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Original Article

The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis

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Abstract

Background. While frequent or occasional symptomatic intradialytic hypotension (IDH) may influence patient well-being, its effects on survival—independent of comorbidities—has not previously been investigated. In this study, therefore, our objective was to assess the effect of frequent IDH (f-IDH) or occasional IDH (o-IDH) on survival.

Methods. During a 10 month run-in period in 1998, 77 patients with f-IDH ($\geq$10 hypotensive events/10 months, responding only to medical intervention) and 101 patients with o-IDH (1 or 2 events/10 months) were identified among all 958 patients of a dialysis network. Eighty-five patients who had no hypotensive episodes (no-IDH) during this run-in phase served as controls. Patients were followed for a median of 27 months (range: 0.3–37) and survival of patients in the three groups was compared by log-rank test. Independent association of f-IDH and o-IDH with survival, compared with no-IDH, was assessed by a proportional hazards model that included patient demographics, laboratory data and antihypertensive medication as well as comorbidity.

Results. Forty-five patients (58%) with f-IDH, 47 (47%) with o-IDH and 33 (39%) with no-IDH died during the follow-up. Mortality rates (deaths/100 patient years) were 37 (log-rank $P = 0.013$ *vs* no-IDH), 26 (log-rank $P = 0.375$ *vs* no-IDH) and 21 in the three groups, respectively. This indicates significantly decreased survival in patients with f-IDH as compared to those with no-IDH. In multivariate proportional hazards regression, however, where age, sex, time spent on dialysis, presence of coronary heart disease, diabetes, Kt/V, albumin level and use of β-blockers, calcium-channel blockers and long-acting nitrates has been adjusted for, neither f-IDH nor o-IDH was associated with survival.

Conclusions. Mortality in patients with f-IDH is significantly higher than in those without such events. After adjustments for covariates, however, there is no independent effect of frequent or occasional episodes of IDH on mortality.

Keywords: clinical study; cohort study; comorbidity; haemodialysis-complication; hypotension; survival

Introduction

Symptomatic intradialytic hypotension (IDH) is probably one of the most common complications associated with the dialysis procedure, occurring in about 10–30% of treatments [1]. IDH is the clinical manifestation of an imbalance between the decrease in plasma volume during dialysis and the counter-regulatory cardiovascular haemodynamic and neurohormonal mechanisms [2–5]. Besides factors directly related to the dialysis procedure itself, several patient-related characteristics and comorbidities increase the risk of IDH, mainly through impairment of the above compensatory mechanisms, such as age, diabetes, ischaemic heart disease, left ventricular hypertrophy and autonomic neuropathy [6–9]. As an increasing proportion of patients possess one or more of these risk factors it may not be surprising that the incidence of IDH is not decreasing substantially, despite improvements in dialysis techniques [10,11]. Indeed, we have previously shown that patients with frequent IDH are the ones who present with the above risk factors, while among those with an occasional IDH other mechanisms may play a role [12].

While the occurrence of IDH is undoubtedly distressing to the patient and disruptive to the unit,

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its main clinical significance lies in its potential association with patient morbidity and mortality. The mechanisms that could cause and underlie such an association are coronary and cerebral ischaemic syndromes, arrhythmia and lower dialysis dose delivered to the patient [13]. While there is accumulating evidence that low pre- and post-dialytic systolic blood pressure [14,15] is associated with increased cardiovascular mortality, there are no previous studies that looked at the direct effects of frequent or occasional IDH on mortality in chronic haemodialysis patients.

In this study, therefore, our objective was to assess the effects of frequent and occasional IDH on the mortality of chronic haemodialysis patients and to determine whether such an association was independent of patient comorbidity.

Subjects and methods

In this cohort study survival of patients with frequent (f-IDH), occasional (o-IDH) and no IDH (no-IDH) was compared during the follow-up. Subjects were identified during a 10 month run-in period in 1998 among all prevalent patients receiving chronic haemodialysis at 11 centers of the EuroCare Nephrological Network in Hungary. This study base represented ~30% of the total Hungarian dialysis population at that time with even geographic distribution, providing external validity to the patient selection. IDH was defined as an event characterized by a sudden drop in systolic blood pressure to <90 mmHg or in absolute value of >30 mmHg, associated with symptoms of hypotension and not responding to the supine position but necessitating resuscitation with intravenous normotonic or hypertonic fluid administration. Patients who experienced 10 or more IDH episodes during the run-in period were considered to have f-IDH, patients with only one or two of these episodes to have o-IDH and those without any IDH to have no-IDH. Patients belonging to this latter group were considered as controls. The cut-off values for f- and o-IHD were chosen arbitrarily.

