Blood Purification

Slow Extended Nocturnal Home Hemodialysis Shows Superior Adequacy Compared to In-Center Dialysis: A Mathematical Analysis

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Key Words

Chronic renal failure · Vascular access · Access recirculation

Abstract

Extended nocturnal home hemodialysis has gained renewed interest. However, no removal data for single/double needle (lumen) (SL and DL, respectively) or for low/high blood flow in extended dialysis are available. Therefore, we studied dialysis adequacy in different nocturnal home hemodialysis strategies. Coupling a kinetic with a dialyzer model, we calculated a reduction ratio from pre- to post-dialysis (RR) and total solute removal (TSR) of urea, methylguanidine (MG), β_2-microglobulin, and phosphate. Simulations were done for dialysis with blood flow Q_b350 ml/min (DL-4h), extended DL high flow with Q_b350 (DL-HF-8h) and low flow with Q_b175 (DL-LF-8h), and SL with Q_b273 (SL-8h). Compared to DL-4h, TSR was 28–59% larger for DL-HF-8h. TSR was most increased for β_2-microglobulin (18%) with DL-LF-8h, and for MG (35%) with SL-8h. Furthermore, RRs were equal (DL-LF-8h), higher (SL-8h), and even more increased (DL-HF-8h) for all studied solutes. In the home setting, DL-LF-8h and SL-8h are safe and promising strategies.

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Background

Extended dialysis has gained renewed interest over the last decade, especially since it has been associated with a better outcome in observational studies [1, 2] and with more solute removal, even with low blood flows [3]. In dialysis centers, mainly short dialysis (4 h) is performed, while extended nocturnal hemodialysis (NHD) is more feasible in the homecare setting. There is however still uncertainty on the optimal blood and dialysate flows for this extended form of dialysis. High flows induce more frequent alarms, higher costs of water and electricity, and higher consumption of dialysate concentrates, with the need to change containers during the night. The question under study is whether the loss of adequacy due to lower flows in nocturnal home hemodialysis (NHHD) versus high flows in short in-center dialysis is compensated by the longer dialysis duration.

Furthermore, in case of a graft or fistula, double needle puncturing in home dialysis is often unpractical if patients are dialyzing without assistance, and is substantial-

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ly more dangerous in case of accidental needle dislodgement with subsequent blood loss out of the venous needle.

Since no data are available on solute removal for single versus double needle/lumen dialysis or for high versus low blood flows in extended dialysis, we developed a mathematical model combining a two-compartment kinetic model for different uremic toxins with a hemodialysis (HD) model. Herewith, we compared total solute removal and reduction ratios in different settings of extended NHHD versus short dialysis.

Methods

In order to compare extended HD adequacy under different operation modes, a two-compartment kinetic model, simulating the solute transfer in a patient, was coupled with a dialysis model, simulating the solute transfer in a hemodialyzer, and reduction ratio (RR) and total solute removal (TSR) was calculated for each parameter setting.

The Calibrated Mathematical Patient/Dialyzer Model
The coupled mathematical patient/dialyzer model in the setting of a double needle (lumen) (DL) and single lumen (SL) approach is shown in figures 1 and 2, respectively. Solute transfer in the patient was simulated according to two-compartment kinetics, distinguishing between a perfused volume V_1 and a non-perfused volume V_2, both characterized by a homogeneous concentration and solute generation rate G_1 and G_2. Furthermore, solute is removed from V_1 by HD with dialyzer clearance K, and transported between both compartments, proportional to the intercompartment clearance K_{12}. Ultrafiltration (Q_{uf}) was assumed to occur proportional in both compartments.

The time variation of the compartment concentrations C_1 and C_2 was, for a particular solute, determined by solving the mass balance equations for both compartments [4]:

$$\begin{cases} \dfrac{d(V_1 C_1)}{dt} = G_1 + K_{12} \times (C_2 - C_1) - K \times C_{bi} & \text{(1a)} \\[2mm] \dfrac{d(V_2 C_2)}{dt} = G_2 - K_{12} \times (C_2 - C_1) & \text{(1b)} \end{cases}$$

Blood concentration variation over the dialyzer was, for a particular solute, determined by solving the mass balance equation in the dialyzer:

$$C_{bi} \times Q_{bi} + C_{di} \times Q_{di} = C_{bo} \times Q_{bo} + C_{do} \times Q_{do} \qquad (2)$$

C_{bi} and C_{bo} are the blood inlet and outlet concentrations, and C_{di} (zero) and C_{do} the dialysate inlet and outlet concentrations with respect to the dialyzer.

