

Developments in Reproductive Health and Reproductive Sciences Infertility

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Abstract

The purpose of this research was to co-evaluate the four mentioned histologic characteristics after the delivery of erythropoietin (Epo). The computation was based on the findings of two initial investigations that assessed two distinct histologic characteristics in an animal experiment with induced ischaemia reperfusion: endometrial oedema (EE) and uterine inflammation (UI) or endometrial karyorrhesis (EK) and uterine congestion (UC).

Materials and procedures: The 60th reperfusion minute (for groups A and C) and the 120th reperfusion minute (for groups B and D) were the two primary experimental endpoints at which the EE, UI, and EK, UC scores were assessed. In particular, groups A and B had drug-free processing, whereas groups C and D underwent Epo administration.

Results: Within the "without lesions" changes 0.05 [-0.2504947 - 0.3504947], the first exploratory investigation demonstrated that Epo has a barely boosting potency for EE and UI combined (p-values=0.7381). Epo has a non-significant recessing potency for EK and UC inside the "without lesions" grade 0.1409091±0.12249148 (p-values=0.2421), according to the second preliminary investigation. Because these two experiments were conducted in the same experimental environment, they were co-evaluated. The four variables' combined diagnostic values were co-evaluated in this research.

Conclusions: Within the "without lesions" grade changes 0.2363636 [-0.4814257 - 0.0086984] (p-values=0.0583), Epo exhibits a marginally significant recessing potency for all these histologic parameters.

Keywords: Erythropoietin, Endometrial Edema, Endometrial Karyorrhesis, Ischemia, Reperfusion Uterus Congestion, Uterus Inflammation

Introduction

The potential antioxidant properties of erythropoietin (Epo) were examined. For this goal, a uterine ischaemia reperfusion (UIR) experiment was used to investigate four histologic factors. Endometrial oedema (EE) and uterine inflammation (UI) were the two variables that were hardly increased (p-values=0.7381) within the "without lesions" changes 0.05 [-0.2504947 - 0.3504947]1. The other variables were uterine congestion (UC) and endometrial karyorrhesis (EK), which were likewise non-significantly recessed within the "without lesions" grade 0.1409091±0.12249148 (p-values=0.2421)2. Only 3.64% of the more than 31,019 published biological papers that meet Epo's requirements discuss its antioxidant capabilities. Using the same rat-induced UIR technique, the current experimental effort attempted to co-evaluate these EE, UI, EK, and UC variables and determine their overall results.

Materials and methods

Animal preparation

The research was approved by two ethical committees under the numbers 3693/12-11-2010 and 14/10-1-2012, completely adhering to the Declaration of Helsinki. Preliminary references include the Pathology Department, the sponsoring organization, and the experiment site [1,2]. Preliminary sources additionally cover the human animal care of Albino female Wistar rats, the seven-day pre-experimental ad libitum diet, the continuous intra-experimental anesthesiologic procedures, the acidometry, the electrocardiograms, the oxygen supply, and the post-experimental euthanasia. The rats were between 16 and 18 weeks old. They were divided into four (4) groups, each with ten members, at random. All four groups shared the 45-minute ischaemia stage. Following that, group A underwent reperfusion for 60 minutes, group B underwent reperfusion for 120 minutes, group C had instant Epo intravenous (IV) treatment and reperfusion for 60 minutes, and group D underwent immediate Epo IV administration and reperfusion for 120 minutes. In early research, the dosage height measurement was defined as 10 mg/kg body mass.

The inferior aorta was laparotomically clamped over the renal arteries using forceps for 45 minutes, which resulted in ischaemia. By removing the clamp, the inferior aorta's patency and reperfusion were restored. Following the cessation of blood flow, each experimental group followed the UIR technique as previously mentioned. Epo was given via inferior vena cava catheter during reperfusion. For the A and C groups, the EE, UI, EK, and UC scores were calculated at the 60th and 120th minutes after reperfusion, respectively. There was no correlation found between the mass of the animals and the

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EE (p-value=0.0861), EK (p-value=0.0692), UC (p-value=0.5769), or UI (p-value=0.7954) scores. The pathologic score grading remained unchanged from the first investigations: (0-0.499) for no lesions, (0.5-1.499) for light lesions, (1.5-2.499) for moderate lesions, and (2.5-3) for severe lesion damage.

