Role of serum erythropoietin level in patients with absolute erythrocytosis

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(Received 17/4/2013, Accepted 23/4/2013)

الخلاصة

ارتفاع الكريات الحمر الحقيقي هواضطراب التكاثر في نقيي العظم بسبب طفرة جينية مكتسبة في الخلايا الجذعية. ان مستوى الارثروبويتين يعطي مؤشرا عن نوع المرض وعن الفحوصات المختبرية اللازمة لتاكيد سبب المرض. تهدف الدراسة لبيان اهمية مستوى الارثروبويتين في تشخيص ارتفاع الكريات الحمر الحقيقي بالاضافة الى معرفة الفرق في مستوى الارثروبويتين قبل وبعد العلاج .تم تقييم (47) مريضا مصابا بارتفاع الكريات الحمر الحقيقي، تضمنت الدراسة (31) ذكرا و (16) انثى تراوحت اعمارهم بين (20-77) سنة. المستوى المعتمد لكريات الحمر المظغوطة هو اكثر او يساوي 52% او نسبة الهيموغلوبين اكثر من 18.5 غم\دل للذكور واكثر او يساوي 48% و اكثر من 16.5 غم\دل. تم اجراء الفحوصات التالية لكل المرضى :فحص الدم الكامل بواسطة الجهاز الاتوماتيكي ،فلم الدم وقياس مستوى الارثروبويتين في الدم .تم فحص نخاع العظم لبعض الحالات التي تستدعي ذلك . اظهرت الدراسة ان متوسط الارثروبويتين 9.82. ليكن هناك ارتباط ذات دلالة إحصائية بين متوسط الارثروبويتين ومتوسط العلامات العامة والسريرية. تبين وجود علاقة احصائية مهمة بالنسبة لمستوى الكريات الحمر المظغوطة ومستوى الارثروبويتين قبل وبعد العلاج. ان مستوى الارثروبويتين المحدد للتشخيص هو (4.9) مع حساسية (71.4%)،والنوعية (86.7%) و ($p <0.001$). نستنتج من الدراسة :ان نسبة الارثروبويتين في الدم تعتبر عاملا مهما وفحصا بسيطا لتحديد العامل المسبب لارتفاع نسبة الكريات الحمر المظغوطة وان هناك اختلاف احصائي واضح بين الحالات المعالجة وغير المعالجة بالنسبة لمعدل الكريات الحمر المظغوطة والارثروبويتين .

Abstract

PRV is a myeloproliferative disorder with an acquired genetic mutation involving the stem cell. Erythropoietin (Epo) is a hemopoietic growth factor which provides some guidance to the diagnosis of PRV.

The study was done to evaluate the diagnostic significance of erythropoietin level in PRV and its role in pre and post treated PRVpatients.The study includes (47) patients diagnosed as PRV including (31) males and (16) females with age range (20-77 years). The criteria for diagnosis of polycythemia is PCV > 52% and/ or Hb ≥18.5 gm/dl for male and PCV >48%and/ or Hb ≥16.5 gm/dl for female.The investigations which were done for all new patients including CBC, blood films and serum Epo, in addition to the BM examination for new indicated cases of PRV. Follow up of old PRV (31) patients were done by PCV and serum Epo. We found thatthe mean Epo was 9.82mIU/ml. There was no statistical significant correlation between Epo mean and mean of other parameters.There was a statistical significance between pre and post treated cases regarding mean PCV and Epo. The acceptible EPO cutoff level to define PRV of (4.9) with sensitivity (71.4), specificity (86.7) and($p<0.001$). So, we conclude that the serum Epo level was a simple reliable test for diagnosis of PRV with a cutoff value of (4.9) andthere was a significant difference between treated and untreated cases of PRV regarding PCV and Epo.

Keyword: polycythemia rubravera, Erythropoietin.

Introduction

The aetiology of an increased Hb concentration and haematocrit is a problem frequently encountered in clinical medicine[1].The increase in the concentration of erythrocytes, whether measured as number of cells, haemoglobin , or packed cell volume(hematocrit) called erythrocytosis[2].

