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Bleeding time in r-HuEPO-treated patients on hemodialysis

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TIEMPO DE HEMORRAGIA EN LOS PACIENTES EN HEMODIALISIS TRATADOS CON EPO

RESUMEN

Es frecuente que los pacientes con insuficiencia renal crónica presenten cierta tendencia a la hemorragia. Hemos podido demostrar en un grupo de 29 pacientes que el tratamiento con EPO produce un aumento de la concentración de hemoglobina con una reducción concomitante del tiempo de hemorragia, aproximándose ambos parámetros a los de los pacientes en hemodiálisis que no precisan EPO. En recuento absoluto de plaquetas no parece estar involucrado en este fenómeno, puesto que no se observarán diferencias entre los recuentos de plaquetas realizados antes de iniciarse el tratamiento, durante el tratamiento y en el grupo de pacientes no tratados. Sin embargo, el tiempo de hemorragia es una prueba global de alta sensibilidad en la detección de alteraciones de la coagulación, se correlaciona bien con la concentración de hemoglobina en los pacientes tratados con EPO. Por lo tanto, concluimos que con la corrección de la anemia se produce también una corrección del tiempo de hemorragia. Ello, sin embargo, aumenta el peligro de trombosis de la fístula. Así, recomendamos que en los casos de pacientes con fístulas con riesgo de trombosis la concentración de hemoglobina no sobrepase los 9-10 g/l, y además, el tiempo de hemorragia debe valorarse y mantenerse por encima de los diez minutos mediante la adición de aspirina (500 mg/día) al tratamiento con EPO.

Palabras clave: ***Tiempo de hemorragia. Uremia. Hemoglobina. Recuento de plaquetas.***

SUMMARY

In patients with chronic renal failure there is usually a bleeding tendency. In a group of 29 patients we could demonstrate that with r-HuEPO-treatment the hemoglobin concentration rises, while there is a concurrent reduction in bleeding time approaching bleeding time and hemoglobin concentrations of patients not in need of r-HuEPO but also on hemodialysis. The absolute platelet count seems not to be involved in this phenomenon as there was no difference at all with respect to platelet counts before start of treatment, during treatment and in the group without r-HuEPO-treatment. Bleeding time, however, which is a highly sensitive global test

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of coagulation, is fairly well correlated with hemoglobin concentration in those patients treated with r-HuEPO. Thus, we conclude that with the correction of anemia also a correction of bleeding time occurs. This, however, also increases the danger of fistula clotting. We therefore recommend that in patients with endangered shunts the hemoglobin concentration should not be rised above a level of 9-10 g/l, and furthermore the bleeding time should be evaluated and kept at a level higher than 10 minutes by adding aspirin (500 mg/die) to r-HuEPO-treatment.

Key words: ***Bleeding Time. Uremia. Hemoglobin. Platelet count.***

Introduction

A prolonged bleeding time is a common finding in patients on hemodialysis. Quite a number of factors have been discussed to result in this phenomenon: abnormal interactions between platelets and vessels, defective formation of primary hemostatic plaques at the side of insured vessels (platelet malfunction, abnormal platelet count and so on) [1, 9].

The bleeding time is the most sensitive laboratory index of primary hemostatic function which tests global coagulation. It is well known that the red blood cell count is correlated with bleeding time and thus with coagulation [3, 7, 13]. This fact has been found in normal human beings and has also been demonstrated in uremics [4]. Livio et al. observed that when transfusing washed red cell concentrates in uremics with prolonged bleeding times, a considerable improvement in anemia correlated with the shortening of bleeding time and the bleeding symptoms occurred [8]. The treatment of renal anemia with recombinant human erythropoietin (r-HuEPO) results also in a considerable improvement of anemia [9]. In addition, it could be demonstrated that under this regimen also a slight rise in the platelet count occurs. Thus, the previously demonstrated improvement in the hemostatic defect of uremia after treatment with r-HuEPO [6, 9] could be both due to an increase in platelet and erythrocyte count.

