Erythrocyte sedimentation rate, an underestimated tool in chronic renal failure

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Abstract
Background. Erythrocyte sedimentation rate is widely used in the general population. It has seldom been studied in patients with chronic renal failure. The purpose of this study was to assess its usefulness in haemodialysis patients.

Methods. Forty-five haemodialysis patients with no evidence of acute or chronic inflammatory illness were studied. Nine were diabetic, and 12 used a non-biocompatible membrane. Erythrocyte sedimentation rate was determined, using a modified Westergren method. Plasma fibrinogen concentration, complete blood count, and serum chemistries were also studied.

Results. Erythrocyte sedimentation rate was normal or mildly elevated in most of our patients, with a median of 30 mm/h. Linear analysis found positive correlation between erythrocyte sedimentation rate and fibrinogen concentration, globulin level, platelet, and white cell counts, and negative correlation with haematocrit. Fibrinogen concentration was normal in 22 patients, and moderately elevated in 14. It was significantly higher in diabetic patients, or those using a non-biocompatible membrane. The same positive correlations were found for fibrinogen concentration as for erythrocyte sedimentation rate.

Conclusions. We conclude that erythrocyte sedimentation rate can be used in haemodialysis patients much in the same way as in the general population, as its baseline value is lower than previously reported. The lower concentration of fibrinogen, an independent predictor of cardiovascular risk, in patients treated with biocompatible membranes may be of clinical relevance.

Key words: biocompatible membranes; chronic renal failure; erythrocyte sedimentation rate; fibrinogen; haemodialysis

Introduction

Erythrocyte sedimentation rate (ESR) is commonly used in the general population for the diagnostic and management of a variety of illnesses [1,2]. It is strongly influenced by the concentration of fibrinogen, alphaglobulins, among which are most of the other inflammatory proteins, and gammaglobulins. There is also a strong negative influence of haematocrit [3].

The utility of ESR in patients with chronic renal failure (CRF) is more debatable. In several retrospective studies [4,5], extremely elevated ESR was attributed to CRF of varying causes, which may themselves have influenced ESR. This seems to have prompted the mention of CRF as a cause of elevated ESR in several reviews [1,6]. Contrasting with the wealth of information on arcane inflammatory mediators in CRF, we found only two papers [7,8] studying ESR in patients with CRF. Both studies were performed in the United States; they concerned a mixture of patients on haemodialysis (HD), with scarce detail on its modalities, and patients not yet treated [7], or on chronic ambulatory peritoneal dialysis [8]. They found a high incidence of elevated ESR with no apparent cause, and concluded that its measurement had little utility in HD patients.

The purpose of this study was to appreciate the utility of ESR in HD patients by answering the following questions: (1) What is the prevalence of elevated ESR in a European population of HD patients with no evidence of inflammatory disease? (2) Is ESR influenced by the same factors as in the general population? (3) What is the influence of associated diseases such as diabetes, or new treatments such as recombinant erythropoietin, or biocompatible HD membranes?

Patients and methods

Patients

All patients receiving routine HD in the morning at our centre were considered for the study. Patients with solid tumours, malignant haemopathies, monoclonal gammopathies, or chronic inflammatory diseases were excluded. Patients with evidence of infection or acute inflammatory illness within 1 month prior to the study were also excluded. Forty-five patients (23 male, 22 female) with a mean age of 59 years (range 20–88 years) were included in the study. Presumed cause of CRF was glomerular nephropathy in 16 patients, chronic interstitial nephritis in 12, vascular nephro-
pathy in three, diabetic nephropathy in seven, hereditary nephritis in four, and unknown in three patients. Average time on HD was 63 months (range 3-256 months). There were nine diabetic patients, 10 patients still had significant residual diuresis, and only nine patients were treated with recombinant erythropoietin at the time of the study. Thirty-two patients received two 8-h HD treatments a week, and 13 received three 4-h HD treatment a week. A bicarbonate-buffered dialysate was used in four patients only. Five patients were dialysed using a cuprophane membrane (Belco®), and seven using a regenerated cellular membrane (Asahi®). A majority of patients was dialysed using a biocompatible membrane, polysulphone (Belco®) in 14 patients and AN 69 (Hospal®) in 19 patients. Dialysis parameters had been stable for at least 3 months. No patient had chronic hepatitis.