Model of ischemia-reperfusion injury

Groups under control

Both the preliminary and current investigation used the same 20 control rats.

Ten control rats with combined EE, UI, EK, and UC uterine scores (cUS) as the mean of EE&UI and EK&UC scores participated in Group A Reperfusion, which lasted 60 minutes (Table 1).

Ten control rats with combined EE, UI, EK, and UC uterine scores (cUS) as the mean of EE&UI and EK&UC scores participated in Group B Reperfusion, which lasted 120 minutes (Table 1).

The erythropoietin group

The preliminary and current studies used the same 20 Epo rats.

Ten Epo rats with combined EE, UI, EK, and UC uterine scores (cUS) as the mean of EE&UI and EK&UC scores participated in Group C Reperfusion, which lasted 60 minutes (Table 1).

Group D

Ten Epo rats with a combined EE, UI, EK, and UC uterine score (cUS) as the mean of the EE&UI and EK&UC scores participated in the 120-minute reperfusion (Table 1).

	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 1.2 +0.4830459	Mildlesions1.275+0.5329426
Group B	moderate lesions 1.55+0.831665	mild lesions 1.1+0.4594683	mildlesions1.325+0.6129392
Group C	mild lesions 1.45+0.8959787	mild lesions 0.85+0.6258328	mild lesions 1.15+0.7187953
Group D	mild lesions 1.4+0.7745967	mild lesions 0.9+0.875595	mild lesions 1.15+0.8181958

Table 1: Endometrial Edema (EE), Endometrial Karyorrhesis (EK), Uterus Congestion (UC) and Uterus Inflammation (UI) And Their Mean and SD Scores Statistical analysis

Every cUS groups score was compared with each other from 3 remained groups applying Wilcoxon signed-rank test (Table 2).

DG	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

Table 2: The values difference for groups (DG) after Wilcoxon signed-rank test for all histologic variables mean scores. Then, the Generalized Linear Models (glm) were applied with dependent variable the cUS scores, and independent variables the Epo administration or no, the reperfusion time and their interaction.

Results

The four histologic variables inside the "without lesions alterations" score 0.275 [-0.713354 - 0.163354] (p-value = 0.2398) were non-significantly impacted by epo treatment after co-calculation using the Wilcoxon signed-rank test and glm techniques. Similarly, after co-calculation using the same techniques, reperfusion time non-significantly recessed the four histologic variables within the "without lesions alterations" score 0.15 [-0.60359645 - 0.30359645] (p-value=0.4438).

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In the "without lesions alterations" score of 0.2363636 [-0.4814257 - 0.0086984] (p-value=0.0583), the combination of Epo treatment and reperfusion duration marginally substantially impacted the four histologic characteristics. Tables 3 and 4 provide a condensed version of the aforementioned results.

Restore	95% c. in.	Reperfusion time	P-values	
			Wilcoxon	Glm
without lesions alterations -0.125	-0.8265626 0.5765626	1h	0.6447	
without lesions alterations -0.075	-.6715472 .5215472	1h		0.7947
without lesions alterations -0.275		1.5h	0.2902	0.1894
without lesions alterations -0.175	-0.652277 0.302277	2h	0.4102	
without lesions alterations -0.1	-0.8003073 0.6003073	2h		0.7676

Restore	95% c. in.		Reperfusion time	p-value
without lesions alterations -0.1	-0.7490549	0.5490549	1h	0.7197
without lesions alterations -0.275	-0.713354	0.163354	1.5h	0.2398
without lesions alterations -0.1375	-0.72629215	0.45129215	2h	0.5889
without lesions alterations -0.15	-0.60359645	0.30359645	reperfusion	0.4438
without lesions alterations -0.2363636	-0.4814257	0.0086984	interaction	0.0583
without lesions alterations -0.15	-0.60359645 0.30359645	reperfusion	0.4099	0.4777
Without lesions alterations -0.2363636	-0.4814257 0.0086984	interaction		0.0583

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

Table 4: Concise form of the table 3.

Discussion

Tsuiji M et al. (2018) [3] identified intrauterine hypoperfusion/ischemia as one of the major causes of intrauterine or fetal growth restriction, preterm birth, and low birth weight. The offspring in their Mild Intrauterine Hypoperfusion (MIUH) model demonstrated persistent alterations in neurological, neuroanatomical, and behavioral outcomes.

