How to prescribe optimal haemodialysis

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Key words: haemodialysis adequacy; haemodialysis prescription; optimal haemodialysis

Introduction

The characteristics of patients starting renal replacement therapy (RRT) have changed significantly over the last few years. The last EDTA-ERA Registry Report [1] showed that 37% of patients starting RRT in 1992 were over 65 years old. The median age of patients starting RRT was 62 years. On the other hand, primary renal disease has also changed considerably over the past years. In Europe, 17% of the patients starting RRT in 1992 had diabetes mellitus. It is important to note that in 1977 only 3.7% of new patients were diabetic. Although this 17% incidence of diabetics is only a little more than half of that in the United States, where the last USRDS report [2] showed that 33% of new patients were diabetic, this still indicates an important change in the characteristics of new patients.

At the beginning of 1995 in Spain, there were nearly 10,000 patients living with a functioning transplant and 15,000 patients on dialysis [3]. Of these patients on dialysis, only 30% are on a waiting list for transplant. This figure is similar to the rest of Europe and is a consequence of the increase in age of the patients and of the existence of co-morbidity. The fundamental conclusion to be drawn then, is that the only possible RRT for the majority of patients is dialysis, and therefore it is of vital importance to define optimal dialysis.

This concept of optimal dialysis seems especially important taking into account that for the majority of patients with end-stage renal disease (ESRD) the only treatment possible is dialysis for the rest of their lives. Besides this, when renal transplant results for the best age group are analysed, the 50% graft survival is approximately 11 years [4].

A possible definition of optimal dialysis is that which offers low mortality and morbidity rates, and therefore a high long-term survival with a good quality of life. Various factors are related to good long-term survival; in different studies, the most important of these is nutrition [5,6]. Nevertheless, the efficiency of dialysis is a factor which influences mortality, possibly through its effect on the nutritional state [6-8]. We consider optimal dialysis not that which presents adequate urea kinetic modelling, but rather we coincide with various authors who affirm that survival is the best index of adequate dialysis [9]. Urea kinetic modelling is probably the most objective way of measuring the efficiency of dialysis, and therefore of prescribing optimal dialysis, but there are a series of alterations in ESRD which cannot be measured by urea kinetic modelling.

In Figure 1 we can observe the mean $Kt/V$ in patients undergoing different treatment techniques, ranging from conventional haemodialysis with a cuprophan membrane and acetate dialysis fluid to dialysis with the same membrane and bicarbonate, including high flux haemodialysis with 1.9 m² polysulfone membrane and two haemodiafiltration techniques (PFD and AFB). All of these patients have very similar $Kt/V$, but show a series of differences which we will analyse and which are now shown by urea kinetic modelling.

The alterations we will review and which should be taken into account when prescribing optimal dialysis are the following: acidosis, hyperphosphataemia, dry weight, $\beta_2$-microglobulin, and biocompatibility.

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Acidosis

The correction of acidosis is different in those patients who are on bicarbonate haemodialysis and haemodiafiltration and those on haemodialysis with acetate. In Figure 2(A and B) we can see the changes in plasma bicarbonate throughout the dialysis session in patients treated with haemodialysis with acetate, haemodialysis with bicarbonate and two haemodiafiltration techniques. When the buffer used in haemodialysis is bicarbonate or bicarbonate is infused intravenously, the plasma bicarbonate normalizes throughout the dialysis, while it remains at a lower than normal concentration in haemodialysis with acetate. If the plasma bicarbonate is studied for a period of 48 h between haemodialyses, acidosis in patients dialysed with bicarbonate or on haemodiafiltration is corrected adequately, but there are patients dialysed with acetate who spend the greater part of their lives in acidosis.

In Europe, 70% of patients are treated with haemodialysis with bicarbonate [1], although there is still a large number of patients treated with acetate. This is extremely important, given that the correction of acidosis is absolutely necessary. The pernicious effects of acidosis are generally seen in the bone, where in vitro studies show that the release of calcium is very high when metabolic acidosis exists, and this does not occur in situations of normal metabolic acid-base, in respiratory acidosis or when metabolic acidosis is corrected [10]. It has been observed in vivo how parathyroid hormone increases progressively in acidotic patients, which does not occur when acidosis is adequately corrected in patients on haemodialysis. This has been observed for a period of 18 months [11].