With a DL approach (fig. 1), blood inlet concentration C_{bi} is equal to the concentration in the perfused compartment C_1 (see equation 1a).

In case of a SL double pump dialysis treatment (fig. 2), one cycle can be subdivided in two phases: an arterial phase during which blood is pumped from the patient into the buffer reservoir at a flow rate Q_{ap}, and a venous phase during which the blood is
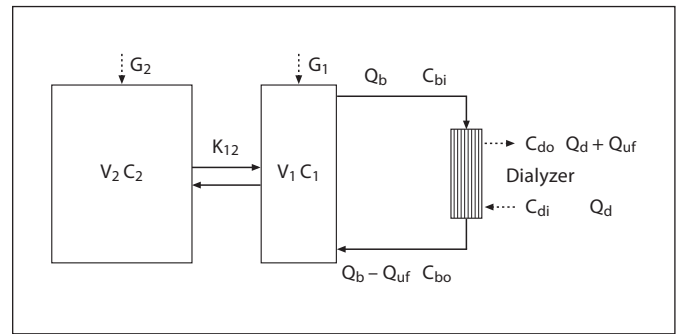

Fig. 1. Extended mathematical model combining a kinetic model and a dialysis model using a double needle/lumen access approach. V_1 = Perfused volume; V_2 = non-perfused volume; C_1 and C_2 = concentration in V_1 and V_2; K_{12} = intercompartment clearance; G_1 and G_2 = generation rate in V_1 and V_2; Q_b = blood flow; Q_d = dialysate flow; Q_{uf} = ultrafiltration flow; C_{bi} and C_{bo} = blood inlet and outlet concentration; C_{di} and C_{do} = dialysate inlet and outlet concentration.
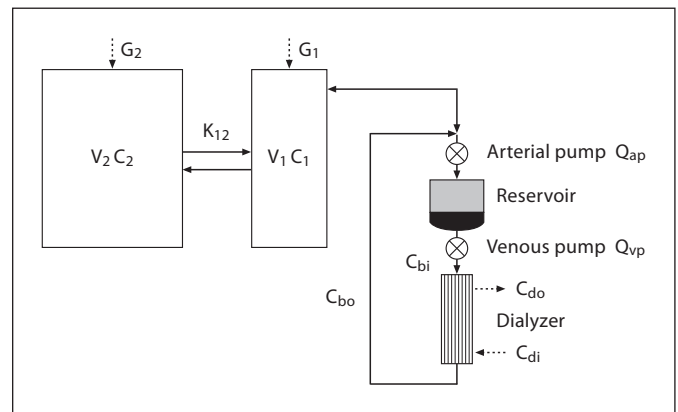

Fig. 2. Extended mathematical model combining a kinetic model and a dialysis model using a single needle/lumen approach. V_1 = Perfused volume; V_2 = non-perfused volume; C_1 and C_2 = concentration in V_1 and V_2; K_{12} = intercompartment clearance; G_1 and G_2 = generation rate in V_1 and V_2; Q_{ap} = blood flow during arterial phase; Q_{vp} = blood flow during venous phase; C_{bi} and C_{bo} = blood inlet and outlet concentration; C_{di} and C_{do} = dialysate inlet and outlet concentration.

pumped, at a flow rate Q_{vp} from the buffer reservoir through the dialyzer and back towards the patient. Herewith, Q_{vp} might be set higher than Q_{ap} according to a pump ratio larger than 1 and, hence, an effective blood flow rate of more than $Q_{ap}/2$ can be obtained. Within each cycle, the blood volume in the buffer reservoir (V_{res}) is strictly controlled between a minimum and maximum level (V_{min} and V_{max}). This implies that blood entering the buffer reservoir during an arterial phase is mixed with V_{min} blood that was still in the buffer reservoir after the previous venous

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Table 1. Kinetic parameters for urea, MG, β_2M, and P

