Orthostatic hypotension at the introductory phase of haemodialysis predicts all-cause mortality

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Abstract

Background. Since the predictive value of orthostatic hypotension (OH) at the introductory phase of haemodialysis (HD) is unknown, we examined the association between OH and all-cause death in patients who started HD between 1987 and 2001.

Methods. More than three consecutive blood pressure measurements before HD treatments (pre-HD BP) were made on each of 304 patients who had recently been started on HD and were in a stable condition. OH was defined as a drop in systolic BP of >20 mmHg or in diastolic BP of >10 mmHg after standing.

Results. Of 304 patients, 42% had OH. OH was significantly associated with pre-HD supine systolic BP; its severity was significantly associated with a past history of cerebrovascular disease and pre-HD supine systolic BP. During a mean follow-up of 4.0±3.0 years (range 0.1–13.2 years), 136 deaths were recorded. A multivariate Cox proportional hazards model analysis demonstrated that OH and a past history of cerebrovascular disease were independent predictors of all-cause death. The comparison by Kaplan–Meier analysis of the overall survival of patients with and without OH was significant.

Conclusions. Our findings validate OH at the introductory phase of HD as a novel independent predictor of all-cause mortality among HD patients.

Keywords: haemodialysis; orthostatic hypotension; survival rate

Introduction

The mortality rate of patients with end-stage renal disease (ESRD) on haemodialysis (HD) is significantly higher than that of the general population. It has been rising even higher due to the increase in number of older patients and those who have co-morbidities, particularly with cardiovascular complications, being started on HD. Besides the detrimental factors inherent in the HD treatment per se, other factors undoubtedly contribute to the high mortality rate. Although anomalies in blood pressure have been implicated as risk factors for cardiovascular events in HD patients [1–8], no study to our knowledge has investigated the long-term impact of orthostatic hypotension (OH) on their survival. It should also be pointed out that most studies have reported the effect of various factors on the mortality of HD patients who are already undergoing HD. In other words, not much is known about the effect of any factor present before starting HD on the prognosis of HD patients.

The aim of the present observational study in a single HD centre was to determine whether pre-dialysis OH affects the mortality of ESRD patients who start HD treatment.

Materials and methods

Patients

We examined the association between OH at the introductory phase of HD and all-cause death in 304 consecutive patients who were started on HD at the National Cardiovascular Center Hospital between 1987 and 2001, and who had been discharged from there for continued care in various dialysis centres. The survival of the patients as of April 2003 was documented using patient records or telephone questionnaires directed to the treating HD clinics or the patients' families. As in many cases, the causes of death were unclear,
we were only able to evaluate the survival or death of the patients without further analysing the causes of their deaths.

Risk factors examined

More than five consecutive blood pressure measurements before HD (pre-HD BP) were obtained from each patient who had recently been started on HD and was in a stable condition. The ‘introductory phase’ was defined as the 2 weeks after a patient was started on HD until discharge from the hospital. Supine measurements were taken after at least 15 min of rest. Standing measures were taken after 3 min of standing. OH was defined as a drop in systolic BP of ≥20 mmHg or of ≥10 mmHg in diastolic BP with standing. Patients were considered to have OH when this drop was observed on more than three of the five measurements. Age, sex and history of diabetes mellitus, ischaemic heart disease, cerebrovascular accident, atherosclerosis obliterans and smoking were recorded. Serum urea nitrogen, creatinine, total protein, albumin, total cholesterol, C-reactive protein, haemoglobin, haematocrit, body mass index (BMI) and left ventricular mass index (LVMI) were measured. LVMI was calculated using the formula introduced by Devereux et al. [9].

Statistical analysis

All values are expressed as the mean ± SD. Statistical analyses were performed with the Stat View V system (Abacus Concepts, Berkeley, CA). The Mann–Whitney U-test and χ² test were used as appropriate for group comparisons. Survival curves were obtained using the Kaplan–Meier estimation method and were compared by the log-rank test. Risk factors of OH were analysed by using logistic regression multivariate analysis. Multiple linear regression analysis was used to assess the predictive variables of the severity of OH. The Cox proportional hazards regression model was used to assess the relative risks of death in univariate and multivariate analyses. A P < 0.05 was considered significant.

Results

Characteristics of HD patients with or without OH

The pre-dialysis clinical characteristics of HD patients with or without OH [OH (+) or OH (−)], respectively) are shown in Table 1. There was no significant difference between the two groups in age, sex, history of ischaemic heart disease, cerebrovascular accident, atherosclerosis obliterans and smoking, serum urea nitrogen, creatinine, albumin, total cholesterol, C-reactive protein, haemoglobin, haematocrit, BMI or LVMI.

The causes of chronic renal failure and the antihypertensive medications used by the subjects are shown in Table 2. There was no significant difference in the causes of chronic renal failure or the use of antihypertensive medications between OH (+) and OH (−) patients.

Systolic BP, diastolic BP and heart rate in the supine and standing positions examined before and after HD treatments are shown in Table 3. Before HD treatments, supine systolic BP and diastolic BP were higher, and standing systolic BP and diastolic BP were lower in the OH (+) group. After HD treatment, supine systolic BP was higher and
Standing diastolic BP was lower in the OH (+) group.

Risk factors of OH and predictive variables of severity of a fall in systolic blood pressure with standing

OH was significantly associated with pre-HD supine systolic BP (Table 4). The severity of a fall in systolic BP with standing was significantly associated with a past history of cerebrovascular disease and pre-HD supine systolic BP (Table 5).