After the run-in phase, patients in the three groups were followed for an average of 27 months (range: 0.3–37 months) and all-cause mortality was considered as the primary outcome. Data were censored at transplantation, leaving haemodialysis, transfer to another dialysis unit or at the end of follow-up. During the follow-up patients received standard thrice-weekly haemodialysis using a bicarbonate bath and, almost exclusively, substituted cellulose and synthetic membranes.

Patient-related characteristics (demographics, comorbidity, biochemistry and medication) were extracted from patient charts by their treating physician at the beginning of the run-in phase as part of a survey at the network. Coronary artery disease was considered to be present if the patient had a history of myocardial infarction, angina, coronary revascularization or had significant ST segment depression on resting electrocardiogram as assessed by the treating physician. Liver disease refers to $>50\%$ elevation of liver enzyme levels, including γ-glutamyltransferase. Laboratory data are the mean of three monthly bloodworks at the beginning of the run-in phase. The data extraction for patient characteristics was performed in an unbiased fashion, i.e. before the patient's hypotensive status was determined. Single-pool Kt/V was calculated according to Daugirdas [16] at the beginning of the run-in period. Reported Kt/V values were corrected to include residual renal function according to Gotch and Keen [17], assessed from 44 h interdialytic urine collections. Pre-dialysis blood pressure and ultrafiltration values for the f-IDH and o-IDH groups were derived from those dialysis sessions that were complicated by IDH. For those patients with no-IDH the mean values of 10 dialysis sessions from the beginning of each month of the run-in phase were calculated.

During the main analysis Kaplan–Meier survival curves were constructed for the three groups and comparison of the curves was performed by log-rank test. The independent association of f-IDH and o-IDH with survival was assessed by Cox's proportional hazards model using the no-IDH group as reference. The covariates to be included in the model were decided a priori: age, sex, time spent on haemodialysis before the run-in phase and those variables that show an association with survival in univariate models. The analyses were performed using SAS statistical software release 6.11. Tests that resulted in two-sided P-values of <0.05 were considered statistically significant. Relative hazards (RH) are presented with 95% confidence interval (CI) in brackets.

Results

There were 96 patients with f-IDH, 130 with o-IDH and 168 with no-IDH among the 958 patients of the network during the run-in phase in 1998. Baseline characteristics of the patients with f-IDH and o-IDH have been published previously [12]. Follow-up data could be retrieved on 77 patients with f-DH, on 101 patients with o-IDH and on 85 patients with no-IDH. Baseline characteristics of patients lost to follow-up and those included in this analysis were not significantly different from each other. The median number (range) of hypotensive episodes in patients with f-IDH during the run-in period was 12 (range: 10–38).

Demographic, clinical and biochemical data of the patients from the three groups are presented in Table 1. Patients with f-IDH were older and there were more females among them as compared to those with o-IDH ($P < 0.001$ for the age and $P < 0.05$ for the gender comparison) or no-IDH ($P < 0.001$ for both comparisons). More patients with f-IDH had coronary artery disease than patients in the other two groups ($P < 0.05$ *vs* o-IDH; $P < 0.001$ *vs* no-IDH). Serum phosphorus level was significantly higher in the group with f-IDH ($P < 0.01$ *vs* both o-IDH and no-IDH). Calcium-channel blocker use was less frequent in patients with f-IDH and significantly more no-IDH patients were treated with a diuretic than patients in the other two groups. Long-acting nitrate use was most frequent in patients with f-IDH.

Figure 1 presents the Kaplan–Meier survival curves for the three groups. During the follow-up 58.4% ($n=45$) of the patients with f-IDH (log-rank $P=0.013$ *vs* no-IDH), 46.5% ($n=47$) of the patients with o-IDH (log-rank $P=0.375$ *vs* no-IDH) and 38.8% ($n=33$)

Table 1. Demographic, clinical and biochemical data of the patients with frequent, occasional and no IDH

