Efficacy of haemodiafiltration

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Introduction

In evidence-based medicine, the database supporting a significant role of so-called uraemic toxins on the clinical outcome of end-stage renal disease (ESRD) therapy is poor. Weekly clearances of urea, probably a surrogate parameter of small uraemic toxins, even in well dialysed patients amount only to one-sixth of physiological clearances. A further reduction of urea clearance by an underdelivery of haemodialysis is correlated with a higher mortality. In a population of dialysis patients with a high basic mortality, a reduction of 0.1 of a Kt/V of < 1.3 was associated with a 7% increase in mortality [1]. Interestingly, the same US Renal Data System data did not reveal a further benefit to the mortality rate as a result of increased small solute clearances, a Kt/V of > 1.3 and an urea reduction rate of > 70%.

With larger solutes in the range of 1–60 kDa, the clearance by low-flux and even high-flux dialysis is practically nil [2]. On the basis of weekly solute clearances, it can be estimated that a surrogate parameter for larger potential toxins, such as β2-microglobulin (β2m), is reduced by < 2% with high-flux haemodialysis compared with healthy kidneys. Although high-flux haemodialysis membranes have comparatively high sieving coefficients for solutes of 1–20 kDa, the limited duration of intermittent haemodialysis/haemofiltration therapy restricts the amount of convection (the principal removal route for larger solutes) to a maximum of 100 l/week, which is still far below the weekly physiological solute clearance of 1200 l.

The progress in dialysis technology and the introduction of on-line methods for producing large quantities of infusate from dialysate allow the application of an enhanced convection. Furthermore, high-flux membranes made of synthetic polymers such as polysulphone F60 or F80 show a tendency to absorb a considerable quantity of low molecular weight proteins, at least under convective conditions [3]. Given these technical prerequisites, haemodiafiltration (HDF) in the form of on-line HDF has become a popular method for routine application in ESRD therapy, at least in Europe. At present it can be estimated that > 2 million on-line HDF sessions have been performed in Europe, primarily in Germany, with no serious complications to cast a shadow on the safety of the method reported so far. On the other hand, due to the absence of respective registries, no data are available to support the notion that on-line HDF might be superior to conventional dialysis methods in terms of prevention of long-term complications. No data are available, however, for the use of widespread methods such as high-flux dialysis, which is the most frequent mode of dialysis in some European countries like Germany and France. Thus, the efficacy of HDF has to be assessed using short-term studies involving few patients, taking into account theoretical considerations and indirect evidence from current registries.

Theoretical considerations

When we performed the first haemodialfiltration in 1976, it soon became apparent that HDF is the most potent blood purification method, assuming that the target is the removal of potential uraemic toxins of different molecular sizes. On the understanding that the same high-permeability dialysis membrane was used and identical blood flows and/or identical substitution volumes were compared, HDF was as efficient as haemodialysis in the removal of small substances such as urea, and as efficient as haemofiltration in the removal of larger molecules such as inulin [4]. Thus, the term ‘simultaneous haemofiltration/haemodialysis’, primarily used for HDF, was very appropriate since it implies the simultaneous action of diffusive and convective transport. HDF allows an individualization of dialysis therapy, where the diffusive and the convective part can be dosed separately. The current on-line technology makes it necessary to distribute a defined volume (produced by the dialysate pump) as either dialysate fluid or as substitution fluid, and it also determines the proportion of this distribution that defines whether HDF is nearer a high-flux dialysis, by
favouring the diffusion aspect, or whether it resembles more closely haemofiltration, by favouring convective transport. Thus, on-line HDF allows individual detoxication therapy.

Operational factors that influence the efficacy of HDF

Efficacy of HDF is dependent on the membrane type and surface, blood flow, dialysate flow and substitution volume, as well as the site of substitution volume (pre/post-dilution). Treatment duration and individual factors such as haematocrit also exert an important influence.

In vivo clearances under ‘standard conditions’

Although standard conditions have not yet been defined, the majority of on-line HDF treatments so far has been performed in a conservative manner by applying a blood flow \( (Q_B) \) of ca. \( 300 \text{ ml/min} \), a dialysate flow \( (Q_D) \) of ca. \( 500 \text{ ml/min} \), and a flow of substitution volume \( (Q_S) \) of ca. \( 60 \text{ ml/min} \). From Figure 1 it can be seen that under such operational conditions and with the use of a highly permeable polysulphone membrane, considerable in vivo clearances for small solutes (urea, creatinine) and larger substances (\( \beta_{2m} \)) can be achieved. In comparison, application of a larger membrane surface results in only moderate increases in clearances (Figure 1). For an HDF duration of 4.5 h, a mean reduction rate (pre/post-HDF) for urea of \( 76 \pm 4\% \) and for \( \beta_{2m} \) of \( 63 \pm 4\% \) can be measured under ‘standard’ operational conditions. However, the reduction rate for urea can be modestly increased to \( 84 \pm 2\% \) for urea and distinctly increased to \( 84 \pm 2\% \) for \( \beta_{2m} \) when blood flow is \( 400 \text{ ml/min} \) and substitution flow \( 100 \text{ ml/min} \).

