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Histologic comparison of the uterine pathologic effects of erythropoietin and U-74389G

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Abstract

Background: This manuscript compared the effects of uterine pathology (UP) after processing with either the drug erythropoietin hormone (Epo) or the lazaroid antioxidant agent (L), U-74389G. This comparison was provided by the outcomes of 2 preceding branches.

Objective: Both studies estimated the effect after each drug use in a planned uterine ischemia-reperfusion (UIR) mouse experimental setting.

Methods: Both principal experiment timepoints, the uterine histology was evaluated, were the minimum 60th after reperfusion (A, C, E groups) and also the minimum 120th after reperfusion (B, D, F groups). Groups A & B were placebo; C & D groups were processed with Epo; and E & F groups were processed after the L process.

Results: The one study branch of Epo has shown a barely significant decreasing potency for the total UP within the "lesion-free" grade alteration of -0.0916667 [-0.1907629 - 0.0074296] (p= 0.0583). However, the other study branch of U-74389G showed a non-significant accentuation of the total UP within the "lesion-free" grade alteration of 0.2229748 [-0.1376592 - 0.5836089] (p= 0.4940). Both branch studies were co-evaluated as they belong to a common experiment. Their outcome was that Epo appears to ameliorate UP status, whereas L appears to worsen it; however, the discrepancy was not significant (p= 0.0677).

Conclusion: There is a slight non-significant superiority of Epo than L in UIR pathology restoration (p= 0.0677), possibly useful in several clinical situations.

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INTRODUCTION

The new lazaroid U-74389G agent (L) has an unknown restoring capacity for uterine pathology (UP) (p= 0.4940)[1]. U-74389G, as a new antioxidant agent, concerns only 265 published works. The ischemic reperfusion (IR) character of those works was noted in 19.62% of all. A histologic protective agent, U-74389G, was found in those IR studies. L also chemically written as 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9[11]-triene-3,20-dione maleate salt, is a known antioxidant agent, inhibiting both lipid peroxidations, iron-dependent and arachidonic acid-mediated. It protects many IR animal tissues, such as the heart, renal, brain microvascular endothelial cells, monolayers, and liver. It also favors anti-shock, endothelium, mononuclear immunity, cytokines, whereas it downregulates the proinflammatory gene and the leukocytes.

Erythropoietin (Epo), almost unknown for its recessing action on UP (p= 0.0583), can be considered an ideal drug as a reference for comparison with L[2]. Epo implicates over 35,095 PubMed works, of which the IR type is disproportionately low at 3.88%. The cytokine classification of Epo supports the study of its effect on UP. This manuscript compares the effects of both agents in a mouse model of uterine IR (UIR). They were co-tested by evaluating alterations in uterine histology. Oxidative stress (OS)—caused by excess reactive oxygen species (ROS)—can harm the uterus, impairing tissue integrity and function[3]. Antioxidants help neutralize ROS, preserving overall uterine health by enhancing enzymes such as SOD, CAT, and GPx, while modulating inflammation via the Nrf2 pathway, ultimately supporting uterine function and hormone regulation.

Since adequate endometrial (uterine lining) thickness is crucial for embryo implantation, antioxidants help to encourage healthy endometrial development and improve implantation conditions in assisted reproduction. Indeed, supplementation has been shown to improve endometrial thickness and implantation outcomes[4]. During early pregnancy, controlled ROS levels facilitate processes like implantation and placental development. But excessive ROS can lead to complications such as placental dysfunction, miscarriage, intrauterine growth restriction, and gestational diabetes. Antioxidants help maintain this delicate balance — supporting uterine and placental function—and may reduce risk of such complications[5]. OS is increasingly recognized as a contributing factor in the pathogenesis of uterine fibroids (leiomyomas) through its effects on genetic, epigenetic, angiogenic, and fibrotic pathways. Antioxidants — both dietary and pharmacological — are being explored as therapeutic agents for the prevention and management of fibroids[6]. Antioxidants protect against methotrexate-induced oxidative damage in uterine tissues, reducing lipid peroxidation and inflammatory damage. Endometriosis involves oxidative damage to reproductive tissues, and antioxidants have shown efficacy in lowering oxidative markers, reducing lesion development, and suppressing inflammation. These compounds may help protect uterine tissue and support fertility. Antioxidants also show promise in reducing endometriotic lesion growth and angiogenesis by regulating signaling pathways, including

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VEGF and MMPs, thereby contributing to uterine health[7-11].