	Urea	MG	β_2M	P
Reference	Eloot et al. [5]	Eloot et al. [5]	Stiller et al. [6]	Spalding et al. [7]
MW	60 Da	73 Da	11,800 Da	31 Da
$V_{1\text{-pre}}$	6.4 l	8.0 l	2.56 l	13 l
$V_{2\text{-pre}}$	36.3 l	94.6 l	7.44 l	27 l
$C_{1\text{-pre}} = C_{2\text{-pre}}$	24.0 mmol/l	3.7 μmol/l	33 mg/l	1.7 mmol/l
K_{12}	822 ml/min	1,025 ml/min	56.3 ml/min	300 ml/min
G_1	310 mmol/24 h	46 μmol/24 h	0	0
G_2	0	0	218 mg/24 h	0
ER	0.84	0.79	0.19	0.57

MG = Methylguanidine; β_2M = β_2-microglobulin; P = phosphate; MW = molecular weight; $V_{1\text{-pre}}$ = predialysis perfused volume; $V_{2\text{-pre}}$ = predialysis non-perfused volume; $C_{1\text{-pre}}$ and $C_{2\text{-pre}}$ = predialysis concentration in V_1 and V_2; K_{12} = intercompartment clearance; G_1 and G_2 = generation rate in V_1 and V_2; and ER = dialyzer extraction ratio, defined as the concentration reduction from inlet to outlet.

Table 2. Operating parameters in the different dialysis settings

	DL-HF-4h	DL-HF-8h	DL-LF-8h	SL-8h
Session duration, min	240	480	480	480
Post dialysis rebound, min	60	60	60	60
Q_b, ml/min	350	350	175	273
Q_{uf}, l/h	1	0.5	0.5	0.5
Pump ratio, Q_{vp}/Q_{ap}	n/a	n/a	n/a	1.2
V_c (12 Fr), ml	n/a	n/a	n/a	2.9
V_{min}, ml	n/a	n/a	n/a	10
V_{max}, ml	n/a	n/a	n/a	55

DL = Double lumen; SL = single lumen; HF = high flow; LF = low flow; Q_b = blood flow; Q_{uf} = ultrafiltration flow; Q_{vp} = blood flow during venous phase; Q_{ap} = blood flow during arterial phase; V_c = catheter volume; V_{min} = minimum buffer volume; V_{max} = maximum buffer volume.

phase. Equation 1a should in this case be changed into equation 3a for the arterial phase (with $Q_{bi} = Q_{ap}$) and 3b for the venous phase (with $Q_{bo} = Q_{vp} - Q_{uf}$):

$$\frac{d(V_1 C_1)}{dt} = G_1 + K_{12} \times (C_2 - C_1) - Q_{ap} \times C_{bi} \tag{3a}$$

$$\frac{d(V_1 C_1)}{dt} = G_1 + K_{12} \times (C_2 - C_1) + (Q_{vp} - Q_{uf}) \times C_{bo} \tag{3b}$$

Furthermore, the concentrations C_{bi} and C_{bo} are not constant within one phase, since both phases can each be split into two extra phases. During the arterial phase the cleansed blood (from the previous venous phase) in the needle/catheter volume (V_c) first enters the buffer reservoir, followed by uncleansed blood from the patient's perfused compartment. During the venous phase the uncleansed blood in V_c (from the previous arterial phase) first flows back to the patient's perfused compartment, followed by cleansed

blood. During all phases, we accounted for the number of cycles it takes for the blood to flow through the dialysis circuit.

Studied Solutes
Four representative solutes were studied, each with a remarkably different kinetic behavior. The data of two-compartment calibrated kinetic models were taken from literature for urea and methylguanidine (MG) [5], β_2-microglobulin (β_2M) [6], and phosphate (P) [7] (see table 1).

Studied Vascular Access and Dialysis Strategies
For each of the four solutes, four different scenarios were studied: the standard double needle (lumen) 4 h dialysis at high flow Q_b350 ml/min (DL-HF-4h), and three extended 8 h dialysis sessions: two double lumen with either high flow Q_b350 ml/min (DL-HF-8h) or low flow Q_b175 ml/min (DL-LF-8h), and one single lumen (SL-8h). All treatment parameters in case of using a 12-Fr central venous catheter can be found in table 2. For the SL approach, also the use of a needle ($V_c \approx 0.5$ ml) was considered.