Predictors of survival

During a mean follow-up of 4.0±3.0 years (range 0.1–13.2 years), 136 deaths were recorded. A multivariate Cox proportional hazards model analysis demonstrated that age, OH and a past history of cerebrovascular accident were independent predictors of all-cause death (Table 6).

Cumulative survival

The cumulative survival curve for all HD patients after the initiation of HD is shown in Figure 1.

The cumulative observed survival of HD patients without OH was significantly better than that of patients with OH. Further analyses were conducted to investigate the effects of age and diabetes mellitus. First, patients were divided into two groups based on age: above \( n = 142 \) or below \( n = 162 \) 65 years. In the older age group, the cumulative survival rate
was significantly lower in the patients with OH, whereas in the younger age group, there was no significant difference in the cumulative survival rate between the patients with or without OH (Figure 2).

Secondly, patients were divided into two groups: with \( (n=134) \) or without \( (n=170) \) a history of diabetes mellitus. The presence of OH had a significant negative effect on the cumulative survival rate in each subgroup (Figure 3).

**Discussion**

Although many studies have identified clinical or laboratory predictors of the survival of HD patients, most of them have investigated the effect of those factors on patients already undergoing HD. There is much less known about the effect of various factors which were in existence before starting HD on the prognosis of HD patients. Some factors leading to premature death in HD patients may already be present when the patients are started on HD. It is therefore important to identify, during the early phase of HD therapy, those patients who are at risk of premature death. The early identification of baseline risk factors that may be treatable is of great practical interest, because their correction may reduce the mortality of patients on dialysis.

The role of the status of blood pressure at the introductory phase of HD as a predictor of mortality remains controversial. Although there are many reports on the association between BP control and mortality, only a few reports deal with pre-dialysis BP and patient mortality. We have shown previously, comparing 132 HD patients who survived with 46 patients who died during a 3-year follow-up, that the survivors had a lower systolic BP than non-survivors. Diastolic BP did not differ between them [7]. A contradictory study was reported by Salem [8], who investigated the effect of hypertension on the 2-year survival of 149 patients starting HD. He found a 27% reduction in mortality among hypertensives compared with normotensives. The explanation for the discrepancies between this report and other reports was not clear [8]. In summary, there has been only a limited number of reports on the effects of BP at the initiation phase of HD on patient mortality. Those reports generally suggest that hypertension is associated with poorer survival. No reports

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**Fig. 2.** Comparison of cumulative survival rate in patients with or without orthostatic hypotension. Patients were divided into the two groups based on age: ■ patients with orthostatic hypotension; ○ patients without orthostatic hypotension.

**Fig. 3.** Comparison of the cumulative survival rate in patients with or without orthostatic hypotension. Patients were divided into the two groups based on the history of diabetes mellitus: ■ patients with orthostatic hypotension; ○ patients without orthostatic hypotension.
exist, however, on the effect of OH on survival. Our study is the first to demonstrate that OH at the introductory phase of HD is a strong and independent predictor of all-cause mortality in ESRD patients.

OH, often found in elderly hypertensives with autonomic nervous system dysfunction, is well recognized as a risk factor for falls, syncope and cardiovascular events [10]. Recent studies have shown that patients with Parkinson’s disease and OH have a diffuse loss of sympathetic innervation throughout the left ventricular myocardium [11]. The finding fits with the notion that OH results from deficient cardiovascular reflexes that depend on the release of the sympathetic neurotransmitter norepinephrine in the heart and blood vessels. Frequent episodes of increased blood pressure variability during daily activity can be the underlying mechanism explaining excess death in patients with OH. In support of this hypothesis, in a recent study, hypertensive patients with OH were shown to have an increased risk of advanced silent brain lesions and greater cardiac burden [12].

There have been a few reports on the prognostic value of OH in the general population. The Honolulu Heart Program investigated the association between OH and 4-year all-cause mortality among a cohort of 3522 Japanese-American men, 71–93 years old. There was a total of 473 deaths in the cohort over 4 years; of those who died, 52 had OH. OH was a significant independent predictor of 4-year all-cause mortality and there was a significant linear association between the change in systolic BP from the supine to standing positions and 4-year mortality rates [13]. A Finnish group studied the prevalence of OH and factors predisposing to it, and also the effect of OH on 10-year vascular mortality, in an elderly population (65 years or older). Of their subjects, 28% had OH. There were no sex or age differences between the subjects with and without OH, and no factors predisposing to OH other than elevated blood pressure were found [14]. In our study, the presence of OH was significantly associated with a past history of cerebrovascular disease and pre-HD supine systolic BP. During a mean follow-up of 4.0 ± 3.0 years (range 0.1–13.2 years), we recorded 132 deaths. A multivariate Cox proportional hazards model analysis demonstrated that OH and a past history of cerebrovascular disease were independent predictors of all-cause death. Comparison by Kaplan–Meier analysis of overall survival of patients with and without OH was significant. In the younger patients (under 65 years), the effect of OH on survival disappeared. In the patients with a history of diabetes mellitus, the effect of OH on survival was still significant, which implied that OH is a stronger predictive factor of poor survival than diabetes mellitus. Indeed, diabetes mellitus had no statistically significant influence on survival in our study (Table 6). The reasons for this are unclear, but this finding may simply imply that other factors, including OH or a history of cerebrovascular disease, have overwhelming influences on survival.

In summary, our findings validate OH at the introductory phase of HD as a novel independent predictor of all-cause mortality among HD patients. The ease and minimal expense of measuring OH may make it a useful tool for identifying a population with a higher mortality rate. Measures to ameliorate OH may improve patient survival.

Conflict of interest statement. None declared.

References

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