Has Thrice Weekly Short Dialysis Become Obsolete in 2002?

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Addressing the question of the adequacy of short (3 to 4 hours per session) hemodialysis (HD) needs to put it in perspective with other types of available maintenance HD treatments. The following analysis is based on the Tassin long empirical dialysis used since 1968.

Tassin method and patients

In Tassin the long slow dialysis 3×8 hours on a 1 square-meter (or 1 m^2) area Kiil dialyser as designed and developed by the Seattle group[1] and considered as the "gold standard" in the 70's [2] was maintained almost unchanged for over 30 years. The typical Tassin treatment has been performed using a poorly biocompatible set-up (acetate buffer, plain softened water, cuprophane membrane) but providing a large dose of dialysis (average urea Kt/V slightly over 6.0 per week), and a normalized PCR of 1.25. The average protein and calories intakes are unrestricted. Their intake is estimated to 1.2 g/kg BW/day and 31 kcal/kg BW/day respectively. The only real dietary restriction the patients are asked (out of excessive K^+ containing foodstuff overuse) is to maintain a low salt diet. The actual mean sodium intake is reduced to 5 g per day and the mean interdialytic weight gain about 1.8 kg. A very important point of the Tassin regime is that antihypertensive medications are stopped in each and every patient over a few days or weeks at initiation of dialysis. At 3 months of follow-up only 3% of patients are under antihypertensive medication[3].

If the treatment method has remained stable along calendar years but the patient population has (as almost everywhere) changed a lot in the same time[4], at opposite, the age at hemodialysis start increased from a mean 36 y.o. When the unit was started in 1968 to 65 in 2001. The proportion of patients with a significant cardiovascular story (angina, myocardial infarction, peripheral vascular disease, transient ischemic attack, or stroke) crept in the same time from 4 to 62%. Besides, the causes of renal diseases leading to end-stage renal failure have changed drastically. Vascular disease (including nephrosclerosis) and diabetes mellitus were the cause of renal failure in less than 10% of the patients started on dialysis in 1968. This proportion increased to 56% in 2001. The overall population of the unit has been split in five calendar cohorts. They differ by the demography and case-mix as by the survival although the treatment was maintained without change. The Kaplan-Meier analysis of survival shows that the worsening case mix was correlated with an important crude survival drop. The first cohort starting dialysis before 1975 (patients' mean age 39 years, 9% of patients with positive cardiovascular story, 8% of 'high risk' -diabetes mellitus or cardiovascular disease-) survived very well (mean half-life of 18 years). At opposite, the more recent cohort (patients' mean age of 63, cardiovascular antecedents in 63 %, and 'high risk' cause of renal failure in more than half of them) had a poor survival (mean

half-life 5.5 years). The intermediate calendar cohorts had intermediate mortality rates.

But of course adjusting for age, race, and cause of renal. failure using the standardized mortality ratio as suggested by Wolfe et al.[5] shows (Table 1) that the probability of mortality in Tassin has remained quite stable along the last ten years in spite of the population change. The mortality is stable about 45% of expected mortality according to the USRDS standard mortality tables.

The dialysis dose and time issue

The National Cooperative Dialysis Study (NCDS) results were published in 1981[6]. Although it was opened to critics (small number of patients, limited follow-up time, doubtful targets, etc) it was the first prospective randomized study on dialysis and it has had a powerful impact on nephrologists all over the world. It concluded that time-average concentration of urea had a very important impact on clinical outcome while the session time had only a marginal (p=0.06) effect.

The consequences of the NCD Study have been even more important. A few years after it was published, Gotch and Sargent based on its results the integrated urea clearance (Kt/V) concept[7]. The Kt/V concept had the merit to achieve for small molecules what Babb had not achieved ten years earlier with his middle molecule concept[8], i.e. providing a simple numerical tool to measure the amount, and supposedly, the adequacy of dialysis.

Besides, in their mechanistic analysis of dialysis, Gotch and Sargent, opposite to Keshaviah who had proposed for the observed NCDS results a continuous relationship between dose and clinical outcome[9], described a discontinuous, stepwise relationship. According to them the clinical outcome was poor if the patient received less than a Kt/V dose of 0.9 per session. On the other hand, they stated in the mean time that there was no benefit to be expected in increasing the delivered dose over 1.0 or so. This was in line with the "minimal dialysis" concept described earlier by Gotch[10].

