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Comparison of the restoring effects of erythropoietin and U-74389G on creatine phosphokinase MB levels

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Abstract
Aim: This study calculated the effects on creatine phosphokinase MB (CK-MB) levels, after treatment with either of 2 drugs: the erythropoietin (Epo) and the *Antioxidant lazaroid* (L) drug U-74389G. The calculation was based on the results of 2 preliminary studies, each one of which estimated the certain influence, after the respective drug usage in an induced ischemia reperfusion (IR) animal experiment.
Materials and Methods: The 2 main experimental endpoints at which the serum CK-MB levels (CK-MBl) were evaluated was the 60th reperfusion min (for the groups A, C and E) and the 120th reperfusion min (for the groups B, D and F). Specially, the groups A and B were processed without drugs, groups C and D after Epo administration; whereas groups E and F after the L administration.
Results: The first preliminary study of Epo presented a non-significant CK-MBl restoring effect by 2.85%±3.80% (p-value=0.4430). The second preliminary study of U-74389G presented a significant CK-MBl restoring effect by 11.40%±3.08% (p-value=0.0005). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that Epo is 3.989339-fold [3.980903 - 3.997794] more recessing than Epo (p-value=0.0000) on CK-MBl.
Conclusions: The anti-oxidant capacities of U-74389G ascribe 3.989339-fold less recessing effects than Epo (p-value=0.0000) on CK-MBl.

Keywords: ischemia, erythropoietin, U-74389G, creatine phosphokinase MB levels, reperfusion

1. Introduction
The lazaroid U-74389G (L) may be not famous for its CK-MBl restore[1] capacity (p-value=0.0005). U-74389G as a novel antioxidant factor, implicates exactly only 260 published studies. The ischemia reperfusion (IR) type of experiments was noted in 18.84% of these studies. A tissue protective feature of U-74389G was 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 were 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.
Erythropoietin (Epo) even if is not famous for its CK-MBl restore action (p-value=0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 30,717 published biomedical studies, only a 3.59% of them negotiate the known type of IR experiments. Nevertheless, Epo as a cytokine, it is worth of being studied about its effects on creatine phosphokinase MB levels (CK-MB) levels too. This experimental work tried to compare the effects of the above drugs on a rat induced IR protocol. They were tested by calculating the serum CK-MB levels (CK-MBl) reductions.

2. Materials and Methods
Animal preparation
The Vet licenses under 3693/12-11- 2010 & 14/10-1-2012 numbers, the granting company and the experiment location 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 acidimetry, the electrocardiogram, the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16 – 18 weeks old. They were randomly assigned to six (6) groups consisted in N=10. The stage of 45 min hypoxia was common for all 6 groups. Afterwards, reperfusion of 60 min was followed in group A; reperfusion of 120 min in group B; immediate Epo intravenous (IV) administration and reperfusion of 60 min in group C; immediate Epo IV administration and reperfusion of 120 min in group D; immediate U-74389G IV administration and reperfusion of 60 min in group E; and immediate U-74389G IV administration and reperfusion of 120 min in group F. The dose height assessment for both drugs are 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 exclusion of the blood flow, the protocol of IR was applied, as described above for each experimental group. The drugs were administered at the time of reperfusion; through inferior vena cava catheter. The CK-MBl were determined at 60th min of reperfusion (for A, C and E groups) and at 120th min of reperfusion (for B, D and F groups). Along, due to a strong relation was raised between CK-MBl values with animals' mass (p-value=0.0393), the predicted CK-MBl values were used.

Statistical analysis

Table 1 presents the (%) CK-MBl restore influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) CK-MBl restore influence of U-74389G regarding reperfusion time. Chi-square tests were applied using the ratios which produced the (%) results per endpoint. The outcomes of chi-square tests are depicted at Table 3. The statistical analysis was performed by Stata 6.0 software [Stata 6.0, StataCorp LP, Texas, USA].

