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Long nocturnal dialysis: A single-centre experience

Diálise longa noturna: Experiência de um centro

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ABSTRACT

The institution of intensified dialysis regimens (as long treatment time, with reduced ultrafiltration per hour) has been associated with decreased morbidity and mortality in patients with end-stage chronic kidney disease. The performance of the haemodialysis session during the night interval emerged as logical, since it is an "idle" period, and has been associated with better small molecule dialysis, better blood pressure control, reduced medication requirements and improved quality of life. Recently, our centre initiated a long nocturnal dialysis programme and a prospective observational analysis was designed to evaluate the results of this approach. Mean values of clinical and laboratory variables were compared in 2 consecutive semesters: prior and after transition from haemodiafiltration to long nocturnal dialysis. After 6 months of switching, there was an increase in dialysis efficiency (reduction in pre-dialysis urea (129.74 ± 28.7 vs. 114.53 ± 23.94 mg/dl, $p = 0.01$) and an increase in Kt/V (1.75 ± 0.37 vs. 2.09 ± 0.39, $p = 0.005$)), improved hyperphosphatemia control (5.05 ± 0.9 vs. 4.23 ± 0.93 mg/dl; $p = 0.01$) and anaemia control, with a significant reduction in the use of darbepoetin alfa (38.5 ± 24.18 vs. 30.83 ± 22.54 µg/week; $p = 0.04$) and of intravenous iron (189.33 ± 117 vs. 116 ± 67 mg/month; $p = 0.04$) and a much better correction of overhydration (evaluated by the "BCM-Body composition monitor": 10.2% ± 8.63 vs. 4.6% ± 7.2; $p = 0.01$), reflecting the patients' overall better nutritional status. These excellent results were amplified by the patients' perception of improvement in their quality of life. Our findings are consistent with the studies that favour long nocturnal dialysis over conventional regimens, but randomized controlled trials are needed to validate these findings.

Key-words: Anaemia; blood pressure; mineral and bone disease; nocturnal dialysis; outcome; quality of life.

RESUMO

Os esquemas de diálise longa, com taxas de ultrafiltração/hora mais baixas, têm sido associados a menor mortalidade, na maioria dos estudos. Neste contexto, a diálise longa noturna surgiu como uma modalidade de diálise alternativa e atrativa. A diálise longa noturna tem sido associada a maior eficácia dialítica, melhor controlo tensional, com diminuição das necessidades medicamentosas e melhor qualidade de vida. O nosso centro iniciou recentemente um programa de diálise longa noturna cujos resultados nos propusemos analisar num estudo prospetivo e observacional. Com este objectivo, avaliámos a evolução de variáveis clínicas e analíticas em 2 semestres consecutivos, antes e após a transição de hemodiafiltração para diálise longa noturna. Seis meses após a transição, verificámos uma melhoria da eficiência dialítica (redução de ureia pré-diálise (129.74 ± 28.7 *vs*. 114.53±23.94 mg/dl, p=0.01) e subida de Kt/V (1.75 ± 0.37 *vs*. 2.09 ± 0.39, *p* = 0.005)), do controlo da hiperfosfatemia (5.05 ± 0.9 *vs*. 4.23 ± 0.93 mg/dl; *p* = 0.01) e da anemia, com significativa redução do consumo de darbepoetina alfa (38.5 ± 24.18 *vs*. 30.83 ± 22.54 µg/semana; *p* = 0.04) e de ferro endovenoso (189.33 ± 117 *vs*. 116 ± 67 mg/mês; *p* = 0.04), bem como uma excelente correção do estado de híper-hidratação (avaliado pelo monitor de "BCM-Body composition monitor": 10.2% ± 8.63 *vs*. 4.6% ± 7.2; *p* = 0.01), reflexo do melhor estado nutricional dos doentes. A estes benefícios acresceu-se a perceção de melhoria da qualidade de vida dos doentes. O nosso estudo vem juntar-se à lista de trabalhos cujos resultados favorecem a diálise longa noturna em relação à hemodiálise convencional, mas são necessários estudos randomizados para validar estes resultados.

