THE EFFECT OF ERYTHROPOIETIN ON MAGNESIUM DURING ISCHEMIA REPERFUSION INJURY IN RATS

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ABSTRACT

The **aim** of this experiment study was the erythropoietin testing, on rat model and particularly on ischemia reperfusion protocol. The benefit or the non effect of that molecule was studied biochemically on blood magnesium.
Material and methods 40 rats were used of mean weight 247.7 g. Magnesum was measured on these time points: on 60 min after reperfusion (groups A and C), and on 120 min after reperfusion (groups B and D), A and B without but C and D with erythropoietin administration.
Results were that 1) erythropoietin administration decreased non significantly the magnesium by 0.035 mg/dl (-0.2453171 mg/dl - 0.1753171 mg/dl) (P = 0.7381), in accordance also with paired t-test (P = 0.7116), 2) reperfusion time increased non significantly the magnesium by 0.135 mg/dl (-0.0709124 mg/dl - 0.3409124 mg/dl) (P = 0.1924), in accordance also with paired t-test (P = 0.1665), and 3) interaction of erythropoietin administration and reperfusion time decreased non significantly the magnesium levels by 0.0063636 mg/dl (-0.1333617 mg/dl - 0.1206344 mg/dl) (P = 0.9197).
Conclusions are that erythropoietin administration, reperfusion time and their interaction have miscellaneous and not significant effects on magnesium within short-term context of 2 hours. Perhaps, a longer study time may reveal some significant effect.

Key words: erythropoietin, magnesium, reperfusion

INTRODUCTION

Tissue ischemia and reperfusion (IR) remain out of main causes of damage (permanent or transient) with serious implications on near organs and certainly on patients' health. The use of erythropoietin is a well established knowledge a lot of years ago. However, even if important progress has been made, satisfactory answers have not been given yet in fundamental questions, as, by what velocity this factor acts, when should it be administered, and in which dosage. The particularly satisfactory action of erythropoietin in stem blood cells recovery was noted by already performed experiments. It was realized that this certain factor has been tried in (IR) experiments, after international literature (PubMed – Medline) careful examination. However, just few relative reports were found, not covering completely this particular object of action velocity. Also, a lot of publications concerned trial of such particular other molecules of growth factors supprimers in which the studied molecule also belongs to. In the present study, erythropoietin will be tried to find out whether is able to influence serum magnesium (Mg). Aim of present experimental study was the

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trial of erythropoietin in rat animal model and certainly in (IR) protocol. The benefit or not of that particular molecule was studied measuring serum Mg.

MATERIAL AND METHODS

This experimental study was approved by Scientific committee of Ippokrateion General Hospital, Athens University, and by Veterinary Address of East Attiki Prefecture and institutional and national guide for the care and use of laboratory animals was followed. This experimental study was laid out by Exprerimental Research Center of ELPEN Pharmaceuticals Co. Inc. S.A. at Pikermi, Attiki, and all of settings including of consumables, equipment and substances used, were a courtesy of that S.A. Albino Wistar rats were used in accordance with accepted standards of humane animal care. They spent in laboratory 7 days before experimentation with easy access in water and food. They were randomly assigned into the following experimental groups (10 animals in each group). The experiment was acute, that is, the animal usage was completed by following experimentation times expiring as awakening and preservation did not exist.

1. Ischemia for 45 min and afterwards reperfusion for 60 min (group A).
2. Ischemia for 45 min and afterwards reperfusion for 120 min (group B).
3. Ischemia for 45 min and afterwards immediate erythropoietin intravenous (IV) administration and reperfusion for 60 min (group C).
4. Ischemia for 45 min and afterwards immediate erythropoietin IV administration and reperfusion for 120 min (group D).

The molecule erythropoietin dose was 10 mg/kg body weight of animals.

The experiment was beginning by prenarcosis and general anaesthesia administration in animals. Their electrocardiogram and acidometry were continuously monitored. The vessels concerning blood supply, were prepared so as their flow to be excluded by forceps. After exclusion, the protocol of IR was applied, described more in experimental groups. The molecules were administered at the time of reperfusion, through inferior vena cava (catheterization had been preceded at experiment beginning, after general anaesthesia establishment).

The Mg levels measurement was performed on these time points:

1. on 60 min of reperfusion (groups A and C);
2. on 120 min of reperfusion (groups B and D).