	F-IDH	O-IDH	No-IDH
Patient number	77	101	85
Age (years)	63.4 (13.0)[a,b]	56.6 (14.9)	55.2 (14.0)
Male (%)	34 (26)[c,b]	53 (53)	62 (53)
Duration of dialysis (months)	44.9 (29.0)	46.1 (26.1)	40.3 (24.6)
Dry weight (kg)	66.2 (13.9)	68.5 (16.2)	67.7 (14.6)
Coronary artery disease (%)	62 (48)[c,b]	46 (46)	38 (32)
Diabetes mellitus (%)	25 (19)	17 (17)	15 (19)
Current hypertension (%)	68 (52)	63 (64)	79 (67)
Liver disease (%)	4 (3)	11 (11)	13 (11)
Laboratory data			
Haematocrit (%)	30.4 (2.9)	31.0 (4.1)	31.6 (4.5)
Calcium (mmol/l)	2.31 (0.19)	2.33 (0.21)	2.32 (0.20)
Phosphorus (mmol/l)	2.02 (0.51)[d,e]	1.80 (0.47)	1.80 (0.50)
Albumin (g/l)	38.3 (3.65)	38.9 (3.56)	38.8 (4.47)
Kt/V[f]	1.13 (0.33)	1.09 (0.29)	1.16 (0.26)
Medication (%)			
β-Blocker	22 (17)	26 (26)	32 (27)
Calcium-channel blocker	38 (29)[e]	51 (51)	59 (50)
ACEI	39 (30)	54 (54)	46 (39)
Diuretic	35 (27)[e]	29 (29)[b]	57 (48)
α-Blocker	26 (20)	29 (29)	24 (20)
Long-acting nitrate	48 (37)[d]	27 (27)	39 (33)
Dialysis data			
Session length (h)	3.9 (0.24)	3.9 (0.26)	4.0 (0.31)
Pre-dialysis SBP (mmHg)	132 (18)[b]	130 (24)[b]	144 (17)
Pre-dialysis DBP (mmHg)	79 (8)[b]	79 (9)[b]	83 (10)
UF rate (ml/h)	858 (239)	857 (323)	895 (316)
UF as percentage dry weight	5.1 (1.9)	5.1 (2.0)	5.5 (2.3)

Values are mean (SD) for continuous variables and % (n) for categorical variables. [a]$P < 0.001$, [d]$P < 0.01$ and [c]$P < 0.05$ *vs* o-IDH. [b]$P < 0.001$ and [e]$P < 0.01$ *vs* no-IDH. [f]Per session with the addition of clearance contributed by residual renal function. ACEI, angiotensin-converting enzyme inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; UF, ultrafiltration.

of the patients with no-IDH died. Median survival time was 19.9 months (95% CI: 11.8–32.6 months) in patients with f-IDH. In univariate proportional hazards models the following variables were associated with increased risk of death: f-IDH [RH: 1.77 (95% CI: 1.13–2.77) *vs* no-IDH], age [RH: 1.04 (95% CI: 1.03–1.06) for 1 year increase], diabetes [RH: 1.95 (95% CI: 1.30–2.93)], coronary artery disease [RH: 2.07 (95% CI: 1.44–2.97)], Kt/V [RH: 0.89 (95% CI: 0.83–0.95) for 0.1 unit increase], albumin [RH: 0.96 (95% CI: 0.92–0.99) for 1 g/l increase], use of β-blockers [RH: 0.60 (95% CI: 0.38–0.94)], use of calcium-channel blockers [RH: 0.69 (95% CI: 0.48–0.98)] and use of long-acting nitrates [RH: 1.53 (95% CI: 1.08–2.18)]. In a multivariate proportional hazards model after adjustment for age, sex, time spent on dialysis, diabetes, coronary artery disease, Kt/V, serum albumin level, use of β-blockers, calcium-channel blockers and long-acting nitrates, neither f-IDH nor o-IDH increased the risk of death (Table 2).

Table 2. RHs and 95% CIs for all-cause mortality from the multivariate model. RHs are adjusted for all other variables

	RH	95% CI
F-IDH (*vs* no-IDH)	1.02	0.62–1.68
O-IDH (*vs* no-IDH)	0.93	0.58–1.50
Age (1 year increase)	1.04	1.02–1.06
Female (*vs* male)	0.79	0.54–1.14
Time on dialysis (1 month increase)	1.01	0.99–1.01
Diabetes mellitus	1.33	0.87–2.04
Coronary artery disease	1.57	0.99–2.49
Kt/V (0.1 unit increase)	0.90	0.84–0.97
Albumin (1 g/l increase)	0.93	0.87–0.98
Use of β-blockers	0.94	0.58–1.53
Use of calcium-channel blockers	0.67	0.47–1.00
Use of long-acting nitrates	0.90	0.58–1.40