Palavras-chave: Anemia; diálise nocturna; doença óssea; pressão arterial; qualidade de vida; resultados.

INTRODUCTION

The institution of intensified dialysis regimens (long treatment time, with reduced ultrafiltration per hour) has been associated with decreased morbidity and mortality in patients with end-stage chronic kidney disease (CKD)[1,2]. The option for a longer dialysis session is based on the principle that it enables a more 'physiological' process, allowing for the removal of larger volume of fluids and toxins. It also results in fewer side-effects, including hypotension and/or cramps. However, the most important benefit is the improved survival of patients, initially evidenced by the Tassin group[3] and, more recently, by other investigators[4,5].

In this context, the performance of the haemodialysis session during the night emerged as logical, since it is an "idle" period. In addition to the direct benefits stated previously, the indirect advantage of being able to maintain daily activities, with much less restrictions than with conventional daytime sessions, are far from negligible.

Since the late 1960s the Tassin (France) group has adopted long nocturnal dialysis (LND) – 8 hours, 3 times a week – and is now the largest centre of expertise in nocturnal dialysis worldwide. This in-centre nocturnal dialysis regimen offers the advantages of medical staff supervision, while allowing patients to maintain their daily activities. In Portugal, the LND was introduced in 1983, at the "Clínica de Doenças Renais" (Lisbon). Since then, the experience has been replicated in several Portuguese centres. In April 2013, it was the turn of the Nephrocare – Vila Franca de Xira haemodialysis centre to implement an LND programme, creating the opportunity for prospective evaluation. The aim of this study was to find clinical advantages in anaemia, bone metabolism and dialysis dose, from the switch to LND.

SUBJECTS AND METHODS

Study Design

This was a prospective, single-centre study, of a cohort of prevalent haemodialysis patients, switched from daytime on-line haemodiafiltration (HDF) post-dilution (mean time: 240 minutes/session) to LND (mean time: 395 minutes/session). The patients were

followed for, at least, 6 months before and 6 months after the switch. Clinical and laboratory data were assessed monthly, and compared as median values pre-LND and post-LND.

Patients

We evaluated 10 patients, six males, and four females, with mean age of 41.2 ± 7.21 years, and mean dialysis time of 61 ± 38.4 months. Two patients were diabetic, four had arterial hypertension, and one patient had hepatitis C infection.

All patients underwent dialysis with Fresenius® equipment and ultrapure water (endotoxine-free, evaluated monthly with chromogenic kinetic LAL assay). Nine patients used high-flux synthetic membranes, while one required the use of a cellulose triacetate membrane. Vascular access was as follows: 6 arteriovenous fistulas and 4 arteriovenous grafts. All vascular access were subjected to rope-ladder cannulation technique. The average blood flow rate was 310 ml/min, with an autoflow dialysate rate of 1.0.

Systolic and diastolic blood pressure (BP) was measured in all dialysis sessions during the study period, and also kt/v, using OCM module. Normohydration/overhydration (OH) status was evaluated by monthly BCM-bioimpedance spectroscopy. Hypotensive drugs were evaluated at the beginning (6 months before LND) and at the end (6 months after LND) of the study, using the antihypertensive drug index (ADI) – the ratio of the dose of the drug used by its maximum. Erythropoietin stimulating agents (ESA), iron and phosphate binders therapeutic doses were also collected monthly.

The Kidney Disease Quality of Life Short Form (KDQL-SF) was applied to assess the patients' quality of life, after the switch to LND.

Biochemical analysis

Serum levels of haemoglobin, pre-dialysis urea, potassium, phosphorous, calcium, and C-reactive protein were measured monthly, while ferritin, intact parathyroid hormone (PTH), and albumin were obtained every 3 months.

Biochemical analysis including haemoglobin, calcium, phosphorus, ferritin, and albumin was performed using standard methods. The PTH was measured by immunochemiluminescence using a second-generation assay and the normal range is 10 to 65 pg/ml.