The aim of this paper was to analyse whether the phenomenon of an improved bleeding time is mainly due to changes in the platelet count or to the higher erythrocyte count. For that purpose, we analysed in a long-term study the changes in bleeding time in stable hemodialysis patients treated with r-HuEPO. The data of these patients were compared with the data of hemodialysis patients not in need of r-HuEPO due to a sufficiently high hemoglobin concentration.

Patients and methods

21 patients with chronic uremia were treated with r-HuEPO for severe anemia (table I). The initial r-HuEPO dosage was 80 IU/kg per kg of body weight followed by an average maintenance dosage of 45 IU/kg of body weight. No bleeding problems beside a prolonged bleeding time could be detected in these patients. Patients were on regular hemodialysis three times a week and in a stable clinical and biochemical state. The r-HuEPO-treated patients had severe but stable anemia. This group of patients received r-HuEPO supplied either by Behringwerke (Marburg, FRG), Boehringer Mannheim (Mannheim, FRG) or by Cilag (Alsbach-Hähnlein, FRG). The target hemoglobin concentration was 9-10 g/l. The following parameters were analysed: platelet count, hemoglobin concentration, and routine clinical chemistry.

The skin bleeding time was performed under standardised conditions. A blood pressure cuff was fixed at the upper arm. This cuff was inflated up to 40 mmHg. Then, a standardised incision was made by using a snapper (Surgicutt, International Technidyne Corporation, Edison, New Jersey). Thereafter, blood was removed from the incision by filter paper in half minute intervals. Coagulation was assumed to have occurred when no further removal of blood could be achieved. In our laboratory, the normal range for this method is a bleeding time of 3-6 minutes.

For comparison, these data were compared with those of 23 hemodialysis patients not treated with r-HuEPO (table I). No significant differences between the two groups could be detected with respect to routine clinical chemistry.

Data are presented as mean ± SD. Linear regression analysis and t-tests were performed by using the SAS system [11, 12]. Graphs were prepared by using SAS Graph [10].

Results

In the r-HuEPO-treated group a consistent increase in hemoglobin concentration occurred. All patients reached their target hemoglobin value. Initially, there was an overshoot in the hemoglobin concentration (fig. 1). Furthermore, it is obvious that over time a slight rise in hemoglobin concentration occurred up to the 24th month.

After a total treatment time of 378 patient months

Table I. Patient characteristics (f: female; m: male; CGN: chronic glomerulonephritis; DM: diabetic nephropathy; HPTH: primary hyperparathyroidism; IN: interstitial nephritis; LE: lupus nephritis; NX: bilateral nephrectomy; PKD: polycystic kidney disease; UN: renal disease of unknown origin)

a) **r-HuEPO-treated patients**

Sex	Dialysis duration (years)	Age (years)	Cause of renal failure	Time on r-HuEPO (months)
m	3	66	IN	15
f	5	33	LE	24
f	4	81	DM	18
f	13	29	UN	24
f	3	49	NX	24
f	2	59	PKD	21
m	8	38	CGN	24
f	17	50	LE	16
f	4	67	HPTH	22
f	15	55	UN	24
f	1	33	UN	12
f	5	60	PKD	16
m	11	39	CGN	22
m	3	61	DM	12
m	5	46	CGN	22
f	9	59	IN	22
f	6	53	CGN	24
f	4	54	UN	9
f	5	62	UN	24
m	7	70	IN	2
f	1	67	IN	1

b) **Without r-HuEPO-treatment**

Sex	Dialysis duration (years)	Age (years)	Cause of renal failure
m	1	51	DM
f	5	61	UN
f	9	56	PKD
m	1	66	DM
m	1	47	CGN
f	4	60	UN
m	1	74	DM
f	4	58	UN
f	1	50	DM
m	4	50	DM
f	13	59	PKD
m	2	65	UN
m	2	51	UN
m	1	70	IN
m	17	51	IN
f	10	73	CGN
m	5	67	GN
m	4	55	CGN
m	1	45	DM
f	1	78	IN
f	1	31	LE
m	2	81	CGN
m	2	60	IN