**Influence of blood flow \( (Q_B) \)**

With a large surface membrane at constant \( Q_D \) and \( Q_S \) conditions, increase in \( Q_B \) results in a remarkable increase in clearances for small solutes, whereas \( \beta_{2m} \) clearance can only be augmented moderately (Figure 2).

**Influence of substitute flow \( (Q_S) \) in pre- and post-dilution HDF**

When substitution flow is varied over a range of \( 0–150 \text{ ml/min} \) in post-dilution HDF and \( 0–250 \text{ ml/min} \) in pre-dilution HDF, it can be derived from Figure 3 that small solute clearances are only mildly influenced by \( Q_S \). In contrast, \( \beta_{2m} \) clearance is primarily dependent on the magnitude of \( Q_S \), especially in post-dilution mode (Figure 3). There was a discrepancy between predicted and measured \( \beta_{2m} \) clearances, which can be explained by the fact that \( \beta_{2m} \) is primarily distributed in plasma and not in the whole blood. Thus, there is dependency from haematocrit, and ‘relevant blood flow’ for \( \beta_{2m} \) clearances (primarily plasma blood flow), is inversely correlated to haematocrit. It can also be deduced from Figure 3 that post-dilution HDF is the preferable type of HDF when maximal clearances for small and larger solutes are

![Fig. 1. In vivo clearance under standard haemodialysis filtration conditions. \( Q_B = 300 \text{ ml/min; } Q_D = 500 \text{ ml/min; } Q_S = 60 \text{ ml/min.} \) Based on 32 (24) treatment conditions in the range \( Q_B = 300–500 \text{ ml/min and } Q_S = 0–34 \text{ ml/min.} \)](image)

![Fig. 2. Clearance as a function of blood flow \( Q_B \). Fresenius = 2.2 \text{ m}^2, \( Q_B = 800 \text{ ml/min, } Q_S = 60 \text{ ml/min, on-line, post-dilution.} \)](image)
targeted. When the maximal removal of β2m is the aim, convective transport should be maximally applied. Figure 4 shows that, irrespective of blood flow, convection can increase β2m clearances by a factor of two to three when compared with haemodialysis conditions (Figure 4).

Under clinical conditions, however, convection and thereby substitution volume is closely associated to blood flow. Depending on haematocrit in post-dilution HDF, only about one-quarter of blood flow can be maximally filtered. Usually, there is a threshold in Q-filtrate divided by Q-plasma of ca. 0.5, where a further increase can result in considerable albumin losses.

When dialysate flux is 500 ml/min, further increases lead only to insignificant increases in urea and β2m clearances.

**Summary**

Figure 5 summarizes the findings with a focus on small solutes (urea). Efficacy of HDF can be increased only modestly by increasing dialysate surface, whereas increase in blood flow from 300 to 500 ml/min leads to an increase of 40%. The addition of convection (120 ml/min) under such conditions increases urea clearances only moderately.

Figure 6 summarizes the options for optimizing β2m clearances. An increase in surface urea of the dialyser and augmentation of blood flow per se can increase the removal of larger solutes. The decisive factor, however, is the presence of convection.

**Clinical efficacy**

On-line HDF appears to be a safe procedure when applied over 13 years [5]. It has consistently been shown for a long time that pre-treatment blood concentrations of β2m in patients on long-term HDF are lower when compared with haemodialysis patients. In a prospective controlled study, β2m blood levels during on-line HDF were about half of the haemodialysis levels and post-HDF concentrations were nearly normal [6]. Nevertheless, convincing data of the effects of HDF on the development or course of carpal tunnel syndrome or dialysis amyloidosis-related bone cysts are non-existent. The same is true for haemodynamic effects of HDF. It has been stated that on-line HDF is superior to haemodialysis in saving erythropoietin costs. However, when an appropriately efficient low-flux haemodialysis is applied, the so-called superior clinical effects of HDF vanish [6].

The present dilemma of a biochemically efficient method on the one hand and lack of clinical efficiency on the other can only be solved by a prospective randomized study including large numbers of patients. Due to the theoretical advantages of eliminating a similar spectrum of solutes as the kidneys in the physiological setting, on-line HDF appears to be the most promising candidate for such a study.
Fig. 5. Contribution of surface, blood flow and treatment modality for urea clearances (in vivo data). Increase relative to 100%. Based on 32 treatment conditions in the range $Q_B = 300$–500 ml/min and $Q_S = 0$–240 ml/min.

Fig. 6. Contribution of surface, blood flow and treatment modality for β2m clearances (in vivo data). Increase relative to 100%. Based on 32 treatment conditions in the range $Q_B = 300$–500 ml/min and $Q_S = 0$–240 ml/min.

References