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Research Article

The Effect of Erythropoietin on Salpingitis during Ischemia Reperfusion Injury in Rats

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Abstract

Purpose: This experimental study was to examine the effect of erythropoietin in a rat model and particularly in an oviducts Ischemia Reperfusion (IR) protocol. The effect of that molecule was studied pathologically using mean Salpingitis (S) lesions scores.

Methods: 40 rats of mean weight 247.7 g were used in the study. Salpingitis lesions were evaluated at 60 min (groups A and C) and at 120 min (groups B and D) of reperfusion. Erythropoietin was administered only in groups C and D.

Results: Epo administration non-significantly altered the salpingitis scores by 0 without lesions (p= 1.0000). Reperfusion time non-significantly altered the salpingitis scores by 0 without lesions (P= 1.0000). Furthermore, Epo administration and reperfusion time together non-significantly altered the salpingitis scores by 0 without lesions (p=1.0000).

Conclusion: Epo administration interacted or not with reperfusion time non-significantly short-term altered the salpingitis lesions scores. Perhaps, a longer study time than 2 hours may reveal more significant effects.

Keywords: Ischemia; Erythropoietin; Salpingitis; Reperfusion

Introduction

Tissue Ischemia and Reperfusion (IR) remain of the main causes of permanent or transient damage with serious implications on adjacent organs and certainly on patients' health. Although important progress has been made regarding the usage of Erythropoietin (Epo) in managing this kind of damages, satisfactory answers have not been given yet to fundamental questions, as, by what velocity this factor acts, when it should be administered, and in which dosage. The particularly satisfactory action of Epo in stem blood cells recovery has been noted in several performed experiments. However, just few relative reports were found concerning Epo trial in IR experiments, not covering completely this particular matter. A meta-analysis of 13 published seric variables, coming from the same experimental setting, tried to provide a numeric evaluation of the Epo efficacy at the same endpoints (Table 1). Also, several publications addressed trials of other similar molecules of growth factors to which the studied molecule also belongs to.

The aim of this experimental study was to examine the effect of Epo in a rat model and particularly in an oviducts IR protocol. The effect of that molecule was studied by evaluating mean Salpingitis (S) lesions.

Materials and Methods

Animal preparation

This experimental study was licensed by Veterinary Address of East Attiki Prefecture under 3693/12-11-2010 & 14/10-1-2012 decisions. All settings needed for the study including consumables, equipment and substances used, were a courtesy of Experimental Research Center of ELPEN Pharmaceuticals Co. Inc. S.A. at Pikermi, Attiki. Accepted standards of humane animal care were adopted for Albino female Wistar rats. Normal housing at laboratory 7 days before the experiment included continuous access to water and food. The experiment was acute, that means that awakening and preservation of the rodents was not following the experiment. They were randomly delivered to four experimental groups by 10 animals in each one. Ischemia for 45 min followed by reperfusion for 60 min (group A). Ischemia for 45 min followed by reperfusion for 120 min (group B). Ischemia for 45 min followed by immediate Epo intravenous (IV) administration and reperfusion for 60 min (group C). Ischemia for 45 min followed by immediate Epo IV administration and reperfusion for 120 min (group D). The molecule Epo dosage was 10 mg/Kg body weight of animals.

At first, the animals were submitted into prenarcosis followed by general anesthesia. The detailed anesthesiologic technique is described in related references [1,2]. Oxygen supply, electrocardiogram and acidometry were continuously provided during whole experiment performance.

The protocol of IR was followed. Ischemia was caused by forceps clamping inferior aorta over renal arteries for 45 min after laparotomic access had been achieved. Reperfusion was induced by removing the clamp and reestablishment of inferior aorta patency. The molecules were administered along with reperfusion initiation, through inferior vena cava after catheterization had been achieved. The S lesions evaluations were performed at 60 min of reperfusion (for groups A and C) and at 120 min of reperfusion (for groups B and D). Forty (40) female Wistar albino rats of mean weight 231.875 g [Std. Dev: 36.59703 g] were used, of min weight ≥ 165 g and max weight < 320 g. Rats' weight could be potentially a confusing factor,

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Table 1: Meta-analysis of the erythropoietin (Epo) influence (±SD) on the levels of some seric variables concerning reperfusion (rep) time coming from the same experimental setting.