Ugurlu T et al. (2018) [4] demonstrated that the addition of the antioxidant acetyl-L-carnitine to the Histidine–Tryptophan–Ketoglutarate (HTK) organ preservation solution helped prevent the formation of free radicals and mitochondrial damage. Consequently, it provided protection to the uterus during both short- and long-term cold storage periods in female rats.

Ischemia–reperfusion is a complex pathophysiological process involving hypoxia and subsequent reoxygenation, ionic imbalance leading to oedema and acidosis, oxidative stress, mitochondrial uncoupling, coagulation, and endothelial activation. VEGFR-2 plays an important role in angiogenesis, chemotaxis, proliferation, and the migration of endothelial cells.

Sholapurkar SL et al. (2018) [5] proposed an “ischemia and mal-apposition hypothesis” for cesarean scar (CS) niche formation. They suggested that the surgical technique used for uterine incision closure is a major determinant in the development of CS defects. A single-layer closure technique may be most appropriate for thin myometrial edges, particularly during repeat cesarean sections.

Alotaibi M et al. (2018) [6] suggested that uterine tolerance, or preconditioning, occurs primarily in uterine tissues close to term and

the onset of labour. This protective mechanism may help maintain uterine activity despite the prolonged metabolic challenges caused by repeated and intense uterine contractions during labour in term pregnant tissues.

Ren Z et al. (2018) [7] demonstrated that correcting the imbalance between soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) through PlGF infusion reversed the reduction in vascular and uteroplacental matrix metalloproteinase (MMP)-2 and MMP-9 levels. It also reduced the increases in MMP-1, MMP-7, and collagen types I and IV induced by placental ischemia and the antiangiogenic effects of sFlt-1 in pregnancy-associated hypertension. These findings suggest that angiogenic factors and MMP modulators may help restore normal vascular and uteroplacental MMP activity and collagen content, thereby improving hypertension and intrauterine growth restriction associated with preeclampsia.

Clayton AM et al. (2018) [8] reported that placental ischemia induced by reduced uterine perfusion pressure (RUPP) resulted in cerebral edema and increased blood–brain barrier (BBB) permeability. These changes may contribute to an increased risk of cerebrovascular complications, including stroke and other neurological disorders, in women with a history of preeclampsia. Astrocyte numbers increased in both examined regions; however, the area covered by astrocytes increased only in the posterior cortex following RUPP. In addition, posterior cortical occludin expression was reduced. The findings suggest that, two months postpartum, neuroinflammation and decreased occludin expression may partially contribute to posterior cortical edema in rats with a history of placental ischemia.

Simoni M et al. (2018) [9] suggested that insufficient recruitment of stem cells for adequate uterine repair may contribute to conditions such as Asherman syndrome, endometriosis, and other defects in endometrial receptivity. In contrast, excessive stem-cell recruitment may contribute to the development of endometriosis. The normal endometrium is also a rich source of multipotent stem cells, which may have numerous applications in regenerative medicine beyond reproductive health. Inhibition of stem-cell mobilization may therefore also represent a potential therapeutic approach for endometriosis.

Almohanna AM et al. (2018) [10] proposed possible general mechanisms of conditioning that may occur in all types of smooth muscle and summarized tissue-specific mechanistic findings.

Kisu I et al. (2018) [11] achieved the first delivery following autologous uterus transplantation (UTx) in primates and the first periodic recovery of menstruation following allogeneic UTx in nonhuman primate models. However, despite the clinical application of UTx in several countries, further validation using nonhuman primate models is required to address unresolved medical issues and support the continued development of UTx in humans.

Vaka VR et al. (2018) [12] found that mitochondrial reactive oxygen species (ROS) levels were significantly elevated in endothelial cells incubated with serum obtained from rats subjected to reduced uterine perfusion pressure (RUPP), compared with those exposed to normal serum. Impaired mitochondrial function, together with increased mitochondrial ROS production in the vasculature, placenta, and kidneys, appears to play an important role in the development of hypertension and reduced fetal weight associated with placental ischemia in pregnant Sprague–Dawley rats.

Koizumi N et al. (2019) [13] reported the case of a 41-year-old woman who underwent an elective needlescopic procedure using 2- and 3-mm instruments for the treatment of a right broad ligament hernia after bowel decompression. The defect in the right broad ligament was closed with sutures, and the patient was discharged two days after the operation. In cases of broad ligament hernia without bowel ischemia, neither an abdominal incision nor energy devices may be required. The authors suggested that needlescopic surgery could be a promising minimally invasive approach.