Finally, it is important to note that acidosis has a harmful effect not only on hyperparathyroidism, but is also a direct cause of malnutrition. Bergström’s group found a direct relation between acidosis and nutrition, observing that the pre-dialysis plasma bicarbonate correlated positively to the concentration of valine in the muscle, indicating that a significant state of malnutrition is found in acidotic patients [12].

Hyperphosphataemia

Acidosis is not the only hydroelectrolytic disorder which should be corrected during dialysis and which is not measured by urea kinetic modelling. Hyperphosphataemia is another disorder which is not always adequately controlled.

The clearance of phosphate depends on the type of membrane and is directly related to its surface area. When the clearance of phosphate is compared in two highly permeable membranes such as polyacrylonitrile and polysulfone, the clearance of phosphate is demonstrably increased when the surface area is greater. Nevertheless, convective transport does not increase clearance, which indicates that haemodiafiltration is not more effective than haemodialysis in increasing the extraction of phosphate [13].

In consequence, the extraction of phosphate can be increased by increasing the surface area of the dialyser, and, above all, increasing dialysis time. The use of phosphate binders is necessary, but it is important to remember that hyperphosphataemia itself can be a sufficient reason for changing the dialysis prescription in patients even though their $Kt/V$ is correct. This must be taken into account because many patients may need a greater surface area dialyser or more time on dialysis although they have an adequate $Kt/V$. We must not forget that the use of aluminium phosphate binders is to be avoided and that among the calcium-containing binders, calcium carbonate is the most efficient [14]. In Figure 3 we can see how the use of calcium carbonate as a phosphate binder and vitamin D metabolites (calcitrol) intravenously, together with a low calcium concentration in the dialysis fluid, can significantly improve hyperparathyroidism in a group of patients. It is important that the use of calcium-containing phosphate binders and vitamin D metabolites should be accompanied by the use of physiological concentrations of calcium lower than usual in the dialysate [15].
The determination of the patient's dry weight is still based on clinical data, thereby running the risk of being inadequate. An overestimation of dry weight can be the cause of hypertension and, on the other hand, an underestimation can induce hypotenion in dialysis. Volumetric control of ultrafiltration helps to obtain the desired weight, but the clinical assessment of dry weight can be improved with continuous monitoring of extracellular volume, which can be carried out by various techniques (conductivity, ultrasound, measuring ANP as a marker, measuring the diameter of the vena cava by ultrasonography or bioelectric impedance) [16–24]. All of these measurements can help to control dry weight adequately and to maintain it at the desired level. This continuous monitoring can be complemented with a biofeedback that regulates the weight to be extracted in each dialysis.

Excessive dry weight is one of the most important factors related to the presence of hypertension, which is in turn one of the greatest risk factors for co-morbidity and mortality. In a multi-centre study carried out in Madrid which included more than 1600 patients, more than 20% of these were hypertensive at the time the study was done, although the majority of them were receiving anti-hypertensive treatment [25].

### β2-Microglobulin

The extraction of β2-microglobulin is of fundamental importance in relation to dialysis-related amyloidosis. In our experience, patients treated with cuprophan membranes show a progressive increase over time in plasma levels of β2-microglobulin. However, when two groups of our patients were transferred to dialysis with a polysulfone or polyacrylonitrile high flux membrane, these levels decreased significantly, and this decrease continued even after 2 years after the change of membrane [26].

The pathogenetic role of plasma β2-microglobulin in the development of dialysis-related amyloidosis is not totally clear [27–29], but from the epidemiological point of view, the incidence of carpal tunnel syndrome is much less in patients who have always been treated with a membrane permeable to β2-microglobulin in comparison to those who have been treated with cellulose membranes [30,31].

The clearance of β2-microglobulin is practically nil when cuprophan membranes are used, while high flux polysulfone or polyacrylonitrile membranes are able to extract β2-microglobulin [26]. Reuse does not decrease the filter clearance of β2-microglobulin [32], a fact which has important economic consequences. During a dialysis session, β2-microglobulin increases significantly with a cuprophan membrane, while it decreases with high flux polysulfone membrane haemodialysis or haemodiafiltration (AFB or PFD) [26].

Similar to phosphorus, the clearance of β2-microglobulin increases with the surface area of the membrane, as has been demonstrated with polysulfone and polyacrylonitrile, but it also increases with convective transport, which is the reason why haemodiafiltration increases the extraction of β2-microglobulin [13]. Since it is a molecule with a molecular weight of 14600 Da, its clearance increases significantly with convective transport. It is important to note that up to 20% of the extraction of β2-microglobulin with polysulfone or polyacrylonitrile membranes is produced as a consequence of the adsorption of the molecule in the surface of the membrane [33].