Echocardiographic evaluation

Our patients were annually evaluated by echocardiogram, M mode. Left ventricular mass index (LVMI) was calculated using Devereux formula and indexed to body surface area. The presence of left ventricular hypertrophy (LVH) was defined based on a LVMI > 125 g/m^2 for both genders. Ejection fraction was measured using Simpson's modified rule.

Statistical analysis

Data are presented as frequencies for categorical variables, and mean ± SD values for continuous normally distributed variables. Because of the sample size (10 patients), comparisons between HDF period vs. LND period was made using non-parametric test Wilcoxon for paired samples.

All tests were performed using STATA software version 13, and a *p*-value < 0.05 was considered statistically significant.

RESULTS

Clinical and demographic characteristics of patients are listed in Table I. The average results before and

Table I

Clinical characteristics of the population

	Value
N	10
Age (years)	41.2 ± 7.21
Male/female	6/4
Diabetic	2
Hypertensive	6
Dialysis vintage (months)	61 ± 38.36
Vascular access:	
Arteriovenous fistula	6
Arteriovenous graft	4

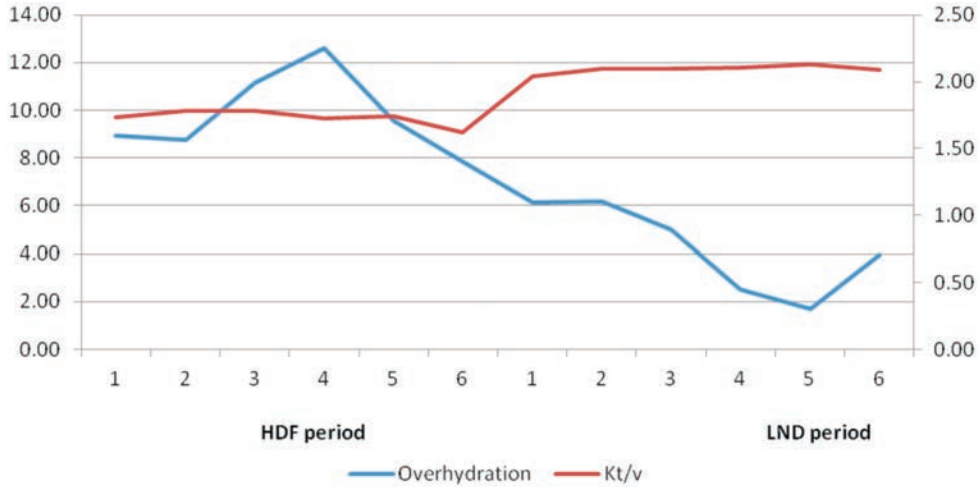
Table II

Laboratory and clinical findings (as mean values) pre- and post-long nocturnal dialysis (LND)

	HDF period	LND period	p-value
Pre-dialysis urea (mg/dl)	129.74±28.7	114.53 ± 23.9	< 0.001
Kt/V	1.75 ± 0.4	2.09 ± 0.4	0.005
Serum potassium (mEq/L)	5.27 ± 0.1	5.29 ± 0.2	NS
Serum phosphorous (mg/dl)	5.05 ± 0.9	4.23 ± 0.9	0.01
Serum PTH (pg/ml)	328.1±161.5	385.9 ± 241.5	NS
Serum calcium (mg/dl)	8.59 ± 0.1	8.85 ± 0.2	0.005
Antihypertensive drug index	3.69 ± 2.5	2.17 ± 2.4	NS
Systolic blood pressure (mmHg)	143.7 ± 10.9	141.5 ± 8.4	NS
Darbepoetin use (µg/week)	38.5 ± 24.2	30.83 ± 22.5	0.04
Intravenous iron use (mg/month)	189.33 ± 12	116 ± 7	0.04
Serum haemoglobin (g/dl)	11.8 ± 0.5	11.8 ± 0.3	NS
Serum ferritin (ng/ml)	450.1 ± 37	469.8 ± 21.2	NS
Serum C-reactive protein (mg/dl)	4.09 ± 2.2	3.79 ± 1.2	NS
Dry weight (kg)	69.14 ± 17.7	68.74 ± 17.1	NS
Normohydration/Overhydration status (%)	10.2 ± 8.6	4.6 ± 7.2	0.01
Serum albumin (g/dl)	4.30 ± 0.4	4.36 ± 0.4	NS
Vascular access complications	3	1	NS