3. Results

The successive application of chi-square tests revealed that U-74389G is 141.313-fold [141.1777 - 141.4484] less recessive than Epo at 1h (p-value=0.0000), 3.883186-fold [3.877018 - 3.889363] less than Epo at 1.5h (p-value=0.0000), 2.509108-fold [2.506038 - 2.512182] less than Epo at 2h (p-value=0.0000), less 1.2876033-fold [1.2902731 - 1.2849389] (p-value=0.0000) without drugs and 3.989339-fold [3.980903 - 3.997794] less than Epo whether all variables have been considered (p-value=0.0000).

4. Discussion

The unique available study investigating the restoring effect of U-74389G on CK-MBl was the preliminary one [1]. Although the most famous activities of neuroprotection and membrane-stabilization properties, it accumulates in the cell membrane, protecting vascular endothelium from peroxidative damage but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchenne muscular dystrophy. It increases γgt, superoxide dismutase (SOD) and glutathione (GSH) levels in oxygen-exposed cells. It treats septic states and acts as immunosuppressant in flap survival. It prevents the learning impairments, it delays the early synaptic transmission decay during hypoxia improving energetic state of neurons. It shows antiproliferative properties on brain cancer cells and is considered as a new promising anti-inflammatory drug for the treatment of reperfusion syndrome in IR injuries.

The same authors confirmed [2] the short-term restoring effect of Epo preparations in non-iron deficient individuals. Gholamzadeh A *et al*. found [3] no significant difference between levels of CK-MB in the 2 groups during 24 hours (P = 0.186) after high-dose administration of EPO in patients with ST-elevation myocardial infarction who have been treated by primary PCI and standard antiplatelet therapy. Jain K *et al*. showed [4] increased myocardial inflammation and infiltration, greater CK-MB activity and elevated the cytoprotective chaperones HSP70 and HSP90 histologically in susceptible animals tolerant adult Sprague-Dawley rats on altitude of 9754 m. Qin YJ *et al*. found that exogenous EPO significantly blocked the increase of myocardial enzyme and inflammatory index [5] within 24 hours after CLP compared with the sham group, so as having cardioprotective effects on sepsis-induced myocardial injury in a rat sepsis model. Senthamizh Selvan O *et al*. significantly prevented [6] the coronary effluents of LDH and CK-MB activities, antioxidant enzyme activities, lipid peroxidation products and activity of TCA cycle enzymes after diosmin treatment. Ge G *et al*. showed [7] that S. miltiorrhiza aqueous extract (SAME) pre-treatment significantly decreased the ST-segment and myocardium CK-MB, lactate dehydrogenase (LDH) levels, increased myocardium antioxidant enzyme activities and inhibit myocardium cell apoptosis in heart IR Sprague-Dawley rats. Wang WD *et al*. studied [8] the protected effect of Yindan Xinnaotong capsule and main components compatibility on myocardium ischemia/reperfusion injury. CK-MB was reduced by the components GBE, SM-E, SM-H, and GSEC exerting a certain protection effect on MIRI. Dianat M *et al*. found [9] a more significant decrease in the levels of CK-MB in groups that had received combined treatment in comparison with vanillic acid VA or losartan, as a selective ANG-II type 1 receptor (AT1R) blocker alone in I/R-induced oxidative stress in isolated rat heart. Nazari A *et al*. found that infusion of vasopressin decreased [10] infarct size and CK-MB by 2-fold compared with control group in male Wistar rats. Moludi J *et al*. concluded [10] that Q10 supplementation 7 days pre-operationally was not effective in reducing CK-MB and troponin after coronary artery bypass operation. Yu Q *et al*. showed [11] a significant reduction in infarct size and decrease in CK-MB and LDH activities leading to cardioprotection after phenylethanoid glycoside-rich extract of Cistanche deserticola treatment in hearts. Hu T *et al*. found [1]2 significantly lower levels of creatine kinase-MB (CK-MB), cardiac troponin I (cTnI) and malondialdehyde (MDA) a lower expression of 8-hydroxydeoxyguanosine (8-OHdG) but markedly enhanced superoxide dismutase (SOD) activity after treatment with Danshensu and/or hydroxysafflor yellow A in a rat model of myocardial IR using H9c2 cells. Xuan F *et al*. revealed [13] that epigallocatechin gallate post-conditioning significantly decreased the levels of CK-MB and the release of LDH, reduced the myocardial infarct size, decreased the apoptotic rate and partially preserved heart function in a rat model of I/R injury. Cheng YY *et al.* demonstrated that PCA effectively reduced infarct size and release of myocardial enzymes (e.g., CK, CK-MB and LDH) whereas, exhibited [14] better cardioprotective potential than caffeic acid phenethyl ester and propyl caffeate in cardiomyocyte H9c2 cells of male Sprague-Dawley rats. Yang L *et al*. significantly improved [15] left ventricular function, inhibited CK-MB release, reduced infarct size after resveratrol treatment in comparison with IR group ex vivo in rat hearts isolated for Langendorff perfusion test and H9c2 cells. Taskin E *et al*. found that TAS was not affected by inhibition of Ang-II production, TOS was significantly lower in the CAP and/or AL groups, whereas creatine kinase-MB was [16] not different among the groups than in the MI/R group. Wang S *et al*. showed [17] that autophagy was evidenced as increases in ratio of LC3 II/I and protein P62 and AMPK and mTOR expressions, significantly increased in diabetic compared with nondiabetic rats, concomitant with increased postischemic myocardial infarct size and CK-MB release after antioxidant N-acetylcysteine (NAC) treatment in myocardial IR. Sun X *et al*. demonstrated [19] that a novel long-term and slow-releasing