The urea Kt/V and the mechanistic analysis have had a deep impact on hemodialysis delivery. They were unfortunately the alibi for a progressive reduction of dialysis dose and time delivery, especially in the United States. The continuous decrease in the delivered dose of dialysis has been followed by a worsening clinical outcome. In 1990 the Morbidity and Mortality conference in Dallas drew the attention to the high and regularly increasing mortality of dialysis patients in the United States[11]. The question was raised again if a higher Kt/V would not be better.

The cross-sectional epidemiological analyses comparing survival results reported in units or registries of countries using high dialysis doses such as Japan[12] to those using small doses such as United States[13] suggested that a higher dose is correlated with a lower mortality. Even more convincing, in several units the dose of dialysis delivered was deliberately increased to analyze the long-term effect on mortality. In all published

Table 1. Standardized Mortality Ratio (SMR) Tassin 1989-2000

Calendar year	O/E deaths*	SMR	p value
1989	24/43.7	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	31/69.9	0.44	<0.001

**O/E : observed/expected number*

cases[14-17] the mortality decreased when the Kt/V dose increased.

The prospective randomized HEMO study[18] has been set-up with a 7-year follow-up to answer the question (out of the issue of the comparative effects of high-flux vs. low-flux membranes) of the level at which the Kt/V increase reaches a plateau. The 2×2 factorial trial compared a single-pool Kt/V of 1.2 (roughly equivalent to a double pool Kt/V of 1.05) to a spKt/V of 1.6 (roughly double pool Kt/V of 1.45). The results of this trial have not been published yet but an early National Institute of Health press release (April 23, 2002) stated "no significant impact of Kt/V on clinical outcome". This, added to the ADEMEX peritoneal dialysis prospective study concluding[19] that "increasing peritoneal clearance to achieve levels recommended by DOQI does not improve survival", has shaken the nephrology world. Can you conclude that a minimal urea Kt/V is necessary and sufficient to define an adequate hemodialysis? One should be careful in drawing such conclusions. Were the 1.2 and 1.6 spKt/V used in the HEMO study delineating a sufficient range to allow for a significant outcome difference[20]? Is the concept of Kt/VF flawed by the independent effect of V on mortality as suggested by Lowrie and al.[21]? Or, is the urea kinetic effect on clinical outcome just "negligible" because of the confounding effect of other more powerful factors (such as middle molecule removal, extracellular control, nutrition, blood pressure control, anemia correction…)?

Separating the effects of dialysis and time is not easy because they are interdependent. The Kt/V depends on the time factor. To increase the delivered urea Kt/V dose over a reasonably high level (1.6 single pool) need to increase the time because factors affecting K are self-limiting (e.g. blood flow limited by recirculation and rebound). The next step in analyzing the long slow HD results therefore needs a review of its available clinical results compared to those of standard hemodialysis.

Clinical issues in long and short hemodialysis

1. Blood pressure control

1) Hypertension

The blood pressure control achieved by long dialysis is quite satisfactory. Over 95% of the patients are normotensive without need for antihypertensive medication[22]. The mean integrated casual pre-dialysis blood pressure of 1030 Tassin patients (using all data for each patient) is 126/78 mmHg, within the normal range according to 6th Joint National Committee[23]. Ambulatory BP values also are within normal range, at least for circadian and daytime values. Due to the lack of nocturnal dip in about 50% of patients, the nighttime values are slightly more elevated than in normal subjects. At opposite literature data on BP control in short HD show a large proportion of hypertensive patients[24-26]. The reduction of dialysis session time has led to a loss of control of hypertension in an increasing proportion of patients[27-29].

Splitting our population in two equal subgroups as a function of integrated pre-dialysis mean arterial pressure, the subgroup with the lower the blood pressure (mean 89 mmHg) has a significantly longer the survival. The lower mortality of the lowest blood pressure subgroup is explained by a much lower cardiovascular mortality than the subgroup with a slightly higher (mean 105 mmHg) blood pressure.

The effect of prolonging the session time on hypertension control is illustrated by observing the effects of changing the same groups of patients from short to long HD and conversely. We had the opportunity to dialyze transiently in Tassin 124 patients from other units waiting for kidney transplantation in Lyon. They were un-