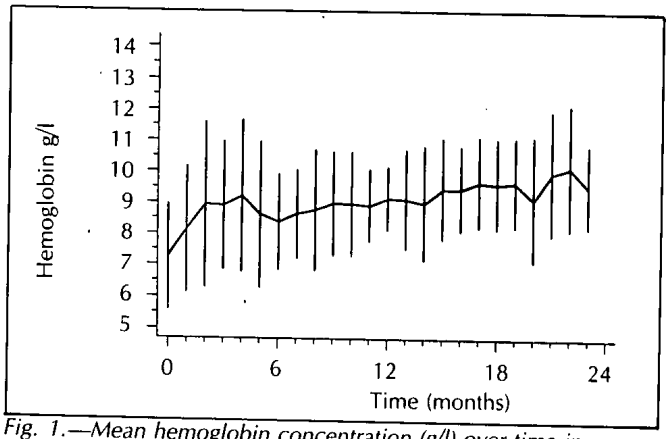

Fig. 1.—Mean hemoglobin concentration (g/l) over time in r-HuEPO-treated patients.

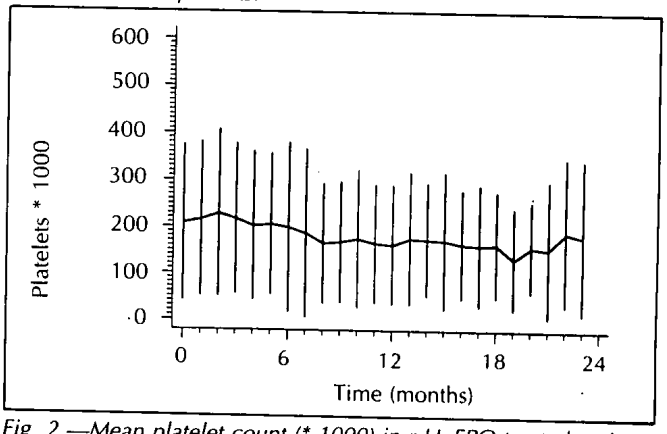

Fig. 2.—Mean platelet count (1000) in r-HuEPO-treated patients over time.*

only two shunt occlusions had occurred in patients already having serious stenosis of their fistula before starting r-HuEPO-treatment.

Platelet concentration, however, did not rise initially but seems to decrease slowly over time (fig. 2).

Initially, bleeding time was considerably prolonged in all patients treated with r-HuEPO (fig. 3c). Bleeding time decreased and even reached normal values in some of our patients. Only the initial and the last observed values are given as some of our patients were transplanted after receiving r-HuEPO. Furthermore, initially we treated most of our patients with aspirin in order to prevent fistula clotting when hemoglobin rises. It is, however, of note that already small amounts of aspirin (e.g. 500 mg per week) prolonged the bleeding time considerably.

In figure 3, the mean values for hemoglobin concentration, platelet count and bleeding time in the two groups of patients, one receiving r-HuEPO, the other not, are given. It is obvious that hemoglobin concentration was significantly lower in the r-HuEPO group before start of treatment than in the group not receiving r-HuEPO ($p = 0.0005$), but increased significantly (comparison: before vs. during r-HuEPO treatment; $p = 0.0234$). A difference in platelet count,