Figure 1

Variation of OH and kt/v over the two studied periods of time



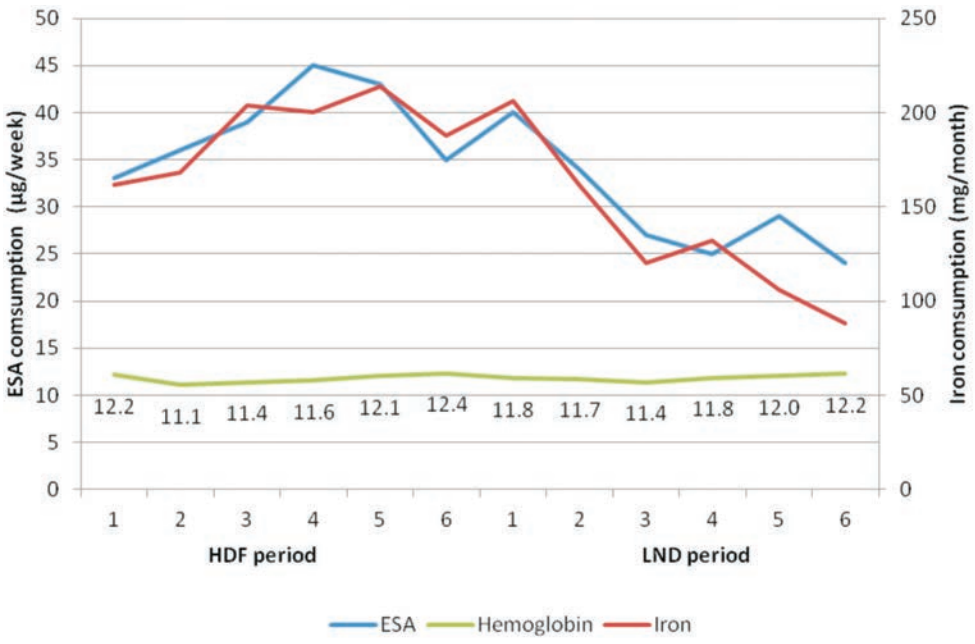
after the transition to LND are summarized in Table II. With more intense dialysis, we observed a reduced pre-dialysis urea (129.74 ± 28.7 vs. 114.53 ± 23.9 mg/dl, $p < 0.001$), and increased average Kt/V (1.75 ± 0.4 vs. 2.09 ± 0.4, $p = 0.005$) – see Fig. 1.

Average systolic BP remained stable 6 months after the switch, with a concomitant progressive decrease in antihypertensive therapy (quantified by the ADI): 3.69 in the month before the transition vs. 2.17 at 6 months after transition, $p = 0.15$. Echocardiography findings indicating left ventricular mass and ejection fraction remained unchanged 9 months after transition (6-12 months).

We verified a correction in overhydration (evaluated by the "BCM-Body composition monitor": 10.2%

Figure 2

Variation of ESA and intravenous iron use over the two studied periods of time



± 8.6 vs. 4.6% ± 7.2; $p = 0.01$), while our patients' weight remained stable.

There was a significant decline in ESA use (darbepoetin doses were reduced from 38.5 ± 24.2 to 30.83 ± 22.5 µg/week; $p = 0.04$) and in intravenous iron use (189.33 ± 12 vs. 116 ± 7 mg/month; $p = 0.04$), with comparable hemoglobin levels, as shown in Fig. 2. Ferritin, C-reactive protein and albumin levels did not differ between the two time periods.