Variable	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of Epo and rep	p-value
white blood cell	+24.01%±13.38%	0.1012	+22.09%±9.11%	% 0.0351	+20.17%±12.94%	0.0902	+14.63%±5.40%	0.0080
hematocrit[2]	+0.14%±2.89%	0.9626	-0.61%±2.37%	0.8072	-1.37%±4.05%	0.7485	+0.24%±1.38%	0.8586
mean corpuscular hemoglobin	+0.01%±1.29%	0.9904	+0.67%±0.80%	0.3549	+1.34%±1.08%	0.1509	-0.36%±0.47%	0.4430
platelet distribution width	+1.60%±0.80%	0.0765	+1.36%±0.58%	0.3549	+1.34%±1.08%	0.1509	0.36%±0.47%	0.0615
plateletcrit	16.47%±10.40%	0.0921	-13.74%±7.01%	0.0158	+1.13%±0.74%	0.0882	-6.88%±3.69%	0.0615
uric acid	+10.13%±15.10%	0.4917	+15.86%±10.21%	0.1408	+21.59%±15.45%	0.1940	+9.33%±6.16%	0.1264
total protein	-0.02%±2.47%	0.9904	1.27%±1.51%	0.3721	2.52%±2.03%	0.1509	0.68%±2.48%	0.4430
alkaline phosphatase	+0.20%±18.57%	0.9904	+10.70%±12.78%	0.3549	+21.20%±17.11%	0.1509	+5.79%±7.72%	0.4430
acid phosphatase	+0.06%±5.79%	0.9904	+3.11%±3.71%	0.3172	+6.16%±4.97%	0.1509	+1.68%±2.23%	0.4430
CPK	+0.15%±14.09%	0.9904	+7.91%±9.44%	0.3549	+15.67%±12.65%	0.1509	+4.28%±5.70%	0.4430
LDH	+0.08%±7.92%	0.9904	+4.48%±5.35%	0.3549	+8.89%±7.17%	0.1509	+2.42%±3.22%	0.4430
sodium	+0.72%±0.74%	0.3054	+0.21%±0.63%	0.7136	-0.29%±1.09%	0.7670	0.11%±0.38%	0.7531
progesterone	-0.20%±18.65%	0.9904	-8.86%±10.58%	0.3549	-17.53%±14.15%	0.1509	-4.79%±6.39%	0.4430
mean	+1.57%±8.76%	0.6894	+3.22%±9.49%	0.3228	+4.87%±12.29%	0.2353	1.99%±5.63%	0.3823

e.g. fatter rats to have more or less S lesions scores. This suspicion was also investigated. Also, detailed histopathological3 study (pathology) and grading of S findings was performed by scores, this is: 0 when lesions were not found, 1 when mild lesions were found, 2 when moderate lesions were found and 3 when serious lesions were found. The previous grading is transformed as follows: (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, because the study concerns score ranges rather than point scores.

Model of Ischemia-Reperfusion Injury

Control groups

20 control rats of mean weight 252.5 g [Std. Dev: 39.31988 g] suffered by ischemia for 45 min followed by reperfusion.

Group A

Reperfusion which lasted 60 min concerned 10 controls rats of mean weight 243 g [Std. Dev: 45.77724 g], mean without S lesions score 0 [Std. Dev: 0] (Table 2).

Group B

Reperfusion which lasted 120 min concerned 10 controls rats of mean weight 262 g [Std. Dev: 31.10913 g], mean without S lesions score 0 [Std. Dev: 0] (Table 2).

Table 2: Weight and salpingitis (S) score mean levels and Std. Dev. of groups.