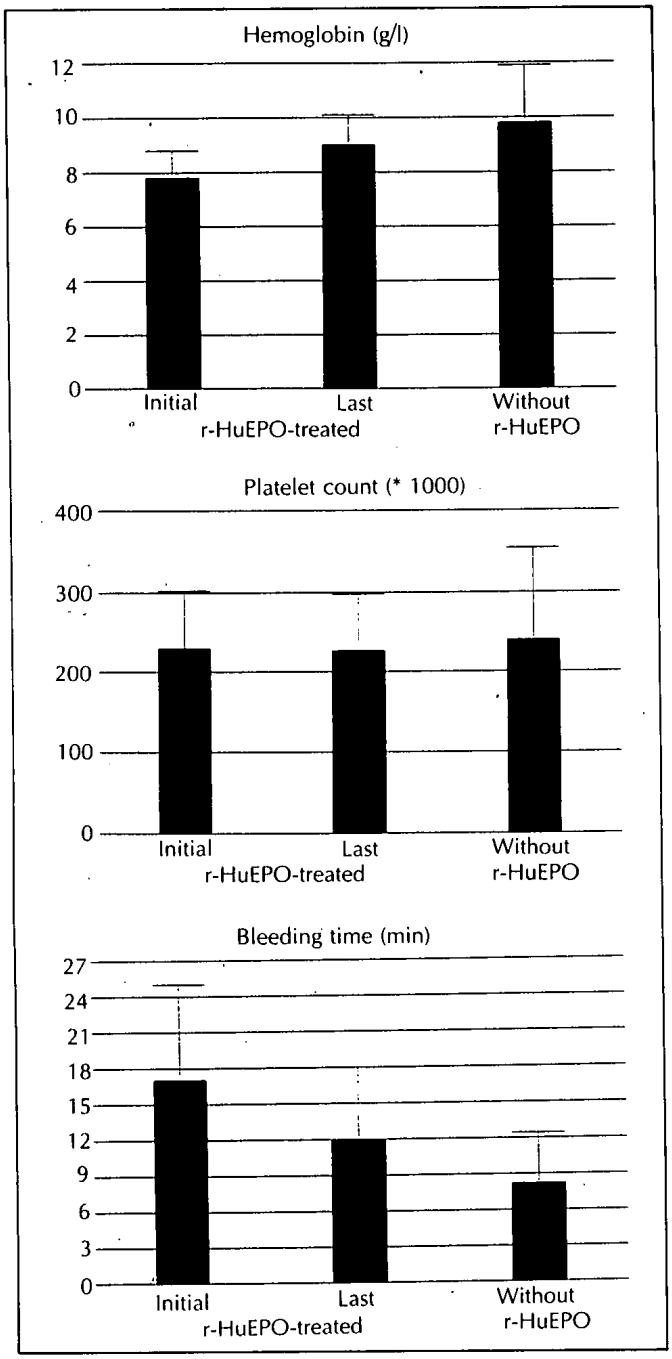

Fig. 3.—Mean values for (a) hemoglobin concentration (g/l), (b) platelet count (1000) and (c) bleeding time (min) for r-HuEPO-treated patients (before start of treatment and at last observation) and in hemodialysis patients without r-HuEPO-treatment.*

however, did not occur ($p = 0.7633$; resp. $p = 0.9281$). As with the hemoglobin concentration, there was also a significant difference in bleeding time between the two groups of patients ($p = 0.0136$). After r-HuEPO treatment, however, the difference between the two groups of patients persisted ($p = 0.0231$) despite the fact that bleeding time improved considerably in the r-HuEPO-treated group.

In the initial period of r-HuEPO-treatment and in the group of patients without such a therapy no relationship between hemoglobin concentration and bleeding time could be observed ($r = -0.070$ and $p = 0.7491$; resp. $r = -0.221$ and $p = 0.4905$). In the period after r-HuEPO-treatment, however, a correlation was detected ($r = -0.597$ and $p = 0.0409$).