Laboratory studies

After informed consent was obtained, additional blood specimens were obtained from all patients during routine monthly blood drawing, before any heparin injection. ESR was determined by a modified Westergren method. Blood was collected in ethylenediamine-tetraacetic acid (EDTA) and transferred to standard Westergren tubes. ESR was read following a 60-min interval at room temperature. Other laboratory tests were performed simultaneously. Fibrinogen concentration was determined according to the Clause method (normal 2-4 g/l). Haematocrit, white blood cell count, and platelet count were determined by standard coulter methods (STKR coulter). Automated determinations (Hitachi 713) of urea (normal 2.5-7.5 mmol/l), creatinine (normal 27-130 μmol/l), total protein (normal 60-80 g/l), albumin (normal 33-50 g/l), calcium (normal 2.12-2.62 μmol/l) and alkaline phosphatase (normal 80-220 IU/l) were also done. Globulin was obtained by subtracting albumin to total protein.

Statistics

Quantitative values were expressed as the mean, range, and median. Subgroups of patients differing by one qualitative variable (sex, diabetic state, type of membrane, number of HD treatments per week, presence of residual diuresis, treatment with erythropoietin) were compared using the Wilcoxon rank-sum test. Linear regression analysis by the method of least squares was used to relate ESR or fibrinogen concentration to individual quantitative variables (ESR, fibrinogen concentration, age, time on HD, haematocrit, white cell or platelet count, urea, creatinine, total protein, albumin, globulin, calcium and alkaline phosphatase levels). A P value of less than 0.05 was considered significant. Calculations were made using the Kwikstat 2.00 program.

Results

ESR

As can be seen in Table 1, which gives laboratory results in our 45 patients, mean ESR was mildly elevated at 39 mm/h (range 6-140 mm/h). ESR was indeed less than 30 mm in one-half of the patients. More precisely, ESR was normal (0 to 24 mm/h) in 16 patients, mildly elevated (25-49 mm/h) in 16 patients, moderately elevated (50-74 mm/h) in eight patients, markedly elevated (75-99 mm/h) in three patients, and extremely elevated (>100 mm/h) in only two patients.

Wilcoxon test found no correlation between ESR and sex, type of HD membrane, cause of CRF, presence of a diabetic state or significant residual diuresis, number of HD treatments per week, or treatment with recombinant erythropoietin.

Linear analysis found positive correlation between ESR and fibrinogen concentration (r=0.74, P<0.0001), globulin level (r=0.49, P=0.001), platelet count (r=0.46, P=0.001), and white cell count (r=0.31, P=0.039). Negative correlation was found between ESR and haematocrit (r=-0.42, P=0.004), and time on HD (r=-0.38, P=0.011). Only correlation of ESR with fibrinogen concentration, haematocrit, and white cell count achieved statistical significance in multivariate analysis. No correlation of ESR was found with age, urea, total protein, albumin, creatinine, or calcium levels.

Fibrinogen

Mean fibrinogen concentration was 4.3 g/l (range 2.2-7.6 g/l). More precisely, it was in the normal range (2-4 g/l) in 22 patients, and moderately elevated (4-5 g/l) in 14 patients. It was between 5 and 6 g/l in five, between 6 and 7 g/l in two, and between 7 and 8 g/l in two.