Simulations and Adequacy Parameters
The coupled mathematical patient/dialyzer model was written in Matlab (R2010b; The MathWorks Inc., Natwick, Mass., US) and iteratively solved the mass balance equations for a complete dialysis session. We calculated the RR (%) for all studied solutes in the perfused (RR_C1) as well as in the non-perfused compartment (RR_C2), from the pre- and immediate post-dialysis solute concentrations:

$$RR\_Cx = \frac{C_{x\text{-pre}} - C_{x\text{-post}}}{C_{x\text{-pre}}} \times 100 \tag{4}$$

Furthermore, TSR was calculated during an entire dialysis session as the amount of solute found in the spent dialysate. From the mass balance equation in the dialyzer, TSR at time point T can be calculated as:

$$TSR = \int_0^T C_{bi} \times \left(ER \times Q_{bi} + \left((1 - ER) \times Q_{uf}\right)\right) \times dt \tag{5}$$

Table 3. Adequacy parameters for different solutes and different dialysis settings

	RR_C1, %				RR_C2, %				TSR, mmol*			
	4 h	8 h			4 h	8 h			4 h	8 h		
	DL-HF	DL-HF	DL-LF	SL	DL-HF	DL-HF	DL-LF	SL	DL-HF	DL-HF	DL-LF	SL
Urea	73.6	90.5 (23)	71.8 (−2)	84.1 (14)	66.8	88.5 (32)	68.6 (3)	81.6 (22)	787	1,031 (31)	851 (8)	957 (22)
MG	51.0	70.8 (39)	47.3 (−7)	61.0 (20)	38.6	63.7 (65)	41.1 (6)	54.0 (40)	0.17	0.27 (59)	0.18 (6)	0.23 (35)
β_2M	66.3	83.8 (26)	60.2 (−9)	80.6 (22)	31.0	66.3 (114)	39.6 (28)	62.2 (101)	298	380 (28)	353 (18)	338 (13)
P	68.6	87.8 (28)	68.0 (−1)	81.5 (19)	52.8	81.6 (55)	60.3 (14)	74.5 (41)	44	59 (34)	47 (7)	54 (23)

RR = Reduction ratio; TSR = total solute removal; DL = double lumen; SL = single lumen; HF = high flow; LF = low flow; MG = methylguanidine; β_2M = β_2-microglobulin; P = phosphate.
* mg for β_2M. The value in parentheses is the percentage increase of the adequacy parameter, compared to 4 h DL-HF.

With ER, the extraction ratio, as defined as the concentration reduction across the dialyzer from the inlet to the outlet:

$$ER = \frac{C_{inlet} - C_{outlet}}{C_{inlet}} \tag{6}$$

Results

RR and TSR are presented in table 3 for the four scenarios and the four solutes under study. Compared to the 4 h HD, RRs are equal in DL-LF-8h, higher in SL-8h, and even more increased in DL-HF-8h mode, and this for all studied solutes.

For the DL-LF-8h and the SL-8h approach, TSR was for all solutes higher compared to 4 h HD (range 6–18 and 13–35%, respectively). TSR with the SL-8h approach was even larger compared to the DL-LF-8h, except for β_2M.

By further increasing the flow during extended dialysis (from low flow DL-LF-8h to high flow DL-HF-8h), TSR increases but is not doubled compared to 4 h HD: only 7–30% higher compared to DL-LF-8h, and even only 7–15% higher compared to SL-8h HD. For β_2M, differences in TSR with DL-HF-8h are limited to only 7% (DL-LF-8h) and 11% (SL-8h).

Finally, with the single needle approach, RR and TSR, respectively, were only 1 and 2% higher compared to the values found with the SL CVC (data not shown).

Discussion

We demonstrated that TSR during extended HD is higher when compared to 4 h HD for all studied solutes, even with low flow or using a single lumen approach. Although there was more solute removal with DL-HF-8h HD as compared to DL-LF-8h HD, these differences were rather limited, especially for solutes which are difficult to remove, such as β_2M. Even in the 8 h single lumen HD approach, TSR was higher than with 4 h standard HD. Hence, our data demonstrate that vascular access has only a limited impact on TSR during extended dialysis regimens, especially for solutes with retarded multicompartment behavior.

