From adequate to optimal dialysis Long 3 x 8 hr dialysis: a reasonable compromise

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SUMMARY

Long dialysis (3 × 8 hours/week) has been used in Tassin for three decades now, without method modifications. Results have been excellent considering both morbidity and mortality. Best survival compared to short dialysis is mainly due to low cardiovascular mortality. It is probably due to a good control of arterial hypertension, without antihypertensive medication, and the low rate of intradialytic hypotension. Slow ultrafiltration, allowed by the extended dialysis session, associated with a low-salt diet and a moderate interdialysis weight gain, tend to normalize extracellular volume and ensure normotension. Long hemodialysis assure a good dialysis dose in terms of small and even middle molecules, with good nutrition, anemia correction, phosphate and potassium control with few drugs. Optimal dialysis needs several conditions, each of them necessary. Time seems a central factor, providing a high treatment safety margin. While it is quite difficult to achieve excellent dialysis results with short sessions, long-dialysis is easy to perform with high reliability.

Key words: ***Long hemodialysis. Optimal dialysis. Cardiovascular mortality.***

DE LA HEMODIÁLISIS ADECUADA A LA ÓPTIMA. DIÁLISIS LARGA 3 × 8 H: UN COMPROMISO RAZONABLE

RESUMEN

La diálisis prolongada de 3 × 8 horas/semana ha sido usada en Tassin durante tres décadas sin modificaciones en el método. Los resultados han sido excelentes en términos de morbilidad y mortalidad. La mejor supervivencia respecto de la referida en la diálisis corta es debida principalmente a una mortalidad cardiovascular baja. Esta a su vez se debe al buen control de la tensión arterial, sin necesidad de medicación antihipertensiva, y a la baja incidencia de hipotensiones intradiálisis. La ultrafiltración suave gracias a la duración prolongada de la sesión, asociada a una dieta baja en sal y a una ganancia de peso interdiálisis moderada tienden a normalizar el volumen extracelular y aseguran la normotensión. La diálisis prolongada asegura una buena dosis de diálisis en términos de pequeñas e incluso medianas moléculas, con una buena nutrición, la corrección de la anemia, el control de fosfato y el control de potasio con pocas dosis de medicación. La diálisis óptima necesita de varias condiciones, todas ellas obligatorias. El tiempo parece un factor clave, aportando un alto margen de seguridad para el desarrollo del tratamiento; mientras que es bastante difícil realizar una diálisis corta excelente, la diálisis prolongada es fácil de llevar a cabo con gran fiabilidad.

Palabras clave: ***Hemodiálisis prolongada. Diálisis óptima. Mortalidad cardiovascular.***

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INTRODUCTION

Long hemodialysis (HD) 3 × 8 to12 hours per week on 1 square-meter flat plate cuprophan dialyzers- was in the 70's the empirical most achieved form of dialysis, the «gold standard»[1]. Technical advances, changing scientific views on uremia pathophysiology, but even more social and economical pressure to make a better use of the scarce HD stations led to the apparition and development of shorter dialysis sessions. In Tassin the 3 × 8 hr/wk dialysis has remained the unique treatment method for all patients for three decades. Since 1995, a «short» dialysis schedule (3 × 5-6hr/wk) has been set up. About one third of the patients are using this shortened schedule. The overall Tassin experience represents about 8,200 patient-years.

PATIENTS AND METHODS

Three sessions of 7-8 hours per week are performed overnight during the sleep or in the daytime according to the patient's possibility and preference. Home dialysis has been used in more than half of the patients up to the 80's. But the increasing number of dialysis units, the higher transplantation rate and the worsening patients case-mix have led to a steady decrease of the proportion of patients treated at home. Only 5% of Tassin patients are now treated at home and 10% in limited care facilities.

Until 1995 the technical setting was poorly biocompatible, using cuprophan® membranes, acetate buffer and plain softened water. A 220 to 250 ml/min blood flow has been used throughout the experience (300 ml/min for the patients on the 5-6 hr/wk schedule). Since 1996 bicarbonate buffer has been substituted to acetate. In 1998 low-flux polysulfone dialyzers have replaced cellulosic ones. For «short» HD patients large area size dialyzers (1.7 to 2.5 sq-meter) are used. Since 2001 reverse osmosis completed by ultrafiltration has replaced the simple water softening system.