Wilcoxon test showed that fibrinogen concentration was significantly (e=2.75, P=0.009) more elevated in diabetic than in non-diabetic patients (Figure 1). Eight of the nine diabetic patients had indeed a fibrinogen concentration over 4 g/l. Fibrinogen concentration was also significantly (e=2.58, P=0.01) more elevated in patients dialysed with a non-biocompatible membrane than in patients dialysed with a biocompatible membrane (Figure 2). Fibrinogen concentration was not correlated with sex, number of HD treatments per week, presence of significant residual diuresis, or treatment with recombinant erythropoietin.

Linear analysis found positive correlation between fibrinogen concentration and platelet count (r=0.63, P<0.001), white cell count (r=0.59, P<0.001) and globulin level (r=0.34, P=0.022). Negative correlation was found between fibrinogen concentration and time.

Table 1. Biological data in 45 patients treated by haemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>Median</th>
</tr>
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<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>39</td>
<td>6–140</td>
<td>30</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>4.3</td>
<td>2.2–7.3</td>
<td>4.1</td>
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<tr>
<td>Haematocrit (%)</td>
<td>25.6</td>
<td>17.7–38.5</td>
<td>25.2</td>
</tr>
<tr>
<td>Blood leukocytes (10⁹/l)</td>
<td>7.3</td>
<td>3.2–21.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Platelets (10⁹/l)</td>
<td>232</td>
<td>115–577</td>
<td>215</td>
</tr>
<tr>
<td>S. urea (mmol/l)</td>
<td>29</td>
<td>11.2–42.8</td>
<td>28.7</td>
</tr>
<tr>
<td>S. creatinine (μmol/l)</td>
<td>990</td>
<td>442–1440</td>
<td>981</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>61.7</td>
<td>55–78</td>
<td>68</td>
</tr>
<tr>
<td>S. albumin (g/l)</td>
<td>41.3</td>
<td>31–47</td>
<td>42</td>
</tr>
<tr>
<td>S. globulins (g/l)</td>
<td>26.4</td>
<td>15–35</td>
<td>26</td>
</tr>
<tr>
<td>S. calcium (mmol/l)</td>
<td>2.16</td>
<td>1.92–2.57</td>
<td>2.17</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>228</td>
<td>81–1439</td>
<td>93</td>
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on HD ($r = -0.34, P = 0.023$). Only correlation of fibrinogen concentration with platelet count, and with duration of HD, achieved statistical significance in multivariate analysis. No correlation was found between fibrinogen concentration and haematocrit, unlike ESR, or between fibrinogen concentration and age, urea, creatinine, total protein, albumin, and calcium levels.

Others

Wilcoxon test showed that total globulin level was significantly ($e = 2.11, P = 0.035$) more elevated in diabetic patients (mean 29.7, range 24–35, median 32 g/l) than in non-diabetics (mean 25.6, range 15–35, median 25.5 g/l). Duration of haemodialysis was shorter ($e = 2.51, P = 0.012$) in diabetic patients (mean 24.9, range 3–58, median 22 months) than in non-diabetics (mean 72, range 6–256, median 54.5 months); it was also shorter in patients using non-biocompatible membranes than in patients using biocompatible membranes ($e = 1.886, P = 0.06$). Globulin level was not correlated with the type of the membrane used, or any other qualitative variable. Haematocrit was not different in diabetic (mean 25.2, range 20.4–31.5, median 23.7%) and non-diabetic (mean 25.8, range 17.7–38.5, median 25.4%) patients, or in patients treated with non-biocompatible (mean 25.9, range 18.7–31.5, median 25.4%) and biocompatible (mean 24.9, range 17.7–38.5, median 25.2%) membranes.

Discussion

ESR was normal or mildly elevated in most of our patients, with a mean value of 39 mm/h and a median of 30 mm/h. This is in sharp contrast with the only two studies in literature. In Shusterman's study [7], mean ESR was 60 mm/h, with a median about 60 mm/h. In Bathon's study [8], mean ESR was 70 mm/h, with a median above 70 mm/h. The proportion of diabetic patients was not specified in Shusterman's study; it was similar in Bathon's study and in ours, thus not explaining the difference in ESR. The type of membrane used for HD was not specified in Shusterman's or Bathon's studies; it was probably non-biocompatible, which may account for the higher ESR in their patients, as discussed later.