PROTOCOL

Mg is being considered a reliable index substance of metabolism being of great clinical significance. Also, rats weight could be potentially a confusing factor, e.g. fatter rats to have greater blood Mg levels. This suspicion will be investigated. Rats were introduced into general anaesthesia by initial intramuscular (IM) administration of 0.5 cc compound, constituted by 0.25 cc xylazine, (25 cc, 20 mg/cc) and 0.25 cc ketamine hydrochloride (1,000, 100 mg/cc, 10 cc). 0.03 cc butorphanol (10 mg/cc, 10 cc) anaesthesia was administered s.c. before laparotomy. Continuous oxygen supply was administered during whole experiment performance. Ischemia was caused by clapping inferior aorta for 45 min after laparotomic access. Reperfusion was achieved by removing clapping and inferior aorta patency re-establishment.

40 female albino Wistar rats of mean weight 247.7 g (Std. Dev: 34.99172 g) were used, min weight ≥ 165 g and max weight < 320 g.

Control groups

20 control rats mean weight 252.5 g (Std. Dev: 39.31988 g) suffered by ischemia for 45 min and then reperfusion.

Group A

Reperfusion which lasted 60 min concerned 10 controls rats of mean weight 243 g (Std. Dev: 45.77724 g), mean Mg 2.98 mg/dl (Std. Dev: 0.1988858 mg/dl) (Table 1).

Group B

Reperfusion which lasted 120 min concerned 10 controls rats of mean weight 262 g (Std. Dev: 31.10913 g), mean Mg 3.18 mg/dl (Std. Dev: 0.2699795 mg/dl) (Table 1).

Erythropoietin group

20 rats of mean weight 242.9 g (Std. Dev: 30.3105 g) suffered by ischemia for 45 min and then reperfusion in the beginning of which 10 mg erythropoietin/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 Mg 3.01 mg/dl (Std. Dev: 0.5108816 mg/dl) (Table 1).

Group D

Reperfusion which lasted 120 min concerned 10 Epo rats of mean weight 243 g (Std. Dev: 32.84644 g), mean Mg 3.08 mg/dl (Std. Dev: 0.2394438 mg/dl) (Table 1).

TABLE 1. *Weight and magnesium (Mgl) mean levels and Std. Dev. of groups*

Groups	Variable	Mean	Std. Dev
A	Weight	243 g	45.77724 g
	Mg	2.98 mg/dl	0.1988858 mg/dl
B	Weight	262 g	31.10913 g
	Mg	3.18 mg/dl	0.2699795 mg/dl
C	Weight	242.8 g	29.33636 g
	Mg	3.01 mg/dl	0.5108816 mg/dl
D	Weight	243 g	gr 32.84644 g
	Mg	3.08 mg/dl	0.2394438 mg/dl

Weight comparison of each one from 4 rats groups initially was performed with other one from 3 remained groups applying statistical paired t-test. (Table 2). Any emerging significant difference among Mg levels, will be investigated whether owed in the above mentioned significant weight correlations. Mg comparison of each one from 4 rats groups initially was performed with other one from 3 remainder groups applying statistical paired t-test. (Table 2).

TABLE 2. *Statistical significance of mean values difference for groups (DG) after statistical paired t test application*

DG	Variable	Difference	p-value
A-B	Weight	-19 g	0.2423
	Mg	-0.2 mg/dl	0.1012
A-C	Weight	0.2 g	0.9900
	Mg	-0.03 mg/dl	0.8547
A-D	Weight	0 g	1.0000
	Mg	-0.1 mg/dl	0.1278
B-C	Weight	19.2 g	0.2598
	Mg	0.17 mg/dl	0.3399
B-D	Weight	19 g	0.1011
	Mg	0.1 mg/dl	0.3534
C-D	Weight	-0.2 g	0.9883
	Mg	-0.07 mg/dl	0.6636

Applying generalised linear models (glm) with dependant variable the Mg levels and independent variables the erythropoietin administration or no, the reperfusion time and their interaction, results in: 1) erythropoietin administration decreased non significantly the magnesium by 0.035 mg/dl (-0.2453171 mg/dl - 0.1753171 mg/dl) (P = 0.7381), in accordance also with paired t-test (P = 0.7116), 2) reperfusion time increased non significantly the magnesium by 0.135 mg/dl (-0.0709124 mg/dl - 0.3409124 mg/dl) (P= 0.1924), in accordance also with paired t-test (P= 0.1665), and 3) interaction of erythropoietin administration and reperfusion time decreased non significantly the magnesium levels by 0.0063636 mg/dl (-0.1333617 mg/dl - 0.1206344 mg/dl) (P= 0.9197).