Whatever the session duration the dose provided is large: the mean delivered spKt/V (2nd generation Daugirdas method) is over 2.0 per session. The mean normalized PCR is over 1.2. The mean protein and calories intakes are 1.2 g/kg and 32 kgcal/kg/day respectively. The patients are requested to maintain a low salt diet. No salt is added to the food and processed food is avoided. The average sodium chloride intake is 5 g per day. The mean interdialytic weight gain is 1.7 kg (2.5% of mean dry weight). The dialysate sodium is set at 138 mmol/L. The patients are not requested to restrain from drinking. During the initial few weeks of dialysis each patient undergoes a systematic antihypertensive treatment withdrawal in conjunction with the lowering of his extracellular volume to achieve «dry weight» and normotension[2].

Altogether 1,380 patients have been treated by maintenance HD since 1968 in Tassin. As elsewhere the incident population has changed drastically with calendar years. The mean age at start has steadily increased from 35.1 in 1968 to 61.9 years in 2003. During the same period diabetes mellitus and nephrosclerosis prevalence in the incident population crept up from 2 to 40% and from 3 to 20% respectively. In the same time the proportion of patients starting dialysis with cardiovascular (CV) comorbidity increased from 6 to 61%.

Table I. Demographic and Comorbid factors *vs.* Survival at 5, 10, 15 and 20 yrs of Dialysis

		% patients surviving				
Initial age:	**patient #**	**5 yr**	**10 yrs**	**15 yrs**	**20 yrs**	**p**
< 35 y.o.	186	91	85	79	71	
35-44 y.o.	176	85	76	60	34	
45-54 y.o.	269	81	67	45	19	
55-64 y.o.	257	70	40	16	5	
65-74 y.o.	263	47	24	5	3	
≥ 75 y.o.	197	24	2	–	–	< 0.001
Etiology:						
Chronic Glomerulonephritis	290	80	69	51	37	
Intersticial nephritis	183	83	65	49	27	
Polycystic kidney disease	129	87	70	36	31	
Nephrosclerosis	236	51	28	13	8	
Diabetes	233	36	10	2	–	
Systemic disease/ cancer	85	48	30	15	9	
Others	64	67	59	49	32	
Unknown	128	78	56	33	12	< 0.001
Atheroma:						
2 cardiovascular antecedents	222	32	14	3		
1 cardiovascular antecedent	281	55	27	10	3	< 0.001
no antecedent	650	84	69	52	35	
Gender:						
Females	453	73	56	38	27	
Males	895	63	46	29	19	0.005
TOTAL	1,348	69	46	34	20	

Table II. Evolution of age and cause of renal failure in 6 Tassin calendar cohorts

Calendar years	68-'73	74-'79	80-'85	86-'91	92-'97	98-'03
Age at dialysis start	39.2	45.0	46.4	56.8	62.0	62.8
Diabetes mellitus (%)	3.2	4	4.9	31	36.5	36.7
Nephrosclerosis (%)	6.1	10.4	17.2	23.1	21.3	20
Glomerulonephritis	39.2	33.5	23.1	20.6	16.9	11.9
Other causes (%)	51.5	52.1	54.8	25.3	25.3	31.4

RESULTS

1/Mortality

Due to the increased risk factors, crude mortality has steadily increased along calendar years. On table I the proportion of patients surviving after 5 to 20 years of treatment is reported as a function of age, cause of renal failure, cardiovascular story and gender. Females tend to survive better than males. Age, cause of renal failure and CV story have a strong impact on survival. These risk factors prevalence has changed over years as shown on table II. The mean age at dialysis start has crept up by about 25 years between the first and the sixth calendar cohorts. In the same cohorts the proportion of diabetic patients has been multiplied by a factor of 10. The important change in the case mix has a crucial influence on mortality (table III). Although all patients received the same unchanged treatment, due to the change in risk factors, survival has steadily decreased.