Groups	Variable	Mean	Std. Dev
A	Weight	243 g	45.77724 g
	S	without lesions 0	0
B	Weight	262 g	31.10913 g
	S	without lesions 0	0
C	Weight	242.8g	29.33636 g
	S	without lesions 0	0
D	Weight	243g	32.84644 g
	S	without lesions 0	0

Erythropoietin group

20 rats of mean weight 242.9 g [Std. Dev: 30.3105 g] suffered by ischemia for 45 min followed by reperfusion in the beginning of which 10 mg Epo/kg body weight were IV administered.

Group C

Reperfusion which lasted 60 min concerned 10 Epo rats of mean weight 242.8 g [Std. Dev: 29.33636 g], mean without S lesions score 0 [Std. Dev: 0] (Table 2).

Group D

Reperfusion which lasted 120 min concerned 10 Epo rats of mean weight 243 g [Std. Dev: 32.84644 g], mean without S lesions score 0 [Std. Dev: 0] (Table 2).

Results

Initially, everyone from 4 rats weight groups was compared with each other from 3 remained groups applying statistical paired t-test (Table 3). Any emerging significant difference among salpingitis scores was investigated whether owed in the above mentioned significant weight correlations. Also, everyone from 4 rats salpingitis scores groups was compared with each other from 3 remained groups applying statistical Wilcoxon signed-rank test (Table 3). Applying generalized linear models (glm) with dependant variable the salpingitis scores and independent variables the Epo administration or no, the reperfusion time and their interaction, resulted in: Epo administration non-significantly altered the salpingitis scores by 0 without lesions (p= 1.0000). This finding was in accordance with the results of Wilcoxon signed-rank test (p= 1.0000). Reperfusion time non-significantly altered the salpingitis scores by 0 without lesions (P= 1.0000), also in accordance with the Wilcoxon signed-rank test (P= 1.0000). However, Epo administration and reperfusion time together non-significantly altered the salpingitis scores by 0 without lesions (p=1.0000). Reviewing the above and (Table 3 and 4) sums

Table 3: Statistical significance of mean values difference for groups (DG) after statistical paired t test application for weight and Wilcoxon signed-rank test for scores.

DG	Variable	Difference	p-value
A-B	Weight	-19g	0.2423
	S	without lesions 0	1.0000
A-C	Weight	0.2g	0.9900
	S	without lesions 0	1.0000
A-D	Weight	0g	1.0000
	S	without lesions 0	1.0000
B-C	Weight	19.2g	0.0478
	S	without lesions 0	1.0000
B-D	Weight	19g	0.2113
	S	without lesions 0	1.0000
C-D	Weight	0.2g	0.9883
	S	without lesions 0	1.0000

up concerning the alteration influence of Epo in connection with reperfusion time. Inserting the rats weight as independent variable at glm, a non significant relation turns on (p= 1.0000), so as further investigation is not needed.

Discussion

Salpingitis is part of a complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants [4]. It is a protective response involving host cells, blood vessels, proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult. Along it initiates the process of repair. The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. It is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even though the two are often correlated. Inflammation can even occur in absence of infection, although such types of inflammation are usually maladaptive (such as in atherosclerosis). Inflammation is a stereotyped response and therefore it is considered as a mechanism of innate immunity. General chronic salpingitis might lead to a host of diseases, such as hay fever, rheumatoid arthritis and even cancer (as it happens e.g. on cholecystitis for gallbladder carcinoma). Salpingitis can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured oviductal tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of oviductal tissues from the inflammatory process. Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus [5]. It is characterized by the above mentioned five cardinal signs, from which loss of function has multiple causes [6]. These five

Table 4: The alteration influence of erythropoietin in connection with reperfusion time.

