidative insult as the cell overcompensates its antioxidant efforts to counteract such an insult. Despite this rigorous antioxidant effort by the cells, the damage may be too great and continue its course, and progressive destruction leads to the greatest loss observed at the endpoints of reperfusion. 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 [20] (Table 5).

35 Variables	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of Epo and rep	p-value
Mean	0.2929	0.2168	0.296	0.1836	0.315	0.2389	0.159	0.2016

Table 5: The L influence (+SD) on the levels of 35 seric variables of complete blood count and blood chemistry tests versus reperfusion (rep) time20.

Conclusion

L administration non-significantly accentuated the 4 histologic variables within the "without lesions alterations" score 0.0758471 [-0.1464624 - +0.2981566] (p-value=0.4940) disputing for beneficial usage in obstetric situations such as intrauterine/fetal growth restriction, preterm birth, hypertension, low/reduced fetal weight due to placental ischemia, uterine activity during the repeated strong labour contractions, preeclampsia, after bowel decompression out of right broad ligament hernia or correction of a rotated pregnant uterus, uterine torsion, post-partum hemorrhage and cesarean scar niche formation.

Many gynecologic situations also could be benefited such as endometriosis therapy, Asherman syndrome, Alzheimer's disease, stroke, posterior cortical edema and cerebrovascular complications in women with a history of preeclampsia, angiogenesis, chemotaxis, proliferation and migration of uterine endothelial cells in regenerative medicine beyond reproduction and development of autologous or allogeneic stored uterus transplantation protocols curing women with uterine factor infertility.

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