In extended slow dialysis (i.e. low blood and/or dialysate flow with DL-LF-8h HD), the lower solute clearance is counterbalanced by a financial benefit and better patient quality of life. Especially in the home dialysis setting, the use of low dialysate and/or blood flows is of relevance, as this reduces the frequency of alarms, and avoids the necessity to wake up during the night to exchange dialysate concentrate bags. All this substantially adds to the quality of sleep and thus quality of life of the patient. Furthermore, lower dialysate flows also reduce costs related to electricity and water consumption, again of high relevance in the home dialysis setting, where these extra expenses in many countries are directly on the patient's costs.

A single needle access can be of importance for patients who dialyze without assistance, as double needle puncturing is cumbersome under these conditions. A single puncture also results in slower deterioration of vascular access and less access-related problems [8]. In addition, single needle dialysis enhances safety in case of disconnection of lines. Even for patients dialyzing with a central venous catheter as access, our findings are relevant, as several observational studies reported a lower incidence of complications in single versus double lumen catheters [9–11]. Our results indicate that these low blood and dialysate flows, even in a single needle setting (i.e.

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SL-8h), can be used without jeopardizing solute removal. Notably, the calculated TSR with SL-8h is very likely an underestimation since the same extraction ratio as with DL HD was used in our setup, while the higher blood inlet flow during the venous phase (see fig. 2) results in more internal filtration and with it, more solute removal.

It can be remarked from the present results that increasing dialysis duration has most impact on TSR, with none or only limited impact on RR. A similar trend was found previously in an in vivo cross-over study of 4, 6 and 8 h HD [3]. This seemingly discrepancy can be explained by the fact that during (slow) 8 h dialysis, more solute can be transported from the non-perfused into the perfused compartment where it can be removed by dialysis. Hence, this higher TSR results in a smaller post-dialysis rebound with 8 h dialysis, which is not necessarily reflected in a higher RR.

The fact that our study is purely based on mathematics should not be regarded as a drawback. Our simulations can be considered as being performed in an 'average patient on dialysis' since we used kinetic models that were previously calibrated on patient's data [5–7]. However, some weaknesses of the modeling approach should be highlighted.

First, for all scenarios, we started, per solute, from the same conditions as indicated in table 1, although several parameters could be different between 4 and 8 h dialysis, and between the first, second, and third dialysis session of the week (i.e. pre-dialysis concentrations and compartment volumes). In steady state, for instance, pre-dialysis concentrations will be lower with 8 h dialysis, while TSR, which is equal to generation rate, will become equal again to that during 4 h dialysis. Over a longer period, time-averaged concentrations will be lower with extended dialysis. The aim of our study, however, was to compare the adequacy of different scenarios for a single session, such that a mathematical model based on an 'average patient' with same pre-dialysis conditions is a useful tool.

Second, the solute extraction ratio was considered constant for all scenarios due to a lack of knowledge of how ER exactly changes with blood and/or dialysate flows. Hence, since ER should be increased for slower dialysis, our RR and TSR results for low flow dialyses (i.e. DL-HF-8h and SL-8h HD) will be even higher in vivo.

And third, per studied solute, the calibrated kinetic models were taken from literature. Herewith, phosphate modeling was performed using the calibrated two-compartment model, although it cannot accurately describe plasma concentrations as compared to the three- and four-compartment models [7], i.e. the modeled concentrations decrease slower during the first and faster during the second half of dialysis. Since the use of more complex models would need too many additional assumptions, and since we are mainly interested in pairwise comparisons of RR and TSR between different scenarios, our method seems quite defendable.

Besides these weaknesses, our mathematical study has some important strengths as well. Different types of solutes were modeled with a totally different kinetic behavior in the patient. Furthermore, the mathematical modeling of SL dialysis included several details like stroke volumes, arterial-venous pump ratio, buffer volumes and recirculation.

Although the present findings might not all be very surprising to each clinician [11], it is worthy to see the conclusions based on mathematical modeling, independent from the variability present in the general patient population, and from the variability present in the starting conditions of different dialysis strategies. Our data clearly shows that the loss of adequacy due to lower flows in NHHD can be compensated by longer dialysis duration, compared to short in-center dialysis.

Conclusion

Although high blood and dialysate flows still result in higher TSR during extended 8 h dialysis as compared to lower flows, the gain is limited, especially for solutes with more complex compartment behavior, such as $\beta_2 M$. Even when using a single lumen approach, TSR is superior in extended 8 h dialysis compared to standard 4 h dialysis. In view of the practical constraints of the home dialysis setting, low flow dialysis, even with single lumen approach, is a defendable option.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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