ESR is strongly influenced by fibrinogen concentration both in vitro [3,9] and in vivo, in the general population [10]. In our patients, a high degree of positive correlation between ESR and fibrinogen concentration was found, as well as a similar repartition of normal and elevated values. These results favour the use of ESR as a cheap surrogate of fibrinogen concentration determination in HD patients. Anaemia causes an elevated ESR even in the absence of any inflammation in the general population [11]. Accordingly, a significant negative correlation was found in our patients between haematocrit and ESR, but not between haematocrit and fibrinogen concentra-
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Haematocrit was not higher in our patients than in those of Bathon [8] (27.4%, range 16.3–42.5%) and Shusterman [7], as estimated from their figure 1, thus not explaining the lower ESR in our patients. A weaker positive correlation was found between ESR or fibrinogen concentration, and total globulin level, platelet count, and white cell count, which are often elevated when inflammation is present. We found no correlation between ESR and calcium level, as described by Bathon [8], possibly reflecting differences in control of calcium metabolism.

Fibrinogen concentration was significantly higher in our diabetic patients than in our non-diabetic patients, and in patients using non-biocompatible membranes than in those using biocompatible membranes. An increased level of fibrinogen has been reported in non-uremic diabetics [12]; its mechanism is unknown. Complement activation during haemodialysis is higher in patients treated with a non-biocompatible membrane [13], leading to higher anaphylatoxin liberation, macrophage stimulation, liberation of interleukin 1, interleukin 6 and tumour necrosis factor, and increased hepatic synthesis of inflammatory proteins [14]. Some studies found indeed higher levels of interleukin 1 [15], interleukin 6 [16] or tumour necrosis factor [17] after haemodialysis with a non-biocompatible membrane. It is therefore not surprising that our patients treated with non-biocompatible membranes had higher fibrinogen concentrations. The influence of diabetic state or membrane biocompatibility was not found when studying ESR in our patients. The important influence of such other parameters as haematocrit on ESR may have blunted the influence of these factors, and prevented difference between subgroups from reaching statistical significance.

We found negative correlation between duration of haemodialysis and ESR or fibrinogen concentration in our patients, unlike those of Shusterman [7] and Bathon [8]. Mean duration of haemodialysis was much shorter (24 months) in Bathon’s patients than in ours, which may have prevented the correlation from emerging for lack of time. One possible explanation is that patients with a shorter life expectancy on HD often have higher ESR or fibrinogen concentrations, for varying reasons. For example, they are often treated with non-biocompatible membranes, as the long-term occurrence of beta 2 amyloidosis is less of a concern. Another more disturbing possibility is that a high fibrinogen concentration is directly related to a shorter life expectancy in patients on HD. In the general population, a high fibrinogen concentration is a strong independent predictor of cardiovascular risk [18,19]. Similarly it could be implicated in the accelerated atherosclerosis [20] which has been described in HD patients. The results of our study suggest that the use of biocompatible membranes may decrease the cardiovascular risk in HD patients by decreasing their fibrinogen concentration.

We conclude that ESR can be used in HD patients much in the same way as it is used in the general population, as it is under the influence of the same factors, and its baseline value in stable patients is lower than previously reported. Moreover the incidence of diseases increasing ESR is a priori higher in HD patients than in the general population, thus increasing the positive predictive value of the test [21]. Further studies are needed, in patients with a higher haematocrit, where the influence of a diabetic state or of the type of membrane on ESR may appear, or to compare ESR with other inflammatory markers than fibrinogen concentration.

References


Received for publication: 26.1.96
Accepted in revised form: 9.7.96