Alteration	95% c. in.	Reperfusion time	p-values	
			Wilcoxon	glm
without lesions 0	undefined	1h	1.0000	1.0000
without lesions 0	undefined	1.5h	1.0000	1.0000
without lesions 0	undefined	2h	1.0000	1.0000
without lesions 0	undefined	reperfusion time	1.0000	1.0000
without lesions 0	undefined	interaction	_	1.0000

signs appear [7] when acute inflammation occurs, whereas acute salpingitis may not result in the full set. Pain happens only where the appropriate sensory nerve endings exist in the inflamed area e.g., acute inflammation of endosalpingium does not cause pain unless the inflammation accesses the muscular stratum, which does have pain-sensitive nerve endings. The process of acute inflammation is initiated by cells already present in oviducts, mainly resident macrophages, histiocytes, and mastocytes. These cells present on their endosalpingeal and serosal surfaces, have receptors named Pattern Recognition Receptors (PRRs), which recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as Pathogen-Associated Molecular Patterns (PAMPs). At the onset of an infection, burn, or other injuries, these cells undergo activation (one of their PRRs recognize a PAMP) and release inflammatory mediators responsible for the above mentioned clinical signs of inflammation. Some of the released mediators such as bradykinin increase the sensitivity to pain (hyperalgesia, dolor). The mediator molecules also alter the blood vessels to permit the migration of leukocytes, mainly neutrophils and macrophages, outside of the blood vessels (extravasation) into the tissue. The neutrophils migrate along a chemotactic gradient created by the local cells to reach the site of injury. The loss of function (functio laesa) is probably the result of a neurological reflex in response to pain. In addition to cell-derived mediators, several acellular biochemical cascade systems consisting of preformed plasma proteins act in parallel to initiate and propagate the inflammatory response. These include the complement system activated by bacteria and coagulation and fibrinolysis systems activated by necrosis, e.g. a burn or a trauma. The acute salpingitis response requires constant stimulation to be sustained. Hence, acute inflammation ceases once the stimulus has been removed. The plasma cascade systems which are activated during acute inflammation are the complement system, the kinin system, the coagulation system and the fibrinolysis system. Specific patterns of acute and chronic salpingitis are seen during particular situations that arise in oviducts, such as when inflammation occurs on an epithelial surface [endosalpigeal or serosal]: granulomatous inflammation, serous inflammation, ulcerative inflammation, but mainly fibrinous or purulent inflammation. Fibrinous inflammation resulting in a large increase in vascular permeability allows fibrin to pass through the blood vessels. If an appropriate procoagulative stimulus is present, such as cancer cells, a fibrinous exudate is deposited. This is commonly seen in serous cavities, where the conversion of fibrinous exudate into a scar can occur between serous membranes, limiting their function. The deposit sometimes forms a pseudomembrane sheet. During inflammation of the endosalpingium, intraoviductal synechiae can be formed. During inflammation of the serosal, pelvic

adhesions can be formed. Purulent inflammation resulting in large amount of pus, which consists of neutrophils, dead cells, and fluid. Neisseria gonorrhoeae and Chlamydia trachomatis were originally thought to be the only pathogens that caused acute salpingitis. The immune system is often involved with inflammatory disorders, demonstrated in either allergic reactions or immune system disorders resulting in abnormal inflammation. Non-immune diseases with etiological origins in inflammatory processes include cancer and local ischemic disease. Examples of disorders associated with salpingitis include: autoimmune diseases, auto inflammatory diseases, celiac disease, glomerulonephritis, hypersensitivities, pelvic inflammatory disease, reperfusion injury, rheumatoid arthritis, transplant rejection, vasculitis and interstitial cystitis.