In summary, the extraction of β2-microglobulin depends on the type of membrane. It can improve with highly permeable membranes, with greater surface areas of these membranes and with the addition of convective transport (haemofiltration or haemodiafiltration).

### Biocompatibility

The interaction between the blood and the dialyser membrane activates a series of systems, among which the most important are the complement system, the coagulation system, kallikrein, bradykinin, activation of neutrophiles causing neutropenia and adhesion of the same with the activation of C3b and C5a receptors, CD11b (adhesion molecules), the degranulation of neutrophiles with the release of lactoferrin, elastase, inhibitor of proteinase A1, myeloperoxidase, ROS, PAF, leukotrienes, depression of phagocytosis and of the oxidative metabolism demonstrated by chemiluminesence, and others. Also activated are monocytes with release of cytokines, interleukins, IL-1, IL-2, IL-6, tumour necrosis factor α (TNF-α), an increase in the expression of HLA and DR antigens and expression of the complement receptors, as well as lymphocytes with an increase in HLA1 and 2 expression, an increase in the release of β2-microglobulin in cultures, an increase of IL-2 receptors, the synthesis of DNA and a decrease in natural killer cells.

Platelets increase their adhesion and there is a release
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of β2-thromboglobulin and platelet factor IV, thromboxane and 12-hydroxyeicosatetraenoic acid. Finally, the erythrocytes show alterations in the structure of their membranes and instability. All of these effects have been the subject of numerous studies [34–37].

However, we must concentrate on the interaction between the blood and the dialysis fluid. In effect, biocompatible dialysis does not consist of using a biocompatible membrane because bacterial contamination of the dialysis fluid and the presence of acetate in the same can produce a series of effects which are especially important when highly permeable membranes, precisely the most biocompatible, are used. Bacterial contamination of the dialysate with Gram-negative bacteria can cause the appearance of endotoxins (lipopolysaccharides), which can be detected with the LAL test and which are especially frequent when using bicarbonate dialysis, because of the biofilm which can appear on the conducting surfaces of the dialysate [38,39]. The presence of LAL-negative exotoxins has also been described [40]. Because of the high permeability of biocompatible membranes, toxins can enter through backfiltration or backdiffusion. Their effects include hypersensitive reactions, fever, and above all, the activation of monocytes with cytokine production, especially IL-1 and TNF-α [41,42]. It is important to remember in dialysis with acetate that the acetate can produce monocyte activation with an increase in IL-6, TNF-α and β2-microglobulin in monocyte cultures [43].

The epidemiological importance of water and dialysate contamination has been clearly demonstrated in various studies [44], in which bacterial contamination was found in 35% of the centres studied and contamination in the dialysate in almost 20% of them. The production of TNF-α during biocompatible dialysis is well documented, as is that of interleukins, especially IL-1 and IL-6, all of which can play an important role in the appearance of acute complications in haemodialysis (fever, headache, hypotension) as well as chronic effects (amyloidosis, muscle waste, immune depression) [45,46].

We have studied the pre-dialysis plasma IL-6 in patients treated with different dialysis membranes, studying simultaneously the presence of bacterial contamination in the dialysate [47]. We have observed that when the dialysate is sterile, the pre-dialysis plasma IL-6 is greater in patients treated with cellulosic membranes (cuprophan) than in patients treated with more biocompatible membranes such as polysulfone or polyacrylonitrile. However, when the dialysate was bacteriologically contaminated, the pre-dialysis IL-6 was much higher in those patients treated with more permeable membranes, i.e. polysulfone, polyacrylonitrile and cellulose triacetate. No increase in the IL-6 levels was observed when a cuprophan membrane was used (Figure 4A).

We obtained similar results when plasma TNF-α was measured (Figure 4B). There was a significant increase of up to eight times in patients dialysed with a polysulfone membrane with contaminated dialysate. No variations were observed with other membranes.

We have also measured the per cent fractional increment of plasma IL-6 throughout a dialysis session in both situations, i.e. with sterile fluid and with bacterial contaminated dialysate (Figure 4C). When the dialysate was sterile, IL-6 decreased throughout dialysis with a polyacrylonitrile membrane and increased slightly with other membranes. However, when the dialysate was contaminated there was a marked increase in IL-6 during the haemodialysis session in the same patients. AN 69, polyacrylonitrile; FS, polysulfone; CU, cuprophan; CAT, cellulose triacetate.
brane must be accompanied by strict control of dialysate contamination, since this contamination can make the procedure more bioincompatible. Some recent publications corroborate that bacterial contamination of the dialysate provokes chronic mononuclear stimulation with high production of TNF-α and IL-6, which corroborates our findings [48].

