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The impact of haematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity—the experience of the Lombardy Dialysis Registry

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Mortality and morbidity of dialysis patients

The major aims of dialysis therapy consist in prolonging patients' survival, reducing the patients morbidity and improving their quality of life. However despite many technical advances in the medical care and in the delivery of dialysis over the past years, mortality and morbidity of dialysis patients remains persistently high and their quality of life is rather poor.

Anaemia as cardiovascular risk factor

Hypertension and anaemia play a pivotal role in the increased mortality and morbidity in uremic patients and should be managed appropriately. In fact anaemia has been found to be an independent risk factor for developing cardiac morbidity and mortality in dialysis patients [1,2] and cardiovascular disease is the major cause of death in these patients. It is well known that cardiac hypertrophy is very frequent in dialysis patients and anaemia and hypertension are very important risk factors in this complication, clearly related to the cardiovascular mortality, as anaemia is accompanied by an increase of cardiac work that induces left ventricular hypertrophy. Of course other factors are important in inducing left ventricular hypertrophy, as arteriovenous fistula and, among other hormones, parathyroid hormone [3].

Importance of correcting anaemia

A reduction of cardiac hypertrophy by controlling hypertension and correcting anaemia in dialysis patients has been demonstrated [4,5]. The improvement of anaemia by erythropoietin (rHuEpo) is accompanied by beneficial effects; however, opposing the changes advantageous for uraemic patients are the adverse effects of rHuEpo(mainly hypertension). The long-term effects of normalized haematocrit values in uraemic patients have not been exhaustively evaluated in prospective randomized multicentre studies. Therefore the question arises as to what extent anaemia should be corrected in order to avoid undesirable side-effects.

The Japanese data

A Japanese retrospective study [6], analysing a total of 2116 patients has reported that the administration of rHuEpo might be responsible for an increased risk of cardiovascular disease (especially stroke and acute myocardial infarction), although only a trend towards an increase in the incidence of stroke and acute myocardial infarction was noted. However, some relevant methodological drawbacks were underlined [7,8]. This study prompted us to further clarify this important aspect. We performed a historical prospective study concerning the clinical effects of the use of rHuEpo in patients dialysed in Lombardy. The study aimed at clarifying the clinical impact of anaemia and rHuEpo treatment on general and cardiovascular mortality and morbidity.

The Lombardy data

Lombardy is a region of Northern Italy with 8 910 451 inhabitants (31 December 1994). It has a registry for end-stage renal disease (ESRD) patients with a 100% response rate from the 44 Lombardy dialysis units).

A detailed study of Lombardy 1983 to 1992 dialysis and transplantation results has been reported elsewhere [9]. The Lombardy Registry is permitted to track the modality of treatment and the outcome of ESRD patients alive at 1 January 1983 and of the incident patients with ESRD from the same date. In order to address the above-mentioned clinical questions, we selected the live patients on dialysis treatment on 31 December 1995. Four main parameters of outcome

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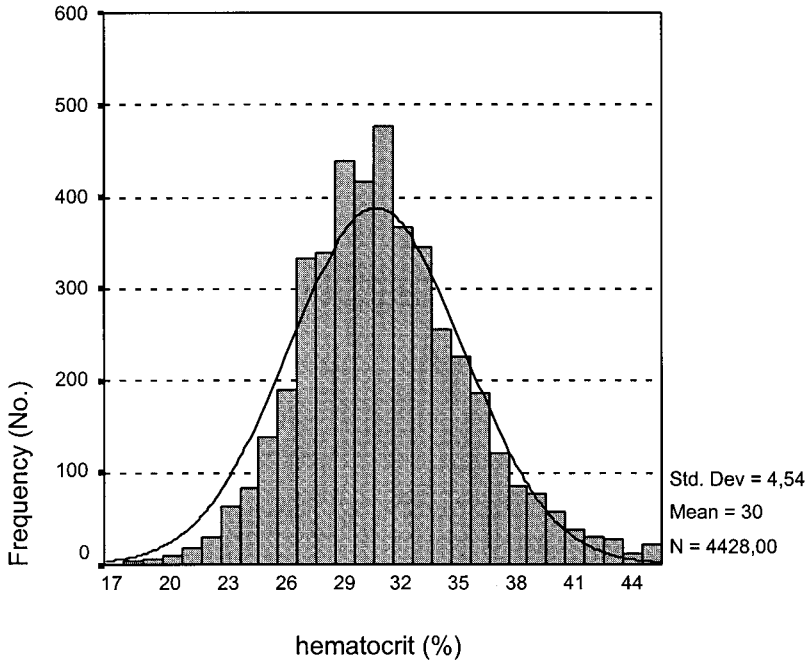

Fig. 1. Distribution of haematocrit levels at 31 December 1995 in the evaluated patient group and idealized normal distribution curve.

were evaluated: (i) all-cause mortality, (ii) cardiovascular mortality, (iii) cerebrovascular mortality, and (iv) cerebrovascular morbidity. The relationship between the outcome during the calendar year 1996 and haematocrit levels with or without rHuEpo therapy was adjusted for the age at the beginning of renal replacement therapy (RRT), gender, presence of comorbid conditions as of 31 December 1995, modality of treatment, and time spent on dialysis treatment before 31 December 1995.

On 31 December 1995, 5302 patients were on dialysis treatment in Lombardy. The main characteristics of this population are reported in Table 1. The mean haematocrit of the patients was $30.1 \pm 4.5\%$, and 70.7% of them had been treated with rHuEpo. Figure 1 shows the distribution of the patients according to haematocrit level.