To adjust for patients' risk factor the Standardized Mortality Ratio (SMR)[3] adjusts for age, race, sex and cause of renal failure using USRDS standard mortality table as the reference. The average observed mortality in Tassin is about 45% of the expected value for US patients similar in age, race and cause of renal failure (table IV). It has remained quite stable over the last 15 calendar years in spite of the impressive worsening of the patients case-mix.

Table III. Demographic and Comorbid factors and Patient Survival at 5, 10, 15 and 20 years Percentage of Patients Surviving

Calendar cohort	patients number	5 yr	10 yrs	15 yrs	20 yrs
< 1975	165	88	75	58	40
1975-1979	168	82	71	50	36
1980-1984	141	82	62	36	13
1985-1989	234	69	47	25	–
1990-1994	275	52	27	–	–
1995-1999	165	49	–	–	–
≥ 2000	212	–	–	–	–

Table IV. Standardized Mortality (SMR) *vs* USRD

Calendar year	O/E* death	SMR	p value
1989	23/43,7	0,53	< 0,005
1990	14/42,4	0,33	< 0,001
1991	18/44,7	0,40	< 0,001
1992	15/46,1	0,33	< 0,001
1993	23/47,7	0,48	< 0,001
1994	20/50,3	0,40	< 0,001
1995	23/57	0,40	< 0,001
1996	27/56,4	0,51	< 0,001
1997	25/48,5	0,52	< 0,001
1998	26/47,6	0,55	< 0,005
1999	27/67,5	0,41	< 0,001
2000	38/71,1	0,53	< 0,001
2001	27/74,1	0,36	< 0,001
2002	32/75,33	0,42	< 0,001
2003	35/70,6	0,50	< 0,001

* O/E = observed/expected deaths.

A comparison of Tassin mortality to the only available long-term French series of 4-5 hr HD reported several years ago[4] shows that long HD mortality was lower (52.4 *vs*. 99 deaths per 1,000 pt-yrs, $p < 0.001$). There was no difference in specific (infection, cancer, or others) causes of death between the 2 series out of CV mortality which was much lower on long HD (19.8 *vs*. 44.6 CV deaths per 1,000 pt-yrs, $p < 0.001$).

We splitted the Tassin long dialysis population in 2 equal number cohorts according to the integrated pre-dialysis mean arterial pressure (MAP) and analyzed their survival. The cohort with the lowest MAP (MAP = 89 mmHg) had a significantly lower mortality ($p = 0.003$) than the one with a slightly elevated MAP (MAP = 107 mmHg). The difference was mainly explained by the lower CV mortality in the

Table V. Tassin patients mortality using Cox proportional hazard mode

	Regresion coefficient	95% Confidenc. e interval	Relativ. e risk	95% Confidenc. e interval
Age at start	0,049	(0,033, 0,067)	1,05	(1,033, 1,069)
Diabetes	0,606	(0,131, 1,081)	1,833	(1,139, 2,947)
CV[1]	0,631	(0,204, 1,057)	1,879	(1,226, 2,878)
MM[2] index	-0,404	(-0,681,-	0,668	(0,506, 0,880)
kt/V urea	0,153	(-0,348, 0,675)	1,165	(0,706, 1,964)
Mean MAP[3]	0,033	(0,011, 0,056)	1,034	(1,011, 1,057)
Serum Albumin	-0,029	(-0,064, 0,007)	0,971	(0,938, 0,993)

[1]: CV = Cardiovascular antecedent (Myocardial infarction, angina, cerebrovascular transient ischemic attack, peripheral iscemia).
[2]: MM = Middle Molecule.
[3]: MAP = Mean Arterial Pressure.