H_2S donor DATS-MSN; has superior cardioprotective effects over NaHS, associated with greater survival rates, reduced CK-MB and troponin I levels, decreased cardiomyocyte apoptosis index, increased antioxidant enzyme activities, inhibited myocardial inflammation and greater reduction in the infarct area in IR cardiomyocyte models. Wang X *et al*. found that metformin treatment significantly improved [18] left ventricular (LV) function, reduced infarct size and CK-MB release in comparison with IR group in rat cardiomyocytes (H9c2) on myocardial IR injury. Ramezani-Aliakbari F *et al*. improved [19] significantly LVDP, ±dp/dt, infarct size, LDH, CK-MB ($p<0.001$), blood glucose, the heart weight ($p<0.01$), body weight, RPP, hypertrophy index, antioxidant enzyme and cTnI levels ($p<0.05$) after GA administration in adult male Sprague-Dawley diabetic rats. Yu X *et al*. significantly suppressed [20] the increased expression of cytokines (TNF-α and IL-6), LDH, CK-MB and cTnI after propofol pretreatment in an I/R Langendorff model injury of heart RBL-2H3 cells. Li X *et al*. showed [21] that low-dose celastrol (20 and 50 nM) treatment significantly increased cell viability and decreased LDH and CK-MB activity in cardiomyocytes HR. Nozari Y *et al*. demonstrated [22] a significantly larger reduction in hs-TnT ($P = 0.02$) but the peak CK-MB level was [25] comparable between the two groups of patients receiving high-dose N-acetylcysteine. Zeng C *et al*. revealed [23] that oral pre-administration of high dose-tilianin reduced the release of LDH, MDA, and CK-MB, increased the plasma SOD level and significantly attenuated the infarct size in IR rats for 14 days. Sun X *et al*. demonstrated [24] superior cardioprotective effects of a novel long-term and slow-releasing H_2S system, namely DATS-MSN application; over the control and traditional H_2S donors, associated with greater allograft performance, including left ventricular developed pressure (LVDP) and dP/dt_{max}, reduced plasmic CK-MB and troponin I levels, inhibited myocardial inflammation, increased antioxidant enzyme activities, preserved mitochondria structure and function and decreased cardiomyocyte apoptosis index in heart IR. Zhang L *et al*. found [25] that alprostadil treatment significantly reduced myocardial infarct size, serum troponin T levels and CK-MB and LDH activity ($P<0.05$), malondialdehyde (MDA) content ($P<0.05$), myonecrosis, edema and infiltration of inflammatory cells in rats.