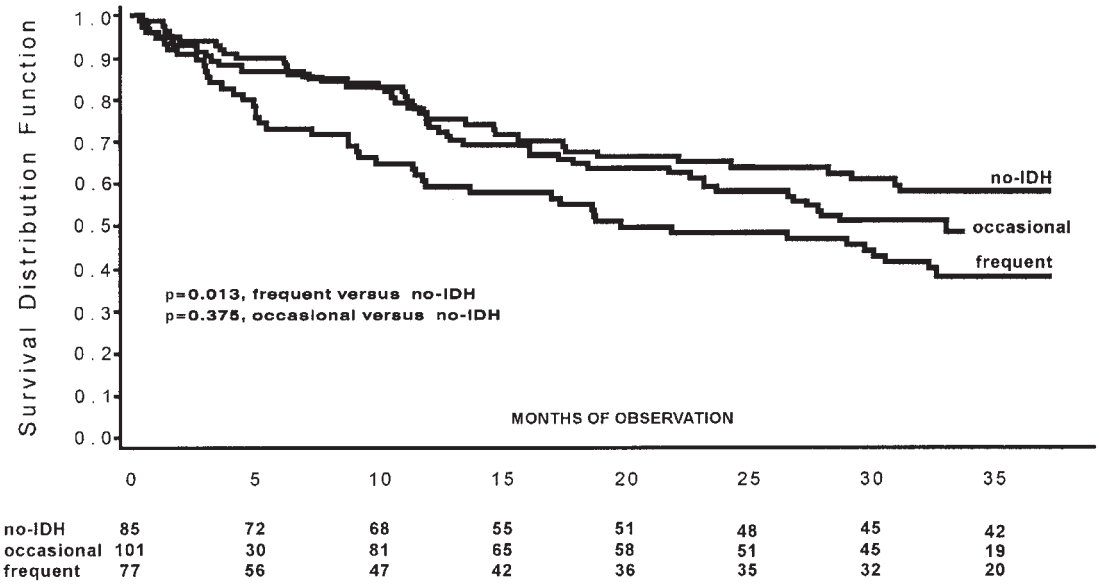

Fig. 1. Kaplan–Meier survival curves of patients with frequent, occasional and no IDH.

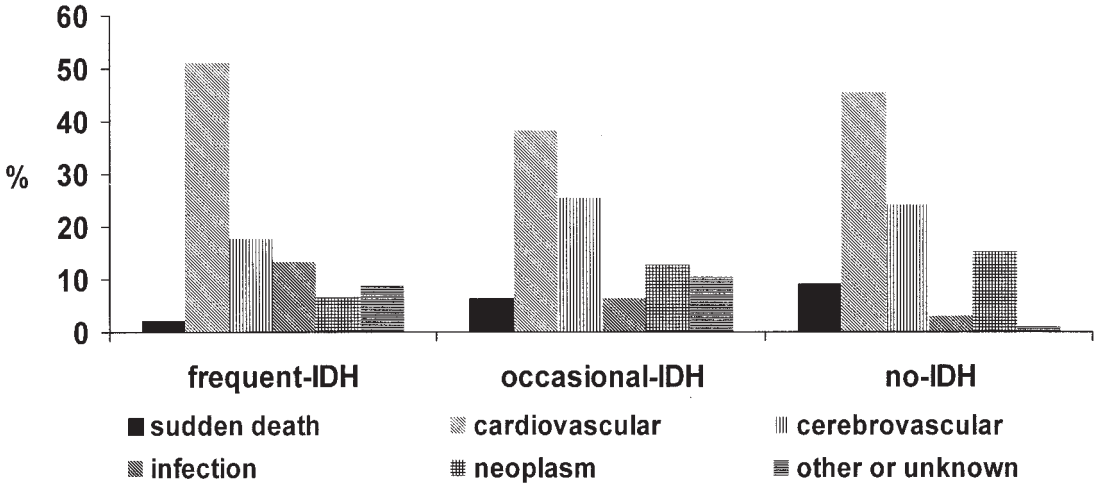

Fig. 2. Causes of death in patients with frequent, occasional and no IDH.

Figure 2 shows the causes of death in the three groups of patients. The majority of deaths were attributed to cardiovascular causes (sudden or cardiac or cerebral death) in all three groups: 71.1% in the group with f-IDH, 70.2% among those with o-IDH and 78.8% in the group with no-IDH. We repeated the analysis considering only cardiovascular mortality as outcome. Similar to the results of the main analysis, neither f-IDH nor o-IDH showed an association with cardiovascular mortality in the multivariate model.

Discussion

In this follow-up study of prevalent chronic haemodialysis patients our objective was to determine survival differences among patients with frequent, occasional and no IDH and to assess whether IDH showed an association with survival independent of patient characteristics. Our main finding was that in patients with f-IDH survival was significantly shorter compared to those with no-IDH. Once differences in baseline patients' characteristics were accounted for in the multivariate model, however, f-IDH did not seem to increase the risk of death.