The causes of erythroctosis may either be due to true increase in the red cell mass (RCM) or an apparent increase due to decreased plasma volume. Thus, the causes of erythrocytosis can largely be divided into relative or absolute erythrocytosis[3].

True polycythaemia (Absolute erythrocytosis, AE) refers to an absolute increase in total body red cell volume (or mass), which usually manifests itself as a raised haemoglobin concentration (Hb) and/or packed cell volume (PCV) [4].

Causes of an absolute erythrocytosis can be primary where there is an intrinsic problem in the bone marrow, polycythemia rubravera (PRV), and secondary where there an event outside the bone marrow driving erythropoiesis [5].

Erythropoietin (Epo) is a hemopoietic growth factor that is essential in terminal maturation of erythrocyte precursor to mature erythrocytes. The Epo level provides some guidance as to the direction in which to proceed and the order and the extent of investigation necessary in an individual patient. Identifying the cause of erythrocytosis is vital as this affect both patient management and prognosis[6].

PRV is a myeloproliferative disorder involving the stem cell characterized by hyperplasia of all three major myeloid cell lineages [7]. The increased RCM is independent of Epoand usually due to an acquired genetic mutation [8].

The rate of red cell production is increased in true polycythemias which lead to increased viscosity and vascular space which are responsible for many of the signs and symptoms of polycythemia [9].

A majority of patients will be symptom free or have nonspecific symptoms, including fatigue and headache.Patient with PRV present with signs and symptoms of myeloproliferative disorders like splenomegaly,weight loss, gout, etc,in addition to other thrombotic and haemorrhagic complications[10].

Aims of the study: To evaluate the diagnostic significance of erythropoietin level in polycythemiarubravera and its role in pre and post treated polycythemia rubravera patients.

Material and methods

This study was carried out in haematology center in Al-yarmouk hospital from September (9) 2012 to Fabruary (2) 2013,including 47 patients presented with polycythemia ,31 patients of them are previously diagnosed as PRV, and 40 control patients from the medical staff and patient relatives .The patients were randomly selected regarding age and sex . The patients include 31 males and 16 females, with their ages range from 20 -77years.

A detailed history including smoking , respiratory , renal and cardiac problem , in addition to family history or other haematological disease were done .A physical examination also were done and the relevant information were noted including the clinical history and the physical examination are { headache, vertigo, blurred vision, joint pain, fatigue, plethora, hypertention ,splenomegaly, hepatomegaly and renal problem }.

The criteria for diagnosis of polycythemia is PCV > 52% and/ or Hb ≥18.5 gm/dl for male and PCV >48%and/ or Hb ≥16.5 gm/dl for female. A PCV level of ≤ 45% was considered as a response level.

The investigations which were done for all new patients including CBC, blood films and serum Epo, in addition to the BM examination for new indicated cases of PRV (16 cases). Follow up of old PRV (31) patients were done by PCV and serum Epo.

Materials

-Blood: 5 cc of blood was taken by clean venosection, 2cc in an EDTA tube for CBC and blood film and the other 3cc in plane tube for serum Epo measure.

-BM aspirates: were done for indicated cases in special hematological center under supervision of hematologist and proper diagnosis were made, in addition to reevaluation of BM of the previously diagnosed cases of PRV.

Results

Out of (47) patients diagnosed as PRV (31) were males accounting 65.96% and (16) were females accounting 34.04% .The male to female ratio was 1.93 : 1.

Clinically, (20) patients were smoker and plethoric and constitute (42.55%), (10) patients complaining of hypertention (21.27%), (13) case with a history of itching(27.65%), (4) patients had a hepatomegaly (4.87%) and (32) patients have splenomegally (68.08%).

The mean of the general andhaematological parameter were as table(1).

Table1: The means of the general and haematological parameters in PRV.

Parameter	Age years	PCV %	Hb g/dl	RBC $\times10^6$/l	WBC $\times10^9$/l	Platelets $\times10^9$/l	MCV Fl	Epo mIU/ml
Means	50.19	57.17	19.67	5.75	10.34	441.60	83.19	9.82

There is no significant correlation between Epo level and all hematological parameters and also no correlation with age and SM in PRV.