A reduction in the mean phosphorous level (5.05 ± 0.9 vs, 4.23 ± 0.9 mg/dl; $p = 0.01$), and a concomitant increase in the mean calcium level (8.59 ± 0.3 vs. 9.1 ± 0.3 mg/dl; $p = 0.005$) were observed. An upward trend was noted in PTH levels, although not statistically significant (328.1 ± 161.5 vs. 385.9 ± 241.5 pg/ml; $p = 0.38$). Phosphate binders were used by nine patients prior to transition, with six of them either reducing or discontinuing its use.

We did not witness an increase in vascular access complications (3 vs. 1).

Six months after the transition, we applied the Kidney Disease Quality of Life Short Form (KDQL-SF) to assess our patients' quality of life, and observed a statistically significant improvement in the patients' perception of their health, sensation of breathlessness, anorexia, perception of fatigue and the degree of satisfaction with the amount of time spent with family and friends.

DISCUSSION

Overall, and in a short period of time, our results finds attractive effects of LND. Let us appreciate them separately.

LND and Clearance of solutes

Several studies have shown that prolonged dialysis schemes, including LND, are clearly superior with regard to the clearance of solutes when compared with conventional haemodialysis or HDF. This is reflected by lower urea[6], phosphate[7] and beta-2microglobulin[8]

serum levels and by an increase in the value of Kt/V[9]. Similar changes were observed in the study conducted in our centre. While the HEMO trial[10] reported no significant impact of the Kt/V dose on survival after 5 years of follow-up, replacing kidney function is not restricted to the clearance of small molecules. Other factors, such as nutrition, extracellular volume and blood pressure need to be optimized to achieve optimal dialysis, and they are easier to attain with a longer or more frequent dialysis sessions. While the ideal dose of dialysis is hard to determine, the long session thrice weekly is at least thought-provoking.

LND and Cardiovascular effects

Regarding cardiovascular effects, LND has shown marked benefits, with improved BP control being reported across most studies[11]. The Tassin group documented survival improvement in their patients, verifying that this is predominantly due to a lower cardiovascular mortality[5]. In turn, these effects were more pronounced in the subgroup of patients with better BP control. This aspect is reflected directly with lower pre- and post-dialysis BP[9], as well as indirectly by a reduced need for antihypertensive medications[11], probably reflecting the greater facility in reaching the normohydrated weight with longer dialysis sessions. The benefits of LND and better BP control are also demonstrated by a regression of left ventricular mass[12] and improved left ventricular ejection fraction[13]. Some argue that improved BP control is, at least partially, due to a better vascular function, through its total peripheral resistance lowering effect[14]. Of mention, coronary calcification rate in LND was analysed and, although further studies are needed to confirm these observations, it appears to be significantly lower than that observed in conventional regimens[15]. These findings are probably related to the great amelioration in calcium/phosphate metabolism described below.

In our patients, it was possible to steadily cutback in antihypertensive therapy while maintaining their average systolic BP. While the echocardiography findings regarding left ventricular mass and ejection fraction remained unchanged, it must be mentioned that echocardiography evaluation was not performed, neither optimized, to document these changes.

LND and Anaemia & Nutrition

Anaemia control is another frequently stated advantage of nocturnal dialysis[16]. However, negative results have also been published[17]. In our group, we observed a substantial decline in ESA and in intravenous iron use, with other parameters, as haemoglobin, ferritin and C-reactive protein levels, remaining unchanged.

Despite these results being in line with previous studies, we cannot ignore the possible effect of the correction in overhydration status that we also verified. This result, in association with the fact that our patients' weight remained stable, reflects their overall better nutritional status[18]. More intensive dialysis regimens have been associated with better nutrition, more liberated dietary intake, and with higher protein intake (frequently encouraged, since the loss of aminoacids is higher in prolonged dialysis regimens[19]). Albumin levels in these patients usually remain steady[20], and the same happened in our group of patients. Furthermore, dyslipidemia may also improve in LND, as it is associated with uraemia in a syndrome characterized by an elevation of triglyceride rich lipoproteins, a reduction in high density lipoprotein (HDL) levels, and a higher fraction of atherogenic, small dense low density lipoprotein (LDL)[21]. We did not study this potential effect of LND.