IDH continues to be a common problem complicating a substantial proportion of haemodialysis sessions [1]. Besides factors directly related to the dialysis procedure itself (e.g. ultrafiltration rate, meal during dialysis, temperature, etc.) several patient characteristics increase the risk of IDH, such as older age, diabetes, left ventricular hypertrophy, coronary artery disease and autonomic neuropathy [2–9]. These risk factors may contribute to IDH by interfering with the haemodynamic cardiovascular mechanisms that counterbalance the decrease in plasma volume during dialysis, such as plasma refilling, arterial tone and venous capacitance, cardiac filling and sympathetic nerve activity [2–4]. The presence of these risk factors was confirmed in our study as patients with f-IDH were generally older and there was more coronary artery disease among them compared to those with no-IDH; the data lying in between for those with o-IDH.

While distressing to the patient and disruptive to the unit, the main clinical significance of IDH may relate to its potential association with patient morbidity and mortality. There are several, not mutually exclusive, mechanisms by which IDH could link to increased mortality. First, IDH could be directly causal in increasing the risk of death, independent of other classical risk factors, through myocardial ischaemia, ischaemic stroke or arrhythmias triggered by the drop in blood pressure during dialysis. Support to this hypothesis may come from results of studies indicating lower survival among those chronic haemodialysis patients with low pre- and post-dialysis blood pressure values [14,15]. Furthermore, alterations in endothelial function, arterial wall composition and blood rheology, seen in end-stage renal disease, may create an environment that promotes the occurrence of morbid events, independent of classical risk factors [13]. Alternatively, f-IDH may result in lower dialysis dose delivered to the patient with consequent increased mortality. Third, IDH may be a marker of the presence of risk factors that increase the risk of both IDH as well as mortality, such as age, diabetes and coronary artery disease. In this case, however, IDH is not expected to be associated with mortality once these covariates are accounted for in multivariate analysis. Of course, a combination of the above possibilities is also plausible.

In our study, survival of patients with f-IDH was significantly lower compared to those with no-IDH, while survival of the patients with o-IDH was not significantly different from that of controls. The high mortality observed in patients with f-IDH suggests that f-IDH may be considered as a warning sign for patients being at high risk of death. In multivariate analysis, however, neither f-IDH nor o-IDH showed an independent association with survival once age, comorbidities, medications and laboratory values were adjusted for. Our data, therefore, do not provide

evidence that the first of the above three possibilities would hold true and our findings suggest that IDH may not directly be associated with survival.

As indicated above, lower delivered dose of dialysis may be the result of f-IDH; therefore, we recalculated our data without the inclusion of Kt/V in the multivariate model. Our conclusion has not been altered by the result of this analysis, suggesting that factors other than Kt/V, probably the older age and the high prevalence of comorbidities in patients with f-IDH, might explain for the apparent lack of an independent association of f-IDH with survival.

In our study, higher Kt/V was associated with improved survival independent of other risk factors. This contradicts the results of the recently published HEMO study [18] that found no difference in survival of patients on standard dose or high dose haemodialysis. It is to be considered, however, that the unequilibrated Kt/V values in our study were lower than those in either groups of the HEMO study and that our reported Kt/V values included the urea clearance contributed by the residual renal function.

It should be noted that the sample size of our study may limit the applicability of our conclusion. The wide confidence interval for the adjusted RH for death among those with f-IDH indicates that we might have failed to identify an independent association between f-IDH and survival. Furthermore, it is also plausible that f-IDH indeed contributes to increased mortality, but its ill effects occur primarily among those who are older or have diabetes or coronary artery disease, i.e. among those with less reserve capacity to compensate for a decrease in vital organ perfusion [19,20]. Our data did not allow us to explore this possibility and perhaps a different design and meticulous analysis of the temporal relationship of events could address this alternative. Further limitation of our study to be acknowledged is that these were prevalent patients who, in addition, had to survive the run-in period to enter the follow-up. The possibility of survival bias, therefore, may limit the generalizability of our results. Finally, we did not collect information on IDH episodes after the run-in phase in either of the groups. As no specific interventions were implemented, it is unlikely that significant crossing over had occurred among the groups. If, however, this was the case it would have biased our results towards no association between IDH and survival.

Based on the findings of our study on survival of patients with IDH, we conclude that f-IDH should be viewed as an indicator of significantly increased risk of mortality as compared with no-IDH. Our data, however, did not provide us with evidence that f-IDH in itself, independent of patient age and comorbidities, is causal in the chain of events leading to increased risk of death in these patients.

Conflict of interest statement. All authors except for A. Tislér are employed part-time or full-time as nephrologists by the EuroCare Nephrological network.

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