METHODS

Animal preparation

It is about a randomized controlled trial conducted at Elpen Pharmaceutical Co Ltd SA, lasting 6 months, using biomedical settings, including 60 Albino rats aged 16 – 18 weeks, randomly divided into groups. The consent form was not applicable. Quantitative data collection was used concerning seric and histologic variables. Study tools included laboratory measurements and histology reports. Inferential statistics related to the fitted values of serum and UP with the drug timepoints. The ERC/IRB's wording concerns references 1, 2, 19, and 20. The humanistic management of Albino female Wistar mice, including the full peri-experimental management, can also be retrieved in the above references 1, 2, 19, and 20. Mice, 16 – 18 w. old in age, were randomly delivered to six (6) groups, each containing N = 10 mice. The sample size is the most common in the bibliography, and the 6 groups were created by combining a placebo with 2 drugs across the 2 time points.

A hypoxic stage of 45 min was initiated in all six groups. Then, a common reperfusion of 60 min concerned groups A, C, E; while a common reperfusion of 120 min concerned B, D, F groups. A & B groups received a placebo; C & D groups received reperfusion associated with Epo intravenous (IV) administration, while E & F groups received reperfusion associated with U-74389G IV administration. The preliminary studies also assess the dose-response for both drugs, typically at 10 mg/Kg body mass.

Preliminary work also describes in detail the operational laparotomic protocol for clamping the inferior aorta just above the renal arteries with forceps. Both drugs were administered throughout the entire reperfusion phase via an inferior vena cava catheter. Uteri were extracted at the end of each reperfusion time point, as assessed above, for each group. The uterine histology evaluation was based on the results of 4 histologic variables: (i) endometrial edema (EE), (ii) uterus inflammation (UI), (iii) endometrial karyorrhexis (EK), and (iv) uterus congestion (UC). The pathologic score for every histologic variable alteration was graded as: [0-0.499] the lesion-free ones, [0.5-1.499] the mild lesion ones, [1.5 -2.499] the moderate ones, and [2.5-3] the serious ones. All calculations were performed using Stata 6.0.

Statistical analysis

Rat weights, biochemical findings, and histologic scores were tested for normality using the Shapiro-Wilk test in earlier publications, in which drugs were correlated with individual biochemical or histologic parameters. Since then, any combined study of more or all of the above parameters using parametric methods has been legalized. Data analysis with their descriptive statistics can be found in the individual publications. In this manuscript, the authors focus on the matrix statistics, which are presented extensively in the tables. It goes without saying that the level of statistical significance chosen is < 0.05. Table 2 presents the differences in scores for groups (DG) after applying the Wilcoxon signed-rank test to the mean values of all post-Epo UP variables with respect to reperfusion

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time. Also, Table 3 presents the DG scores after applying the same rank test to the mean values of all post-L UP variables regarding reperfusion time. Table 4 presents the outcome of a paired t-test applied using the DG columns per endpoint. Paired t-test is quoted in Table 1.

No drug, at any time point, demonstrated significant antioxidant activity in endometrial tissue. During ischemia, the oxygen supply is interrupted, causing cellular damage. Once blood flow is restored, the sudden influx of oxygen can lead to OS, worsening the injury. Perhaps earlier administration (closer to the reperfusion event) has shown better outcomes, but the therapeutic window can extend up to 2 hours, depending on the severity of the ischemic injury. Markers of oxidative stress (e.g., MDA) and inflammatory cytokines (TNF-alpha) were not applicable to the uterus.