Kopko J et al. (2019) [14] reported the intraoperative findings of acute appendicitis and approximately 100° levorotation of the pregnant uterus at the 19th week of gestation. As there were no signs of ischemia, the uterus was returned to its normal position. The patient subsequently underwent a cesarean section at 36 weeks of gestation because of premature leakage of amniotic fluid and failure to progress during the first stage of labour.

Padma AM et al. (2019) [15] investigated differences associated with reperfusion injury during organ preservation, which may contribute to the improvement of human uterus transplantation protocols for women with uterine factor infertility. Severe and rapid reperfusion damage affecting all uterine layers became evident following 48 hours of cold ischemia.

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This damage was characterized by substantial extracellular fluid accumulation and the presence of apoptotic cells in the glandular epithelial layer and vascular endothelium. A significant accumulation of lactate in the perfusate, accompanied by a subsequent decrease in pH, was also observed in a novel ex vivo sheep uterus model.

Chen C et al. (2019) [16] assessed the safety and efficacy of transcatheter arterial embolization (TAE) of the inferior mesenteric artery (IMA) for the management of postpartum hemorrhage (PPH). The authors suggested that bleeding from the IMA should be considered when persistent vaginal bleeding continues despite adequate embolization of bleeding vessels arising from the bilateral iliac arteries.

Saat N et al. (2019) [17] reported that melatonin improved fertility and reduced uterine torsion-related tissue damage in pregnant rats. Furthermore, administering melatonin during uterine torsion was found to be more effective than administering it after detorsion.

Tardieu A et al. (2019) [18] demonstrated hypoxia-associated deterioration of the uterus, as indicated by significantly increased lactate levels, cell lysis, and elevated creatine kinase activity ($p < 0.05$). These metabolic findings suggested significant uterine degradation during 24 hours of cold ischemia (CI) before transplantation in explanted ewe uteri.

Tardieu A et al. (2019) [19] reported that the mean cold ischemia (CI) time in studies resulting in births following uterus transplantation ranged from 2 hours and 47 minutes for uteri obtained from living donors to 6 hours and 20 minutes for a uterus obtained from a deceased donor. Muscle contractions were also demonstrated in myometrial samples obtained from women after six or more hours of CI. These findings suggest that the uterus may tolerate a prolonged period of cold ischemia of at least six hours, which is particularly important for the development of uterus transplantation procedures involving grafts from deceased donors.

A numerical evaluation [20] of the efficacy of erythropoietin (EPO) was performed using a meta-analysis of 35 serum variables obtained from complete blood count and blood chemistry tests in relation to reperfusion time under the same experimental conditions, as presented in 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	+3.39%+12.15%	0.5636	+4.44%+14.50%	0.3711	+5.49%+18.55%	0.3496	+2.83%+7.13%	0.4045

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

Conclusion

Erythropoietin (EPO) demonstrated a borderline statistically significant reducing effect on four histological variables classified under the “without lesions alterations” category, with a score of 0.2363636 (95% confidence interval: -0.4814257 to -0.0086984 ; $p = 0.0583$). This finding suggests the potential beneficial use of EPO in various obstetric and gynecological conditions.

Potential obstetric applications may include intrauterine or fetal growth restriction, preterm birth, pregnancy-associated hypertension, reduced fetal weight resulting from placental ischemia, impaired uterine activity during repeated and intense labour contractions, preeclampsia, uterine ischemic conditions associated with broad ligament hernia or uterine torsion, postpartum hemorrhage, and cesarean scar niche formation.

In addition, EPO and related therapeutic approaches may have potential applications in several gynecological and regenerative conditions, including endometriosis, Asherman syndrome, and uterine repair. Other areas of interest include the prevention or management of cerebral edema, stroke, and cerebrovascular complications associated with a history of preeclampsia. Furthermore, the regulation of angiogenesis, chemotaxis, proliferation, and migration of uterine endothelial cells may contribute to advances in regenerative medicine.

These findings may also support further research into autologous and allogeneic uterus preservation and transplantation protocols, with the ultimate aim of improving treatment options for women with uterine factor infertility.

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