Therefore, we can conclude that a dialysate completely free of pyrogens is absolutely essential when dialysing with bicarbonate and high permeability and therefore more biocompatible membranes. A simple procedure to obtain a sterile dialysate is to ultrafilter it with one, or better, two polysulfone filters which only need changing once a month [49,50]. The majority of the modern dialysis monitors have a dialysate filter included.

The clinical repercussions of bacterial contamination have been proven by various authors [51] who demonstrate that the percentage of patients with carpal tunnel syndrome is much less in the long term in patients who have always been dialysed with ultra-pure dialysate. On the other hand, biocompatible dialysis has a catabolic effect which has been demonstrated by some authors by doing sham dialysis on healthy volunteers and demonstrating that there is a release of amino acids from the muscle tissue [52]. This effect does not appear when a biocompatible membrane is used or when indomethacin is administered simultaneously, which suggests that the catabolic effect occurs through local production of prostaglandins. These same authors have demonstrated a similar effect in patients undergoing haemodialysis [53]. The local release of prostaglandins, in turn, could be related to the activation of IL-1.

The relation between dialysis efficiency and nutrition is important and has been demonstrated by various authors [54,55]. There is a direct relationship between \( Kt/V \) and the protein catabolic rate (PCR). However, this relationship seems to be influenced by the type of membrane used. We have studied the relation between \( Kt/V \) and PCR in three groups of patients: some dialysed with cuprophan and others dialysed with polyacrylonitrile or high flux polysulfone (Figure 5). We observed that although mean \( Kt/V \) was lower, PCR was higher in the patients dialysed with polyacrylonitrile and polysulfone membranes, suggesting that these patients had a better nutritional state. These findings are corroborated by other authors [54,55]. Moreover, if we increase the surface area of the filter from 1.2 to 1.6 m² in patients dialysed with a polyacrylonitrile membrane on a haemodiafiltration technique (AFB), we observe that the \( Kt/V \) increases significantly, as does the PCR. A similar effect can be observed in the case of high flux haemodialysis with 1.9 m² polysulfone membrane in which dialysis time has been increased. In this way we have increased \( Kt/V \) and PCR. It could be concluded that with more permeable and biocompatible membranes, higher PCR can be obtained, which means better nutrition for these patients.

These data could bring us to the conclusion that excessive dialysis is not real. In effect, if dialysis efficiency increases, nutrition improves and we know that nutrition is the most important prognostic factor in ESRD patients undergoing dialysis. This concept is important, given that to continue decreasing haemodialysis time and simultaneously increasing the efficiency of the membranes used is an objective which cannot be maintained in haemodialysis. Effectively, more efficiency in the membrane means higher cost. Minimal dialysis can in no way be justified, but rather optimal dialysis, with the use of these high surface area and high flux membranes, or haemodiafiltration techniques, allow us efficiency and good nutrition. Therefore, we must understand that shortening dialysis time is no longer an up-to-date objective.

**Summary**

In summary, to achieve optimal dialysis we must adequately purify small molecules, for which urea kinetic modelling will be useful, but we must not forget the necessity of correcting acidosis (using bicarbonate dialysis or haemodiafiltration), and correcting hyperphosphataemia and β₂-microglobulin. Haemodialysis tolerance and hypertension can be controlled using volumetric control of ultrafiltration and continuous monitoring of body fluids. It is possible that the best method of estimating dry weight is a good clinical assessment, but in doubtful cases numerous techniques have been described which allow us to control body fluids and more adequately estimate dry weight.

Biocompatibility must be understood not only as biocompatibility of the membrane, but also of the dialysate, thereby making the use of pyrogen-free dialysates necessary. Finally, we must not forget that nutrition is a direct effect of biocompatible dialysis.

Therefore, a better quality of haemodialysis means not only better quality of membrane, but also improved dialysate, convective transport and continuous monitoring, if possible, with biofeedback. But all these improvements are costly. This
Optimal haemodialysis means that we must use elective indications and evaluate the cost–benefit ratio of each of these technical advances.