(19)patients of PV that constitute(40.43%) have a positive blood film of CMPDs (leukocytosis, left shifting, basophilia, eosinophilia, thrombocytosis, tear drops and hypochromia).There was a prominent difference in the mean of Epo of patients with positive blood film findings(13.69) and the mean Epo of the negative one(7.82) but this difference is not significant(p=0.277).

The mean Epo of PRV patients with positive BM picture [increased cellularity, panmyelosis ,and enlarged megakaryocytes, (7.3)] is less than the mean Epo in negative picture of PRV(14.5) ,statistically this difference is not significant (p = 0.309) .

There was (24) patients with low Epo level (51.07%) of the whole PV, (17) patients with normal Epo (36.17%) and (6) patients with unreasonable high Epo value (12.7%). The (31) treated cases of PRV were investigated for PCV and Epo to assess the response to treatment and confirm the diagnosis of PRV. There was increase number of normal reading and a little change of the low Epo level, see table 2.

Table 2: Patients number and percentage of Epo and change of EPO level after treatment in treated PRV patients.

	Epo(47)	OldEPO(31)	NewEpo(31)
Normal	17 (36.17%)	5	13
Low	24 (51.07%)	20	18
High	6 (12.76%)	6	0
Total	47 (100%)	31	31

The mean Epo of the treated cases (7.14) is different from the mean Epo before treatment (10.10) and this difference is statistically significant (p< 0.001) see table 3.

Table 3 :Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	EPO	10.1097	31	13.62914	2.44787
	New EPO	7.1484	31	8.92591	1.60314

P <0.001

The mean PCV of the treated PRV (46.322) is clearly different from the mean PCV before treatment (57.774) and this difference statistically highly significant (p < 0.001).

EPO level is clearly low in patients with PRV, but which level could be considered as a critical level below which we can label a patient as having a PRV? , For this purpose we conducted an ROC (receiver operator characteristic curve analysis). The cutoff value obtained is (10.15) with a sensitivity of (76.6%), a specificity of (78.9%) and a significant p value of <0.001. But there was a problem of extreme values in such a way that some of the cases that were diagnosed as having PRV had a very high EPO levels compared to others, so to overcome such a statistical problem we excluded those extreme values and conducted another ROC curve that gave us a lower and more acceptable EPO cutoff level to define PRV of (4.9) with sensitivity (71.4) and specificity (86.7) and(p<0.001).

So after exclusion of extreme high values and determining of a new cutoff value (4.9) with high statistical significance, there was increased percentage of PRV with low Epo that consisting the clinical and hematological diagnosis [30 (63.82%)] patients of 47 of PV have Epo value below 4.9 mIU/ml.

Discussion

A significant adverse statistical correlation was found between PCV and Epo level in PV which is explained by clonal expansion of RBC counts with subsequent suppression of EPo level and this is consisting with [Mossus et al 2004][11].

A significant Statistical correlation was found between pre and post treated patients that EPo and PCV levels are well corrected by treatment.Themean Epo of the previously diagnosed PV patients was lower than those patients after treatment with statistical significance that related with the diagnosis of clonal nature of disease and subsequent suppression of RBC count expansion after treatment and control of EPo from negative feedback. These findings are consisting with Mossus et al 2004and Pascal 2005[12], despite of his lower findings.

There was a significant difference in mean PCV before and after treatment in PV patients, that PCV level decrease with continuous treatment to significant level related to EPo correction and this is consisting with study of Mossuset al2004.

EPo regarded as an important diagnostic marker in PV and possibly differentiated tools in polycythemia or erythrocytosis, however cutoff point is important to design for such purpose so we try to determine the cutoff Epo value below which we can label patients to have PV. The cutoff value was (10.15) with moderate specificity and sensitivity but of high significance ($p<0.001$). This value was unreasonably high in compared with other studies (Angel 1997[13], cutoff value =5) and this difference is obviously due to extremely high Epo levels in few cases of our data, So we did another value after exclusion of the high reading and we got a new cutoff value (4.9) with high specificity and moderate sensitivity and highly significant ($p<0.001$).

Conclusions

-The serum erythropoietin level was a simple reliable test for diagnosis of PRV.
-There was a significant difference between treated and untreated cases of PRV regarding packed cell volume and serum erythropoietin.

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