Discussion

Our data clearly demonstrate that using r-HuEPO results in a significant increase in hemoglobin concentration and at the same time reduces bleeding time. Concerning bleeding time, the comparison of data of r-HuEPO-treated patients with those of patients without such a treatment still reveals a significant difference between the two groups, even after a prolonged period of r-HuEPO-treatment. Despite that fact, some of our r-HuEPO-treated patients had a normal bleeding time. In the r-HuEPO-treated group there was a relevant correlation between hemoglobin concentration and bleeding time during the treatment period, while no correlationship could be detected at the start of treatment and in the group without r-HuEPO. Furthermore, it is of note that platelet count is of no relevance with respect to bleeding time as both initially and during the r-HuEPO-treatment and in the group without r-HuEPO-treatment no difference in platelet count could be detected. Thus, we conclude that under r-HuEPO-treatment bleeding time is mainly dependent on hemoglobin concentration, if no prostaglandin synthesis inhibitors are used.

As pointed out by Moia et al. and Hauglustaine et al., there seems to be a hemostatic effect of r-HuEPO in chronic hemodialysis patients, the effect of which is mainly hemoglobin dependent[6, 9]. Thus, our data confirm previous reports. In contrast to the findings of Hauglustaine, however, we could not detect any increased production of platelets, which would result in an increased platelet count. As we only used a low dosis of r-HuEPO and aimed at much lower target hemoglobin levels, this might explain the differences. This notion is furthermore supported by the statement by Hauglustaine et al.[6] that in parallel with the progressive decrease in the r-HuEPO dose, the platelet count decreased to pre-treatment values, Furthermore, they observed no increase in bleeding time with the decreased platelet count. Thus, the main dependency of bleeding time and hemoglobin concentration/hematocrit seems to be underlined.

The notion that a stimulated platelet production is dependent on the amount of r-HuEPO given, and thus the target hemoglobin concentration/hematocrit level,

is also supported by our finding that no rise in platelet counts occurred in our patients (fig. 2). Furthermore, we observed a slight decrease over time.

Several observations point to the red cells as a variable that influences bleeding time[3]. As early as 1910 Duke noticed that in anemia bleeding time was more prolonged than expected when it was correlated with the reduced platelet count[2]. Furthermore, he pointed out that with the reversal of anemia by blood transfusion there was a parallel shortening of bleeding time. These findings were confirmed by Livio et al., Hellem et al. and Fernández et al.[4, 7, 8]. These studies, however, do not exclude that with the blood transfusion also factors were transfused which could partially influence bleeding time. Thus, showing that r-HuEPO-treatment shortens bleeding time supports the earlier notion of a relationship between bleeding time and hemoglobin concentration/hematocrit level.

Platelets, however, might play a role in bleeding time changes as blood is a non-Newtonian fluid. Thus, increasing the red cell count results in a relative increase of platelets in the periphal blood flow, which means that a relative increase of platelet concentration occurs in the flow close to vessel walls. Thus, the relative platelet count close to the subendothelium and endothelium is enhanced. This interpretation is supported by the correlation of bleeding time and hemoglobin concentration in r-HuEPO-treated patients.

It is, however, difficult to explain why in the group without r-HuEPO-treatment and in the group later on treated with r-HuEPO no relationship between hemoglobin concentration and hematocrit exists. One might speculate that some of our patients in these groups had taken prostaglandin synthesis inhibitors, while during the assessment of bleeding time in the r-HuEPO-treated group a standardised protocol was used. A further explanation might be that a selection bias occurred.

It can, however, not be excluded that there are also some growth factors involved when r-HuEPO-treatment is given. As we recently pointed out[5], there is a considerable loss of renal function and also some arterial wall changes due to r-HuEPO-treatment in normal and uremic rats. Thus, these growth factors might change/improve adhesion of platelets and red cells to vessel walls.

It is of note that during 378 patient months only two shunt occlusions occurred and these were occlusions in patients having serious stenosis of the fistula before starting r-HuEPO-treatment. Thus, our policy to add aspirin during the initial phase of r-HuEPO-treatment and when higher hemoglobin concentrations than 10 were reached, seems to be effective.

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