According to above, table 3 shows that U-74389G has 3.989339-fold [3.980903 - 3.997794] less restoring effect than Epo (p-value=0.0000) on CK-MBl whether all variables have been considered (p-value=0.0000); a trend attenuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 22 other seric variables, provides comparable results (table 4) [26].

Table 1: The (%) hyperkalemic influence of erythropoietin in connection with reperfusion time

Hyperkalemia	±SD	Reperfusion time	p-value
0.10%	±25.64%	1h	0.9904
5.27%	±22.97%	1.5h	0.3549
10.45%	±18.09%	2h	0.1509
-5.27%	±24.72%	reperfusion	0.3721
2.85%	±3.80%	interaction	0.4430

Table 2: The (%) hyperkalemic influence of U-74389G in connection with reperfusion time

Hyperkalemia	±SD	Reperfusion time	p-value
14.76%	±22.46%	1h	0.0663
20.49%	±19.64%	1.5h	0.0001
26.22%	±15.04%	2h	0.0003
-4.09%	±18.63%	reperfusion	0.4103
11.40%	±3.08%	interaction	0.0005

Table 3: The U-74389G / erythropoietin efficacies ratios on serum creatine phosphokinase levels after chi-square tests application

Odds ratio	[95% Conf. Interval]	p-values	Endpoint
141.313	| 141.1777 141.4484	0.0000	1h
3.883186	| 3.877018 3.889363	0.0000	1.5h
2.509108	| 2.506038 2.512182	0.0000	2h
1.2876033	| 1.2902731 1.2849389	0.0000	reperfusion
3.989339	| 3.980903 3.997794	0.0000	interaction

Table 4: A U-74389G / erythropoietin efficacies ratios meta-analysis on 22 hematologic variableς (18 variables with balancing efficacies and 4 variables with opposite efficacies) [26].

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
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
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
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
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
AST	1.149264	0.0391	0.9347365	0.0000	0.6695775	0.0000	0.7631082	0.0000	0.8224656	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
Mean	12.518321	0.0233	2.959056	0.0000	2.992954	0.0024	0.95914084	0.0119	3.4719838	0.0000

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
Mean corpuscular hemoglobin concentrations	-0.2774225	0.0000	-0.5504722	0.0000	-0.8522433	0.0000	+3.044774	0.0000	-0.7793243	0.0000
Platelet crit	-0.2312044	0.0000	-0.6719365	0.0000	-1.330756	0.0886	+5.620077	0.0000	-0.9771515	0.0000
ALT	+0.5955473	0.0000	-1.157335	0.0000	+7.967324	0.0000	+0.4734427	0.0000	-0.6208232	0.0000
γGT	1	1.0000	+0.5367033	0.0000	-0.9428571	0.8982	+2.146813	0.0000	-0.2683513	0.0000
Mean	-0.4757810	0.0250	-0.9450332	0.0000	-0.6052695	0.2467	+2.0421598	0.0000	-0.5968125	0.0000

5. Conclusion

The anti-oxidant agent U-74389G attenuated the recessing effects on CK-MBl by 3.989339-fold [3.980903 - 3.997794] than Epo whether all variables have been considered (p-value=0.0000); a trend attenuated also along the short term time frame of the experiment in rats. A biochemical investigation remains about how U-74389G mediates in these actions.

6. Acknowledgement

Acknowledged in preliminary studies

Ethical approval

"All applicable international, national, and/or institutional guidelines for the care and use of animals were followed."

7. References

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