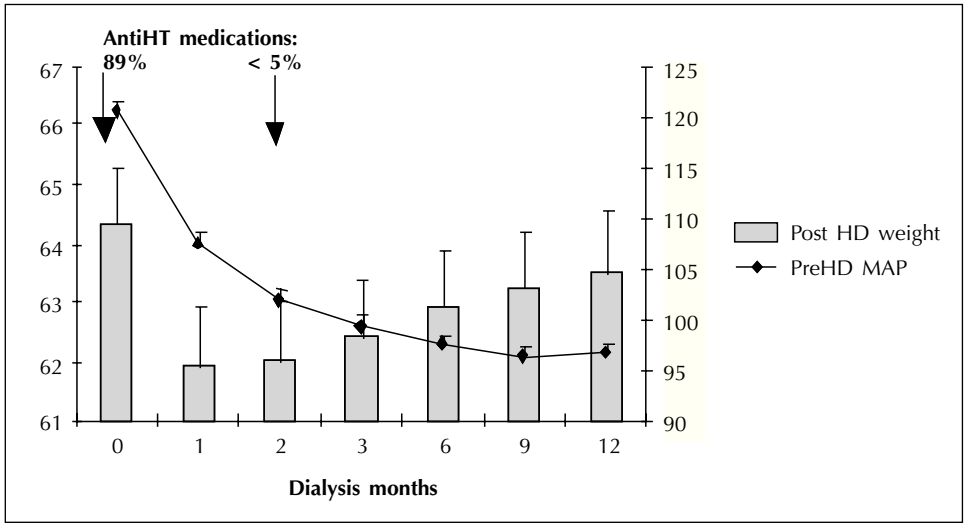

Fig. 1.—Evolution of post-dialysis weight (kg) and pre-dialysis mean arterial pressure (mmHg) in 712 patients 12 first months of long hemodialysis.

lower MAP subgroup, 12.7 *vs.* 28.1 CV deaths per 1,000 pt-yrs ($p < 0,01$)[5].

The Cox proportional hazard model shows that age, cause of renal failure and CV antecedents are very powerful predictors of mortality[6] (table V). These factors are not amenable to medical action. Among treatment-related factors urea Kt/V does not significantly predict survival, while time-dependent middle molecule (MM) index[7] does (the higher the MM removal rate, the longer the survival). But the strongest predictors of mortality are serum albumin and pre-dialysis MAP.

2/Morbidity

An essential feature of long HD is that it regularly achieves a good control of blood pressure (BP). The mean observed casual pre-dialysis BP (128/79 mmHg) is within normal range. Ambulatory BP monitoring values are also within normal.

Intradialytic hypotensive episodes are more scarce on long than on shorter HD: 49 events per 1,000 sessions on 8 hr HD *vs.* 129 events on 5 hr HD ($p < 0.005$).

The relationship between extracellular volume (ECV) and BP is illustrated by the first month of long HD treatment displayed on figure 1. The initial sharp ECV drop contrasts with the more progressive pre-dialysis MAP decrease over months. This lag time between changes in ECV and BP[8] is an important practical point that must be explained to patients. After 2 months of dialysis (fig. 1) BP continues to decrease but weight increases due to a gain in lean and fat body mass (improved appetite and anabolism at start of maintenance HD). One of the main difficulties in assessing clinically the dry weight in HD patients is to distinguish the respective part of weight change due to ECV and to lean and fat body mass change[9].

Tassin average hematocrit is 35% with EPO being used for 55% of the patients. The initial pre-dialysis mean serum albumin (36,7 g/l) increases to 41.6 at 2 years and remains stable after 20 years. Due to its intracellular repartition and slow intercompartimental transfer rate, PO4 can be assimilated to a MM. Hence PO4 control is rather easy in long dialysis. The mean overall pre-dialysis serum PO4 is 1.44 ± 0.33 mmol/l. Only 30% of the long HD patients need to take a PO4 binder.