Ethics Approval

The study has been specifically approved by Veterinary licenses 3693/12-11-2010 and 14/10-1-2012 by the Regional Unit of Eastern Attica of the Directorate of Agricultural Economy and Veterinary Medicine at the Secretariat.

RESULTS

The final application of the paired t-test comparing the DG columns per endpoint found that Epo is not significantly superior to L in UP restoration within the "lesion-free" grade alteration (0.3146415 [-0.13992 - 0.769203]; p= 0.0677), as shown in Table 2, Table 3, and Table 4. The lack of significant effects of antioxidants on UP can be attributed to several complex biological and physiological factors. While antioxidants have well-established roles in reducing OS throughout the body, their specific impact on the uterus has been less studied, and several factors may account for this limited effect. However, the effects of antioxidants may be less pronounced in the uterus than in other tissues, partly because the role of OS in the uterus is less well understood and less directly linked to UP. While antioxidants may help reduce inflammation and oxidative damage, they do not directly affect hormonal regulation, the primary driver of uterine function. The bioavailability of antioxidants can vary, and there may be limitations in delivering them to the uterus at sufficiently high concentrations. For example, the blood-uterus barrier may prevent antioxidants from reaching the uterine tissue at levels that are necessary for therapeutic effects. While OS may contribute to UP, antioxidants alone might not be sufficient to reverse or control the progression of such diseases. The complexity of these disorders involves factors like hormonal imbalances, immune responses, and tissue remodeling, which antioxidants may not directly influence. Further research is needed to better understand how antioxidants might interact specifically with the uterus or contribute to the treatment of uterine disorders.

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Table 1. Paired t – test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
var1	6	.2229748	.1402928	.3436457	-.1376592	.5836089
var2	6	-.0916667	.0385501	.0944281	-.1907629	.0074296
diff	6	.3146415	.1768321	.4331485	-.13992	.769203
Ho: mean [var1 - var2] = mean [diff] = 0						
	Ha: mean [diff]< 0		Ha: mean [diff]~= 0		Ha: mean [diff] > 0	
	t= 1.7793		t= 1.7793		t= 1.7793	
	P<t= 0.9323		P>|t|= 0.1353		P>t= 0.0677	

Table 2. The values difference for groups (DfG) after the Wilcoxon signed-rank test for all postEpo histological variables

DfG	Difference*	P - value
A-B	+ 0.05	0.9181
A-C	- 0.125	0.6447
A-D	- 0.125	0.8370
B-C	- 0.175	0.4425
B-D	- 0.175	0.4102
C-D	0	1.0000

*It is the difference between the mean histologic scores of each group across all possible abstraction combinations for erythropoietin

Table 3. The values difference for groups (DfG) after the Wilcoxon signed-rank test for all post-L histological variables

DG	Difference*	P - value
A-B	- 0.161829	0.6465
A-E	+ 0.4591206	0.0745
A-F	+ 0.2389665	0.3863
B-E	+ 0.6209495	0.0125
B-F	+ 0.4007955	0.0593
E-F	- 0.220154	0.1258

*It is the difference between the mean histological scores of each group across all possible abstraction combinations for L

Table 4. The postL, postEpo, and postL-postEpo value differences for groups (DG) across all histologic variable mean scores.

DG	L Differences	Epo Differences	L-Epo Differences
[A-B]-[A-B]	0.161829	+ 0.05	-0.211829
[A-E]-[A-C]	+ 0.4591206	- 0.125	0.5841206
[A-F]-[A-D]	+ 0.2389665	- 0.125	0.3639665
[B-E]-[B-C]	+ 0.6209495	- 0.175	0.7959495
[B-F]-[B-D]	+ 0.4007955	- 0.175	0.5757955
[E-F]-[C-D]	0.220154	0	-0.220154
Mean	+ 0.2229748	- 0.0916667	0.3146415

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Table 5. A U-74389G / erythropoietin efficacy ratios synthesis on 35 seric variables.