Reviewing the above and Table 2, the Table 3 sums up concerning the alteration influence of erythropoietin in connection with reperfusion time. Inserting the rats weight as independent variable at glm, a non significant relation turns on Mg levels (p = 0.5484), so as to further investigation does not need.

TABLE 3. *The alteration influence of erythropoietin in connection with reperfusion time.*

Alteration	95% c. in.	Reperfusion time	p-values	
			t-test	glm
-0.03 mg/dl	-0.3342272 mg/dl - 0.3942272 mg/dl	1h	0.8547	0.8645
0.035 mg/dl	-0.2453171 mg/dl - 0.1753171 mg/dl	1.5h	0.7116	0.7381
0.1 mg/dl	-0.3397467 mg/dl - 0.1397466 mg/dl	2h	0.3534	0.3924

DISCUSSION

Unpleasantly, there are not described situations concerning whether ischemia can influence the Mg levels in bibliography. On the contrary, there are a lot of cases reporting how the Mg levels fluctuations affect the function of various organs. Such examples are described herein. Since isolated Mg administration is impossible, it is meant that, if Mg was not associated by another drug or a factor influencing the Mg levels was not administered, the administration of Mg was by means of a salt. Siegler JE et al found (1) ischemic stroke patients whose serum Mg(2+) decreased at baseline during the first 24 hours of admission being also not at greater odds of neurologic deterioration (ND), death, discharge disposition or poor short-term functional outcome measures compared with patients with unchanging or increasing Mg(2+) levels. Lee K.C. et al seemed (2) safe the combination of St Thomas cardioplegic arrest and low-pressure perfusion with HTK solution with average short-term ischemia time $\simeq$ 225 minutes survival similar to other approaches during donor heart preservation. Van den Bergh WM et al tried (3) to prevent or reverse delayed cerebral ischemia (DCI) after aneurysmal subarachnoid haemorrhage (SAH) by magnesium – a neuroprotective agent at a continuous intravenous dosage of 64 mmol/L per day, which maintained serum magnesium levels within the range of 1.0-2.0 mmol/L for 14 days. Whitelaw A et al treated (4) hypoxic-ischemic labor – delivery - encephalopathy infants with magnesium sulphate. Ichiba H et al found (5) survival with normal results by 14 days of age, significantly more frequent in treated group with postnatal $MgSO_4$ infusion in infants

with severe birth asphyxia with 5-min Apgar score ≤ 7, than in control group (P = 0.04). Khan IA et al treated (6) the acquired form of long QT syndrome due to causes as stroke, myocardial ischemia and organophosphorus compounds by intravenous magnesium. Hoenicke EM et al found (7) that pinacidil mixed in Krebs-Henseleit solution was equivalent to St. Thomas' solution but inferior to University of Wisconsin solution in rabbit hearts protection. Yano Y et al blocked (8) calcium damage by terminal magnesium cardioplegia in rat hearts after initial ischemic one and reperfusion recovering 79% of control aortic flow. Krause S et al depressed (9) significantly the canine magnesium-dependent ATPase activity by both global ischemia and pH 7.1 acidosis.

Also the majority of the following examples concern the influence of Mg levels fluctuation on Epo and a minority only the influence of Epo fluctuation on the Mg levels. Zhao J. et al investigated (10) magnesium sulphate and erythropoietin as neuroprotective agent for the affected infants regarding to the mechanisms of intrauterine brain injury. Bilotta F. et al tested (11) therapies with magnesium sulphate, and erythropoietin.