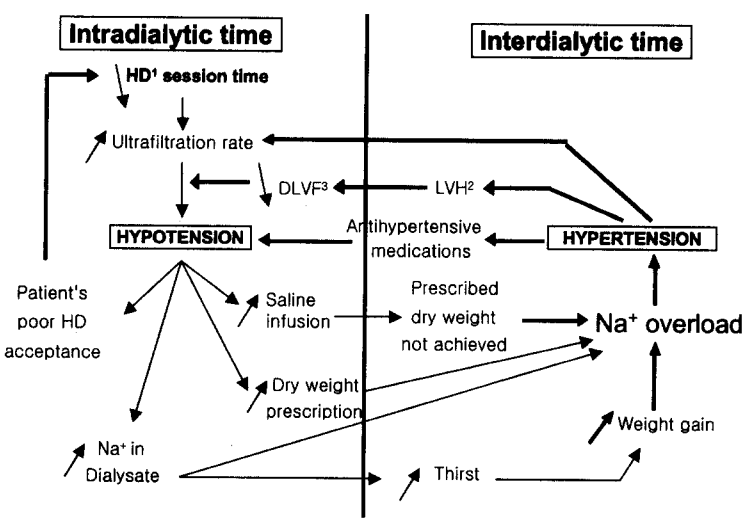
selected. All had been treated for 6 months or more on a 5-hour (or less) thrice-weekly HD schedule. Half of them received an antihypertensive treatment. Three months after they were switched to the 8-hour dialysis treatment, their average post-dialysis weight was reduced by 0.5 kg, their pre-dialysis MAP was back to almost normal (mean=101 mmHg) and antihypertensive medications were stopped in all but one patient. Thereafter pre-dialysis MAP continued to decrease slowly but, due to anabolism, patients' weight increased progressively to plateau after one year around its initial value[30]. Conversely, 49 Tassin 8-hour dialysis patients were switched to a 5-hour schedule. All had been dialyzed 3×8 hours since at least 6 months. All were normotensive without antihypertensive medication. All had a blood access allowing for a dialysis blood flow of 300 mL/min or more. The dialyzer area and blood flow were increased to maintain the urea Kt/V unchanged after they were switched to the shorter schedule. After one year the delivered Kt/V per session had almost not changed (1.86 to 1.77). On the other hand the pre-dialysis MAP had rose significantly by 11 mmHg in spite of a mean 2.5 kg post-dialysis weight reduction and of the introduction of antihypertensive medications in 4 patients[30]. Shortening the session time without decreasing substantially the dialysis dose as judged by urea Kt/V, was therefore associated with an impaired blood pressure control.

2) Hypotension

At the other edge of blood pressure control hypotensive episodes -as well as other intradialytic events- occur less frequently when dialysis session duration is prolonged. In our own unit the incidence of hypotensive episodes on 3×8 hr/week is 5% vs. 12.9% in patients on 3×5 hr/week sessions. Some recent literature data show that hypotension very often occurs in 15 to 25% of sessions[31, 32].

3) Blood pressure variations

Using longer dialysis session reduces both hypertension and hypotension. This can be understood by looking at the Fig. 1. As session time is shortened, a higher UF rate must be used, leading to more hypotensive episodes. This in turn has 3 types of consequences : First, on the



1-HD: hemodialysis
2-LVH: left ventricular hypertrophy
3-DLVF: decreased left ventricular function

Fig. 1.

patient who gets a poor perception and acceptance of the session and wants to make it shorter; second on the nurse who has to give saline or cut down the ultrafiltration rate, so that prescribed dry weight is not achieved, and the patient get saline overloaded; last on the physician who impressed by the hypotension prescribes a higher (too high) dry weight, and often a higher dialysate sodium. This increased dialysate sodium decreases the diffusive drag of sodium out of the body. It increases the body osmolality, the thirst and the interdialytic weight gain. Altogether the patient get even more saline overloaded and hypertensive. As he (or she) is more hypertensive the patient needs more ultrafiltration which leads to more hypotension. The vicious circle is closed. Furthermore, hypertension aggravates the left ventricular hypertrophy, and the incapacity of the heart to adjust its output to face hypotension. If antihypertensive medications are added, they potentialize the hypotensive effect of ultrafiltration (and are usually inefficient on hypertension). Altogether on very short dialysis intradialytic hypotension and interdialytic hypertension keep on increasing each other in a vicious circle. Reduced dialysis session time behaves as a blood pressure variation amplifier. Conversely, prolonging time allows to improve extracellular volume and blood pressure control, allowing blood pressure to fluctuate smoothly within the physiological range.

2. Nutrition and Phosphate control

Looking at the nutrition and phosphate control, a recent 5 yrs follow-up study of 47 long HD patients nutrition showed stable protein (mean dietary protein intake 1.21 g/kgBW/day) and energy (mean calories intake 1.29 kcal/kgBW/day) intakes. Compared to published data in different series [33-35] this turns out to be quite satisfactory.