A possible suggestion regarding which patients would benefit the most from high quality dialysis is summarized in Table 1. In the first place, it would be indicated for patients with added morbidity. This is the case of a patient with an acute infectious complication or in any situation in which catabolism increases causing the risk of malnutrition, risk with poor quality dialysis because of vascular access problems, etc. These patients should have absolute preference in being prescribed efficient and biocompatible dialysis which does not stimulate the inflammatory reaction of bioincompatibility and with no catabolic effect, providing adequate purification of small and middle molecules and favouring the patient's nutritional state [56]. This concept is not sufficiently accepted by clinicians, but without doubt, it is the clearest indication for a biocompatible and highly efficient technique; its temporary use means little repercussion of cost on the treatment.

In the second place, preference should be given to patients not susceptible to transplant and whose only possible treatment is haemodialysis, as well as those with added co-morbidity whose prognosis is in jeopardy.

With regard to cost–benefit analysis, this data is summarized in Table 2. It can be concluded that bicarbonate haemodialysis, the use of low flux and high surface area membranes, i.e. high efficiency haemodialysis, and volumetric control of ultrafiltration are low cost improvements with high short-term benefit. The use of high flux synthetic biocompatible membranes has high cost, but also high benefit, although generally in the long term in the majority of cases. The same is true of the use of convective transport in haemofiltration and haemodiafiltration. They are high cost and high benefit, probably also in the long term. Continuous monitoring will have high cost but the benefit is also high and in the short term.

To conclude and summarize, we must remember that dialysis is only able to correct some uraemic syndrome alterations (Figure 6A), such as the retention of small molecules, acidosis, hyperkalaemia and the control of sodium and water. It only partially corrects medium sized molecules and phosphate retention, and imperfectly restores the balance of calcium, anaemia, bleeding, malnutrition, endocrine anomalies and hypertension, which along with hyperlipidaemia are the most important causes of arteriosclerosis and cardiomyopathy, the fundamental causes of death in patients with ESRD.

We must also keep in mind that dialysis is only one part of the treatment for uraemic syndrome, which we should also correct with the proper use of phosphate binders, vitamin D metabolites orally or intravenously, erythropoetin to correct anaemia, adequate nutrition

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**Table 1. Elective indications of high quality/cost haemodialysis techniques**

<table>
<thead>
<tr>
<th>Acute complications</th>
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<tbody>
<tr>
<td>Hospitalization</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Increased catabolism</td>
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<tr>
<td>Vascular access malfunctioning</td>
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<tr>
<td>Risk of malnutrition</td>
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<tr>
<td>Non-transplantable patients</td>
</tr>
<tr>
<td>High co-morbidity patients</td>
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<tr>
<td>Malnourished patients</td>
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</table>

**Table 2. Optimal haemodialysis. Cost–benefit analysis**

<table>
<thead>
<tr>
<th>Technical improvement</th>
<th>Cost</th>
<th>Benefit</th>
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<tbody>
<tr>
<td>Bicarbonate haemodialysis</td>
<td>Low</td>
<td>Acidosis, tolerance, nutrition; short term</td>
</tr>
<tr>
<td>High efficiency haemodialysis</td>
<td>Low</td>
<td>Urea, phosphate; short term</td>
</tr>
<tr>
<td>Volumetric control of UF</td>
<td>Low</td>
<td>Dry weight, tolerance; short term</td>
</tr>
<tr>
<td>High flux haemodialysis</td>
<td>High</td>
<td>Nutrition, β2-M, biocompatibility; short term, long term</td>
</tr>
<tr>
<td>Convective transport (HF, HDF)</td>
<td>High</td>
<td>Nutrition, β2-M, biocompatibility; short term, long term</td>
</tr>
<tr>
<td>Continuous monitoring (biofeedback)</td>
<td>High</td>
<td>Dry weight, Kt/V, other; short term</td>
</tr>
</tbody>
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**Fig. 6.** (A) Dialysis can completely reverse the retention of some small molecules (continuous arrows). It partially improves some disorders of the uraemic syndrome (discontinuous arrows) and has no effect on others. (B) Other therapeutic interventions are necessary to adequately treat the uraemic syndrome.
which should include amino acid supplements, and in extreme cases, growth hormone [57] as well as proper correction of hypertension using anti-hypertensive medication and of hyperlipidaemia with diet and medication (Figure 6B). In this way, and with the proper use of all the technical possibilities of haemodialysis, we can achieve the objectives indicated at the beginning of our study: long-term survival and good quality of life for our patients.

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