3/Switching the same group of patients from short to long HD and conversely

We had some years ago the opportunity to switch the same groups of patients from short to long HD and conversely[10]. Among 124 unselected patients dialyzed in Tassin while waiting for a kidney transplantation (all treated for 6 months or more on a 3 x 5 hr/wk HD) half were on antihypertensive treatment. After 3 months of 3 x 8 hr HD antihypertensive medications had been stopped in all but one patient, the average post-dialysis weight was reduced by 0.5 kg and pre-dialysis MAP was back to normal (mean = 101 mmHg). Thereafter MAP continued to decrease slowly but, due to anabolism, patients' weight increased progressively to plateau after one year. In the same time the mean pre-dialysis hematocrit level increased from 24 to 29% without EPO and after stopping all blood transfusions in the 27 patients who needed them while on short HD (his-

torical group). Pre-dialysis urea increased by 10% and pre-dialysis creatinine by 25%.

Conversely, 49 patients who had been dialyzed 3 x 8-hr for more than 6 months (all normotensive without antihypertensive medication) were switched to 3 x 5 hr HD[10]. Dialyzer area and blood flow were increased to maintain an unchanged Kt/V. After one year the pre-dialysis MAP was significantly increased (10 mmHg) in spite of a mean 2.5 kg post-dialysis weight reduction. Pre-dialysis urea and creatinine dropped by 8 and 19% respectively. The mean hematocrit decreased from 31.5 to 27.5%. Shortening the session time without decreasing the dialysis dose was therefore associated with an impaired BP and nutrition.

DISCUSSION

Is survival better on long HD?

In 2003 in Tassin the mean age at start was 61.9 years, 51% of patients had diabetes or renal vascular disease and a significant CV story was found in 59% of incident patients. The very slight favorable population selection bias in favor of Tassin does not account for the large mortality discrepancy with US results. One cannot exclude some «center effect» in the achieved results. But other units using long dialysis[11] report the same good survival and low morbidity. Normotension is probably a major factor in reducing mortality[12]. On top of achieving an excellent control of volume and of BP, a long dialysis allows for a satisfactory control of nutrition, anemia, and phosphoremia[13]. The effect of PO4 control on HD patients survival (more specifically on CV mortality) initially reported by Block and cols.[14] has been now widely confirmed.

What is the role of the large urea Kt/V?

Is survival better on long dialysis because the delivered urea Kt/V is higher than in the conventional short HD? When the delivered urea Kt/V is increased —in limited but well controlled groups of patients— the mortality decreases[15,16]. But Kt is a better outcome-based measure of HD dose than Kt/V[17]. Indexing the delivered dose Kt to V which has independent outcome effect of its own confuses the issue. The clearance term K depends of several factors (blood flow, recirculation, urea rebound...) These factors reduce the system performance when shortening the HD time pushes up the necessary dialysis «efficiency». Therefore operational conditions of HD make it is very difficult to substantially increase the urea Kt/V (e.g. over 1.8) without increasing the session time t over the conventional 3 or 4 hours.

Other time-related issues

The effect of increasing the session time is not limited to increasing small molecules epuration. It increases proportionally more the clearance of larger solutes such as MM and of solutes which, due to their body distribution, behave as MM. We have already pointed at the importance of PO4 control to prevent CV calcifications. Identified MM have also been shown to influence strongly nutrition, immunology and infection, BP and vascular disease and to have many other implications[18].

The good ECV and BP control achieved are probably the most clinically relevant features of long HD. The development of shortened dialysis has led to an increased incidence of hypertension[19] and most probably to the epidemics of CV disease in the HD population. Shortened session time and higher ultrafiltration rates lead to a vicious circle[20] amplifying BP variations and driving to both intradialytic hypotension and interdialytic hypertension.

Optimal dialysis needs several conditions not just one. All these conditions are mandatory. Each of them is necessary. Any of them if lacking suffices to sink the whole ship. Time allows not only to provide a good dose of dialysis in term of small and even more middle molecules, but also to provide a satisfactory nutrition, ECV and BP control. This last point is essential: CV morbidity is by far the first cause of death in HD patients. So time appears a key factor to achieve an optimal dialysis treatment. Besides it does not push every operational aspect of dialysis to its maximum, so that it leaves a great margin of safety for treatment for treatment delivery. Practically speaking, while it is rather difficult to perform an excellent very short dialysis, the long slow thrice weekly dialysis is easy to perform with a great liability.

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