The use of magnesium sulphate was associated with a lower incidence of new postoperative neurological deficit and cognitive decline. Siasios I. et al managed (12) patients with aneurysmal subarachnoid hemorrhage aSAH by administration of magnesium sulfate and erythropoietin. Buonocore G. et al investigated (13) promising neuroprotectants erythropoietin and magnesium alone or as additional adjunctive therapy, for reducing brain injury and its long-term sequelae in infants. Zoerle T. et al found (14) erythropoietin effective whereas magnesium not in vasospasm reduction > 3 days after subarachnoid hemorrhage. Barry C. et al found (15) erythropoietin and magnesium particularly promising in delayed vasospasm which may contribute to cerebral ischemia following subarachnoid hemorrhage SAH. Beijers A.J. et al investigated (16) magnesium infusion and erythropoietin as most promising to decrease the neurotoxicity. Musso C.G. et al distinguished (17) normal aging from chronic kidney disease decreased GFRs by erythropoietin synthesis and normal magnesium tubular handling. Kwon B.K. et al pointed out gaps in our knowledge (18) of erythropoietin and magnesium as neuroprotective therapies for acute spinal cord injury. Rowe W.J. et al suggested (19) correction of erythropoietin (EPO) gene deficiencies and subcutaneous magnesium (Mg) replacements related to perfusion for Long space missions. Zhang Z et al achieved (20) a convenient and sensitive determination of recombinant human erythropoietin (rHuEPO-α) in physiological buffer by systematic optimization of parameters and the existence of Mg(2+) cation. Kidd P.M. considered (21) magnesium and the growth factors erythropoietin (EPO) as promising acute neuroprotectant measures. Schouten JW evaluated (22) erythropoietin as promising but did not show neuroprotective efficacy for magnesium. Perlman J.M. included (23) erythropoietin as potential neuroprotection in an evolving process of brain injury after intrapartum hypoxia-ischemia that initiates in utero. Fu ES et al included (24) erythropoietin and magnesium in the initial treatment of brain and spinal cord trauma. Wu C.T. et al needed (25) further clinical trials for magnesium sulfate and erythropoietin for cerebral vasospasm and its ischemic complications. Bayoumeu F. et al addressed (26) erythropoietin and magnesium sulfate for bleeding risks in severe preeclampsia and postpartum hemorrhage prevention. Frietsch T. et al promised (27) neuroprotective strategies (magnesium, erythropoietin) to be further pharmacologically based. Ovbiagele B. et al considered (28) cautious off-label use of magnesium sulfate and erythropoietin in acute stroke. Janjua N. et al evaluated (29) the efficacy of magnesium sulfate and erythropoietin in neurointensive care management of vasospasm after subarachnoid hemorrhage. Pietrzak I. et al found (30) the mean erythrocytes Mg levels significantly lower in HD patients treated by rhEPO than non rhEPO treated control ones observing the inverse relationship between Hb and Mg concentration in erythrocytes in HD rhEPO treated (P < 0.05) and improving the Mg disturbed metabolism in uraemia. Brun J.F. found (31) that the divalent cations magnesium improve red cell deformability and erythropoietin likely influences the regulation of blood rheology. Votrin I.I. et al inhibited (32) the activities of magnesium-dependent endonuclease by erythropoietin in nuclei of rat liver and of colon cancer patients lymphocytes. Moritz K.M. et al found (33) fetal plasma not increased erythropoietin concentrations but approximately twice increased magnesium concentrations in nephrectomized significantly hypoxic ovine fetuses at 100 days of gestation during the second week than intact control fetuses. Hüttner C. et al rose (34) erythropoietin levels by 88.7% after tocolytic therapy for 48 h in pregnant women. The hypervolemia evidenced by the decreased hematocrit was due to the increased oral fluid intake and retention. Vaziri N.D. et al determined (35) platelet cytosolic magnesium concentration in randomized CRF rats after partial nephrectomy and reduced EPO.

Tison A. et al described (36) a successful pregnancy of a 35-year old woman who conceived six months after initiating continuous ambulatory peritoneal dialysis (CAPD) administering and reaching magnesium and erythropoietin required preset objectives. Wintour E.M. et al noted (37) change in plasma chloride values ($P < 0.05$) but not in magnesium concentrations increasing blood loss from sheep by 30% every day until day 3. Wood P.A. et al indicated (38) minimal erythroid precursor cell damage and cisplatin-associated anemia resulted from renal tubular damage, which can be prevented by hormone (EPO) treatment. Lai Y.H. et al did not find (39) the serum ionized magnesium levels changed significantly after 12 weeks rHuEPO treatment of HD patients. Mizuno A. et al increased (40) the bioavailability and absorption of the rectal suppository with (5000 units) rHuEPO by 5% sodium salicylate or caprate at 1.2% of an intravenous injection in rats inserted once a day for 6 consecutive days.

CONCLUSION

Erythropoietin administration, reperfusion time and their interaction have miscellaneous and not significant short-term effects on Mg within narrow context of 2 hours. Perhaps, a longer study time than 2 hours may provide clearer and significant effects.

Acknowledgment

Gratefulness to Exprerimental Research Center of ELPEN Pharmaceuticals Co. Inc. S.A. for kind material support.

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