Endpoint Variable	1h	*p*	1.5h	*p*	2h	*p*	Reperfusion time	*p*	Interaction *	*p*
WBC	0.957451	0.3782	1.396122	0.0000	1.918237	0.0000	1.71622	0.0000	1.601887	0.0000
RBC count	0.961059	0.0000	1.733395	0.0000	6.519657	0.0000	1.039524	0.0000	1.309673	0.0000
Hematocrit	38.424	0.0000	9.076658	0.0000	6.222898	0.0000	1.001356	0.2184	12.66419	0.0000
Hemoglobin	1.268689	0.0000	1.839035	0.0000	13.1658	0.0000	1.252422	0.0000	1.94889	0.0000
MCH	151.125	0.0000	4.246814	0.0000	2.709729	0.0000	1.177347	0.0000	4.362893	0.0000
MCV	150.8518	0.0000	4.236722	0.0000	2.704247	0.0000	1.180156	0.0000	4.352528	0.0000
MCHC	3.6046103	0.0000	1.8166222	0.0000	1.1733738	0.0000	3.044774	0.0000	1.2831629	0.0000
RbcDW	3.306773	0.0000	3.023389	0.0000	2.655885	0.0000	0.2259914	0.0000	2.370353	0.0000
Platelet count	2.42839	0.0000	6.00238	0.0000	6.1333429	0.0000	3.939027	0.0000	37.62979	0.0000
MPV	145.8532	0.0000	4.053619	0.0000	2.603947	0.0000	1.2334644	0.0000	4.164431	0.0000
Platelet DW	0.6940233	0.0000	1.319118	0.0000	2.206972	0.0000	2.2484006	0.0000	2.458888	0.0000
Platelet crit	4.3251772	0.0000	1.4882359	0.0000	0.75145256	0.0886	5.620077	0.0000	1.0233828	0.0000
Glucose	156.4991	0.0000	4.53659	0.0000	2.81397	0.0000	0.9073196	0.0000	4.660603	0.0000
Urea	158.4209	0.0000	4.50889	0.0000	2.850291	0.0000	0.9017775	0.0000	4.632148	0.0000
Creatinine	168.9034	0.0000	4.872332	0.0000	3.039572	0.0000	1.0262016	0.0000	5.005523	0.0000
Uric acid	0.6212533	0.0000	1.106911	0.0000	1.3349	0.0027	0.44218009	0.0000	1.33234	0.0000
Total proteins	155.9562	0.0000	4.421079	0.0000	2.803573	0.0000	0.8842162	0.0000	4.541934	0.0000
Albumins	0.2457507	0.0073	0.5303472	0.0000	0.6243052	0.0465	1.237477	0.0000	0.5000416	0.0000
ALT	0.5955473	0.0000	0.86405406	0.0000	7.967324	0.0000	0.4734427	0.0000	1.6107645	0.0000
AST	1.149264	0.0391	0.9347365	0.0000	0.6695775	0.0000	0.7631082	0.0000	0.8224656	0.0000
γGT	1	1.0000	0.5367033	0.0000	1.0606061	0.8982	2.146813	0.0000	3.7264586	0.0000
ALP	134.0033	0.0000	3.602703	0.0000	2.349961	0.0000	0.7205412	0.0000	3.701187	0.0000
ACP	2.774031	0.0000	5.450674	0.0000	7.86942	0.0000	0.121724	0.0000	8.011334	0.0000
CPK	144.0769	0.0000	3.987264	0.0000	2.567192	0.0000	0.7974539	0.0000	4.09626	0.0000
CK-MB	141.313	0.0000	3.883186	0.0000	2.509108	0.0000	1.2876033	0.0000	3.989339	0.0000
LDH	142.9228	0.0000	3.944068	0.0000	2.543149	0.0000	1.2677226	0.0000	4.051881	0.0000
Sodium	1.695709	0.0000	0.8085706	0.0000	3.008772	0.0455	1.631842	0.0000	2.74914	0.0000
Potassium	1.640618	0.0000	0.968488	0.0000	3.346145	0.0000	2.414214	0.0000	11.4937	0.0000
Chloride	0.5544784	0.0007	0.8643683	0.0000	1.07745	0.5428	1.358293	0.0000	1.012762	0.0000
Calcium	0.00000334	0.0000	0.2490068	0.0000	0.1988753	0.0000	2.063208	0.0000	2.3623042	0.0000
Phosphorus	0.861859	0.1111	0.409606	0.0000	0.167592	0.0000	5.120084	0.0000	0.445513	0.0000
Magnesium	1.331108	0.0000	0.2605466	0.0000	0.5961915	0.0000	1.013227	0.0000	1.823808	0.0000
Amylase	156.4494	0.0000	4.440002	0.0000	2.813682	0.0000	0.8879931	0.0000	4.561391	0.0000
Testosterone	0.8574561	0.5185	0.7325777	0.0000	0.6709677	0.1646	1.313492	0.0000	0.4046004	0.0000
Progesterone	182.0437	0.0000	5.311029	0.0000	3.25928	0.0000	1.062206	0.0000	5.456215	0.0000
Mean	5.8469325	0.0586	1.8949425	0.0000	2.0623306	0.0510	1.1901598	0.0005	2. 2477238	0.0000