The following clinical situations show the association between ischemia and female genitalia. Kannan S et al. implicated intrauterine infection which can lead [8] to a fetal inflammatory response syndrome, as one of the causes of perinatal brain injury leading to Periventricular Leukomalacia (PVL) and cerebral palsy. The presence of activated microglial cells has been noted in autopsy specimens of patients with PVL and in models of neonatal hypoxia and ischemia. Intrauterine inflammation leads to activation of microglial cells that may be responsible for the development of brain injury and white matter damage in perinatal period. Braun M et al. demonstrated [9] the suitability of a new *in vitro* inflammation model of the isolated hemoperfused bovine uterus for the investigation of anti-inflammatory substances especially their COX-2 selectivity. Rigor BM Sr classified [10] pelvic cancer causes in several types of pain, i.e., visceral, neuropathic, and somatic pain. Visceral pain is the results of smooth muscles spasms of hallow viscus; distortion of capsule of solid organs; inflammation; chemical irritation; traction or twisting of mesentery and ischemia, or necrosis and encroachment of pelvis and presacral tumors. Dudley DJ supposed [11] an "intrauterine inflammatory response syndrome" that could account for cases of preterm labor in which no infectious organism could be identified, in addition to culture-proven intrauterine infection. There is potential for corticotropin-releasing hormone to regulate inflammatory responses and vice versa.

The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to oviductal tissues. Failure to do so results in chronic salpingitis and cellular destruction. Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms that serve to terminate inflammation include: short half-life of inflammatory mediators *in vivo* [12], production and release of transforming growth factor (TGF) β from macrophages [13-15], production and release of interleukin 10 (IL-10) [16], production of anti-inflammatory lipoxins [17], down regulation of pro-inflammatory molecules, such as leukotrienes, up regulation of anti-inflammatory molecules such as the interleukin 1 receptor antagonist or the soluble Tumor Necrosis Factor Receptor (TNFR), apoptosis of pro-inflammatory cells [18], desensitization of receptors, increased survival of cells in regions of inflammation due to their interaction with the Extracellular Matrix (ECM) [19,20], down regulation of receptor activity by high concentrations of ligands, cleavage of chemokines by Matrix Metalloproteinases (MMPs) might lead to production of anti-inflammatory factors [21], production of resolvins, protectins or maresins. Emerging evidence now suggests that an active, coordinated program of acute inflammation resolution initiates in the first few hours after an inflammatory response begins. After entering in tissues, granulocytes promote the switch of arachidonic acid–derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence. Neutrophil recruitment thus ceases and programmed death by apoptosis is engaged. These events coincide with the biosynthesis, from omega-3 polyunsaturated fatty acids, of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis. As a consequence, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor-β1. The anti-inflammatory program ends with the departure of macrophages through the lymphatics [22]. The outcome in a particular circumstance will be determined by the layer in which the injury has occurred and the injurious agent that causes it. The possible outcomes of salpingitis are: resolution, fibrosis, abscess formation or chronic inflammation. However, given some antioxidant capacity of Epo, if it prevents both arachidonic acid-induced and iron-dependent lipid peroxidation, its administration will significantly decreases the salpingitis lesions.

Thus, inflammation is associated with Epo in different tissues. Erbayraktar S et al. [23] established that Epo is a member of the cytokine super family, with significant homology to mediators of growth and inflammation. Results from studies have shown that Epo and its receptor are widely expressed in embryonic and adult tissues, including the central nervous system, gut, kidney, muscles (e.g., smooth, skeletal, and heart), uterus, retina, pancreas, gonads, and lung.

Lappin T [24] supposed that the beneficial effects of hEpo may extend to organs such as ovaries, oviducts, uterus which has Epo receptors. Sasaki R et al. [25] claimed that Epo is both estrogen inducible and produced in oviducts. Masuda S et al. [26] found E2 and hypoxia induced transient, rapidly down regulated stimulation of Epo mRNA in oviductal ampulla and isthmus regions. The E2 action is probably mediated through the E2 receptor and de novo protein synthesis is not required for E2 induced Epo mRNA. Ochiai H et al. [27] attained the synthesis of hEpo protein attempting localized *in vivo* plasmid DNA gene transfer in laying chicken oviducts.

Conclusion

Epo administration interacted or not with reperfusion tome non-significantly short-term altered the salpingitis lesions. Perhaps, a longer study time than 2 hours or a greater Epo dosage may provide more significant effects.

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