As far as general mortality is concerned, the frequency of death observed in this population during the calendar year 1996 was 11.1% in those treated with rHuEpo and 15.2% in those not so treated. Figure 2 shows the overall crude mortality of the patients stratified according to three levels of haematocrit (haematocrit $<27\%$: 887 patients, 27–32%: 2043 patients, $>32\%$: 1498 patients respectively). The crude odds ratio associated with the prescription of rHuEpo was 0.70. Adjusting for known risk factors such as age at the beginning of RRT, gender, time on dialysis treatment, comorbid conditions, and haematocrit level on 31 December 1995, yielded an odds ratio of 0.65 (95% c.i. 0.52–0.81, $P<0.001$). If one treats haematocrit levels, spontaneous or because of rHuEpo treatment, as continuous variables, the mean risk of all-causes mortality decreases with increasing haematocrit levels (odds ratio: 0.95 per unit of haematocrit, 95% confidence interval 0.92–0.97). Taking only cardiovascular mortality as an end-point and using the same model, 3.4% of the patients on rHuEpo therapy in 1996 died from cardiovascular causes in comparison to 5.6% in those untreated patients (crude odds ratio 0.59).

Table 1. Main characteristics of the prevalent ESRD population of dialysis treatment in Lombardy as of 31 December 1995

Age (years)*	54.9 ± 16.1
Male (%)	57.2
Diabetics (%)	7.6
Heart disease (%)	16.1
Cerebrovascular disease	7.4
Hepatic cirrhosis	3.0
Severe malnutrition	2.3
Malignancy	9.3
Time on RRT (months)	73.5 ± 72.5
Haematocrit (%)	30.1 ± 4.5
HuEpo therapy (%)	70.7

*Age refers to age at the beginning of RRT.

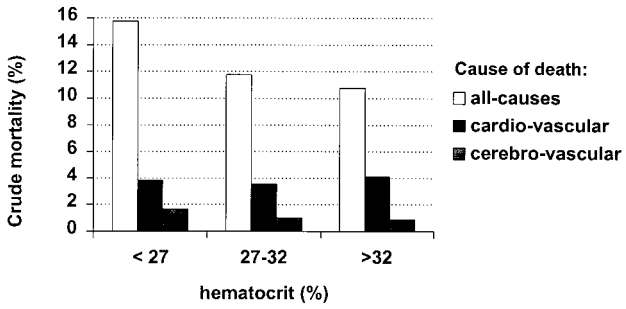

Fig. 2. Crude mortality during 1996 in patients alive as of 31 December 1995 according to causes of death and stratified according to haematocrit level.

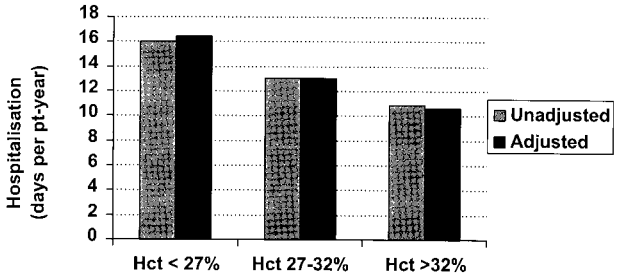

Fig. 3. Unadjusted and adjusted mean hospitalization rates in 1996 stratified according to haematocrit on 31 December 1995.

Adjusting and using the above-mentioned statistical model, the odds ratio did not change significantly (odds ratio: 0.61, 95% confidence interval 0.43–0.86, $P<0.05$). Figure 2 shows similar crude cardiovascular mortality at the three levels of haematocrit: when considering the whole set of predictors, the analysis confirmed the absence of any statistical association between haematocrit (continuous variable) and cardiovascular mortality. The same analysis performed with the death from cerebrovascular cause as end-point showed similar but not statistically significant results for rHuEpo treatment (crude and adjusted odds ratio were 0.79 and 0.56 respectively) as well as for haematocrit levels (Figure 2).

The mean hospitalization of the considered population during the calendar year 1996 was 13.0 days per patient-year, in the patients submitted to rHuEpo therapy and 13.1 days per patient-year in those untreated. Adjusting for the previously mentioned risk factor set, the hospitalization became 12.9 and 13.0 days per patient-year in the patients treated and untreated with rHuEpo respectively ($P=$NS). Stratifying the haematocrit level in the three categories, an increasing hospitalization rate was found in the groups of patient with the lowest haematocrit level (Figure 3). This relationship was maintained when considering the adjusted value (Figure 3).

This study confirmed the role of the anaemia on the outcome of ESRD patients on dialysis treatment. The main question to address was whether the effect was related to the levels of haematocrit values irrespective of rHuEpo therapy or if there was a specific protective effect of rHuEpo treatment. Our data show an unexpected benefit from the rHuEpo therapy *per se*, on all-causes of mortality at least partly independent of the effect on haematocrit levels. However, it should be pointed out that the model for all-causes mortality, even though its prediction rate was generally good +(88%), failed to predict correctly the events (5%). Consequently, we are not able to clearly establish that rHuEpo has some pharmacological effect not depending on the anaemia correction. In any case, the negative findings reported by Iseki *et al.* [6] in Japanese patients are not confirmed by the data of the Lombardy registry.

Conclusion

Higher levels of haematocrit, either spontaneously achieved or resulting from rHuEpo treatment, improve outcome parameters of dialysis patients. According to the data of the Lombardy registry, rHuEpo therapy seems to protect against overall and cardiovascular mortality and morbidity.

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