LND and CKD-MBD

Patients under LND usually have better mineral bone disease control, given the central role of phosphate levels in the prevention and treatment of secondary hyperparathyroidism. Because of its molecular weight, phosphate removal in dialysis is dependent on the session's duration[22], being naturally higher in this group of patients – an effect that we also verified, with a reduction in the mean phosphorous level, and an increase in the mean calcium level. The later can be justified, at least partly, by the increase in PTH serum levels we observed and the reduction of precipitation of the calcium phosphate complexes.

It is not clear what the effect of LND on PTH levels is due to many contradicting studies[9,23,24]. Some justify a decrease in PTH levels with the improved phosphate control, while others explain its increase with the negative calcium balance.

Importantly, despite the more liberal dietary intake previously stated, a reduction in the use of phosphorus binders is a common finding in LND[23]. We also observed this trend in our group of patients, with six out of nine either reducing or discontinuing its use.

LND and Quality of Life

Patients under haemodialysis have low quality of life due, in part, to the amount of time spent with dialysis treatment during the day. This has a huge impact in their daily personal, social, and professional activities, and a high rate of unemployment is the norm. Besides the physiological benefits of longer dialysis, the fact that nocturnal dialysis is performed during an 'idle' period grants to patients the possibility to restore their daily activity. These indirect benefits are hard to quantify, but certainly aids the patients' well-being and overall quality of life. This has been documented previously[25], with patients appearing to prefer nocturnal dialysis. Reduction in pill burden observed in these studies is also important for the patient, since high pill burden results in high rates of medication non-adherence[26]. One domain where benefits would not be expected is sleep quality, but since disturbances are minimal, sleep architecture actually appears to improve. This finding may be related with the improved uraemic toxins clearance discussed previously[27]. Still, some patients might find it hard to get comfortable sleep positions, for fear of alarm generation or needle displacement.

As mentioned above, a statistically significant improvement in the patients' perception of their quality of life was observed. Additionally, three of our 10 patients are currently employed, and refer that the transition has greatly facilitated their daily activities.

Shortcomings

There are also a number of potential disadvantages to LND that have to be considered. Some patients find it hard to sleep away from home three times a week. Patients also have a more limited access to multidisciplinary staff, such as vascular access centre, dietician or social assistant. It has been verified that more frequent dialysis regimens are associated with more pronounced residual renal function decline, which in turn is correlated with lower survival among incident dialysis patients[28]. Another concern is the fact that more prolonged treatments are associated with higher rate of vascular access complications[29]. Nevertheless, these events seem to be related to higher frequency of treatment (and cannulation) rather than with its duration[30]. Studies addressing this particular issue are needed.

Still, one must be cautious when analysing LND studies, since patient selection biases with younger and healthier patients choosing this modality are frequent and hard to avoid. In our study, patients were observed before and after the switch to LND, and each patient was its own case and control, thereby removing the problem of selection bias.

CONCLUSION

While this review is somewhat compartmentalized, it is clear that most benefits are interlinked: benefits of intensified clearance result in better nutrition, which in turn has effects on anaemia and CKD-mineral and bone disorders. After 6 months of switching from a high efficient dialysis (on line HDF) to LND, even in a study with a small sample size, there was a substantial increase in dialysis efficiency, control of hyperphosphatemia and anaemia (with a significant reduction in the use of ESA and iron), and a much better correction of overhydration. These excellent results were amplified by the patients' perception of improvement in their quality of life.

The benefits must, therefore, be balanced with the shortcomings, and while individual studies have generally been supportive of LND over conventional HD, the magnitude of improvement in specific parameters has varied markedly between studies, and randomized controlled trials are needed to validate these findings.

Conflict of interest statement: The author AF received grants from Abbott, Abbvie, Amgen, Genzyme, OM Pharma and Shire. Member of national and international Advisory Boards for Abbott, Abbvie, Amgen, Fresenius Medical Care, Genzyme OM Pharma and Shire.

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