A few years ago Block & colleagues[36] showed that high serum phosphate correlates with an increased CV mortality. Our own data on long dialysis confirm the same trend. Compared to commonly reported data[36, 37] long dialysis achieves a better control of serum phosphate with a minimal use of PO_4 binders.

3. Anemia control

The control of anemia achieved by the 3×8 hr dialysis is satisfactory with an average pre-dialysis hematocrit of 34.2, using EPO in 56% of patients with an average dose of 5700 units per week, i.e. about 1/3 of the USRDS reported typical dose (but within usual French levels).

Optimal versus adequate dialysis

In 2002 after more than 40 yrs of maintenance dialysis the target must be an optimal rather than a just adequate dialysis. This needs additive conditions : sufficient small and middle molecule clearances, protein and calories adequate nutrition, extracellular volume and blood pressure control. All these factors are needed. Each of them is necessary, any of them if lacking will suffice to wreck the whole ship. Optimal dialysis and the factors it depends on, are all related to the same one parameter : dialysis session time (although high small molecule clearance can be achieved within a relatively short session time).

Increasing the session duration is not the only way to increase the time. Increasing the session frequency not only increases time, but it also distributes it more evenly, reducing the unphysiological acute fluctuations of volume, osmolality, and composition. This improves patient's health and quality of life. Theoretically this second way should be preferred.

So why did daily dialysis not appear earlier? In fact it did appear very early! In 1969 John de Palma reported his 2-yr experience with daily dialysis[38] and he was followed by several others [39, 40]. But technology and cost were 2 major barriers to its development.

After a long sleep of nearly 30 yrs Buoncristiani woke up the sleeping beauty when he reported the experience of his group extending over 15 years[41]. In this substantial study of over 200 pt-yrs they showed that daily dialysis was feasible on the long term, with repeated daily use of blood access, good clinical and biological results and without increasing substantially the cost by reducing hospitalization and medication expenses….

The observations of this pioneering experience have been widely confirmed. For instance in their review, Woods et al.[42] pointed at blood pressure control, anemia correction with less need for erythropoietin, excellent nutrition and easy control of serum phosphate, low intradialytic morbidity, large doses of dialysis, and a higher quality of life than usually achieved.

If one compares standard to long and daily dialysis, the small molecule dose is satisfactory with all of them, while middle molecule dose is more difficult to achieve in short thrice weekly dialysis. Nutrition, anemia control, phosphate and calcium equilibrium, and extracellular volume control are well achieved in long or daily dialysis but less well in conventional hemodialysis. Blood pressure control appears very good in long and in daily dialysis but poor in conventional dialysis. Unphysiology is maximum in conventional dialysis, fair in long, but best in daily dialysis. Vascular access is equal in all three situations. Long-term survival is better in long than in short and probably in daily although we lack follow-up data. The cost remains an important problem with daily dialysis especially in the part of the world where reuse is banned.

In regard of the high performances and appeal of long and of daily hemodialysis, several changes have outdated conventional short dialysis. The early 70's appealing short dialysis promised a comfortable, short, simple, cheap, long-term, low morbidity therapy. But it has taken age, discomfort, limited dose, increased morbidity, deceiving mortality, increasing complexity and cost. What made things even worse is the change in patient's case mix. The patients we are treating today have nothing in common with those we treated 30 yrs ago. Today the main limit of the treatment is not any more the technique but the patient. The 1975 assertion that reducing the session time could be done without jeopardizing the quality of treatment due to the technical improvements has to be seriously revised in 2002 because we are aiming at optimal (and not just adequate) dialysis, in an increasingly frail and comorbid population in which short thrice weekly dialysis leads to many problems.

Decreasing the session time without increasing the session frequency decreases delivered dose as well as the extracellular volume and BP control. The decreased dose leads to increase mortality. To compensate for the decreasing dose one try to increase the blood flow rate, leading to blood access problems such as recirculation, and overuse of vascular grafts increasing cost and morbidity. Other compensatory mechanisms include more severe diet (to reduce protein, PO_4, K^+…) leading to nutritional problems, morbidity and mortality, and to an increased use of medications which in turn increase cost and malnutrition. The lack of extracellular volume and blood pressure control on their own increase morbidity and mortality. They lead to use higher ultrafiltration rates, leading to intradialytic morbidity and poor compliance. Compensatory mechanisms consist in using increasingly complex and expensive ultrafiltration control tools and sophisticated biofeedback devices. So, through a complex but very real net of limitations and compensatory mechanisms the short thrice-weekly hemodialysis is responsible for increased morbidity, mortality, and cost. It is particularly unsuitable for the frail highly morbid population we have to treat today. It is obsolete.

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