*"Interaction" is an artificial dependent variable provided by the statistical GLM test combining the variable of time reperfusion and drug effect together; it is the most reliable and useful parameter for such kinds of pharmacodynamics.

DISCUSSION

The same authors published the only available work investigating the histologic effect of L on the uterus[1]. L is established as a neuroprotective and membrane-stabilizing agent that acts at the cell membrane and protects the vascular endothelium from peroxidative damage, without penetrating the blood-brain barrier. It ameliorates Duchenne muscular dystrophy, learning impairments, septic states, and ototoxicity. It up-regulates glutathione (GSH), superoxide dismutase [SOD], and γ-glutamyltransferase (γgt levels in oxygen-excess cells. It immunosuppresses flap transplants, slows early synaptic transmission, and activates hypoxic neurons. It exhibits anti-proliferative activity against brain tumor cells and appears to be a promising anti-inflammatory agent for IR reversion. The same team

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found a slight short-term recessing pathological effect upon Epo administration in non-iron-deficient individuals[2].

Lina Jakubauskiene et al. significantly alleviated the IR UP after pretreatment with 5 μg/kg human relaxin (RLX), 2,400 IU/kg recombinant human Epo (rhEpo), or both in rats, at the same time points and tissue sampling as described above[12]. The process with RLX preserved tissue normality and SOD activity, attenuated TUNEL-positive cell count, MPO, and MDA levels, and up-regulated HES1 and NICD gene expression, while Epo reduced only MDA levels compared to the control group.

Yuma Kitase et al. reported that 24 h after chorioamnionitis (CHR), cerebral levels of MLTR1 mRNA, EpoR (Epo receptor), and Epo were increased compared with those in healthy controls[13]. Notably, CHR brains were $SIRT_1$ (-) mRNA deficient with increasing HIF1α & HIF2α levels, despite normal values of $MLTR_1$, EpoRs, and Epo under elevated serum Epo levels. Fluctuations were observed in serum Epo levels and in MLT levels in CHR rats. Thus, ligand-receptor (LR) mismatching, tissue compartmental (TC) differential adjustment, and non–receptor–mediated (nRm) signals highlight the nuance, complexity, and importance of immune-neural cell development. Also, valuable items for the inflammatory perinatal brain IR mechanism, commensurate with the maternal-placental-fetal axis, were identified in human preterm infants.

Lina Jakubauskiene et al showed that novel RLN - or Epo - as additives to a supplemented Custodiol-N (HTK-N) solution is beneficial as tissue preservative in uterus static cold storage (SCoS) at 4 d. °C in HTK - N solutions of 10 IU/mL or 20 nM Epo model, as proved by the severe damage of UP[14]. TUNEL - positive cell number, SOD, and MDA levels were significantly attenuated after 24 h of preservation in Sprague Dawley rats.

Hiromi Ii et al. indicated that an alternative lazaroid U-83836-E {[2R]-2-[[4-(2,6-dipyrrolidin-1-ylpyrimidin-4-yl)piperazin-1-yl]methyl]-3,4-dihydro-2,5,7,8,-tetramethyl-2H-1-benzopyran-6-ol, dihydrochloride}, may be a beneficial oncogenic γ-Glutamylcyclotransferase inhibitor (GGCT) for the creation of novel tumor therapeutics, using a fluorochrome-conjugated GGCT probe, in NIH3T3 cells extracts overexpressing GGCT in mice[15].

Rachel L. Hill et al. found that intermittent IR after sudden inhibition of lipid peroxidation (LP) by the 21-aminosteroid ("lazaroid") U-74389G (U-74), following any CCI-TBI, provides dose-dependent mitochondrial neuro-protection[16]. The rapid administration of 1 mg/kg U74 (an LP inhibitor) reduced reactive aldehyde levels and improved mitochondrial function in IR rats. Acrolein and mitochondrial 4-HNE have been tested as candidates for LP-mediated oxidative damage. Significantly lower respiration rates were written down than the sham in mitochondria after 72 h post-TBI. U-74 administration at the above dose significantly ameliorated reactive aldehyde levels, RCR, and mitochondrial respiration rates in vehicle-treated animals.

Marwa Atallah et al. found that maternal administration of (3mg/kg) edaravone [free radical scavenger with anti-inflammatory, antioxidant, and neuroprotective effects] provided a beneficial effect against OS and hypoxia (H)[17]. The last two affect the developing fetal brain through the reduced

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uterine perfusion pressure (RUPP) model, which is associated with pro-inflammatory and neurodegenerative damage via Hif-1α and iNOS up-regulation and microglial and astrocyte activation. This study implicates the RUPP model for preeclampsia on fetal developing brain and edaravone as a potential treatment. Edaravone upregulated MMP-9, IL-1β, IL-6, and TNF-α, decreased OS, restored neuronal structure and the fetal brain cortex, and alleviated the inflammatory response, thereby providing more general neuroprotection in a RUPP-placental IR mouse model.

V. Kölükçü et al. reported that 100 μg/kg dexmedetomidine protects uterine tissue against IR injury in rats[18]. Specifically, IL-1β, IL-6, and TNF-α levels were significantly suppressed (p=0.001). Antioxidant enzyme activities (GSH-PX and SOD) were increased, MDA values were decreased, while endometrial stromal and epithelial glandular changes were significantly improved in the treated group (p<0.001).

According to the above, Table 4 shows that Epo is not significantly superior to L in UP restoration within the "lesion-free" grade alteration, with a difference of 0.3146415 [-0.13992, 0.769203] (p= 0.0677). However, a synthesis of the effect ratios from the above experiment across 35 seric variables yields contradictory results, as shown in Table 5[19,20]. Every seric variable is an odds ratio (OR) of L/Epo efficacies. The ORs for each drug and each variable were estimated from GLM tests, with seric values or histologic scores as dependent variables and time points and drugs as independent variables. The final OR was obtained by the synthesis of all OR_i: $OR_f=\sqrt[35]{OR_1*OR_2*\ldots*OR_{35}}$.

Such drugs may be proved beneficial for several clinical situations as the successful uterus transplantation, the tumor growth inhibition in xenograft models, newborns with PBI of singular etiology, prenatal inflammation, (epi)genetic eutrophy, toxins (drugs including opioids and environmental agents), hypoxia or ischemia, preeclampsia, the developing fetal brain protection and postnatal stressors such as seizures and sepsis; but further studies are required.

CONCLUSION

Although the new antioxidant drug U-74389G is biochemically found to be only 2.2-fold (~double) more active than Epo, with a trend attenuating at short time points, the UP findings are discrepant. Perhaps further studies may coincide with the biochemic ones, promising much more for clinical circumstances.

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