

Original Paper

# Effect of Dialysis Day on Intradialytic Hypotension Risk

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## Key words

Hypotension • Hemodialysis • Week • Session • Phosphorus

## Abstract

**Background/Aims:** Intradialytic hypotension (IDH) is a serious and frequent complication of hemodialysis (HD). Thus far, data are scarcely available to assess the impact of first versus subsequent HD sessions of the week in IDH. Therefore, the purpose of this work was to evaluate IDH risk in patients on thrice-weekly HD. **Methods:** We conducted an analysis of all blood pressure (BP) measurements obtained during 492 HD treatments given to 41 prevalent adult patients over a one month period. A logistic regression model for repeated binary observations was used to determine the association between hypotension and patient and dialysis factors. **Results:** The incidence of IDH was 32.5%. First dialysis session of the week was associated with a 9% higher risk of hypotension relatively to the second one. The risk was even higher from the first to the third session of the week (60%) and from the second to the third (50%). A higher hypotension odds ratio was also associated with age (1.03, 90%CI: 1.01-1.06), higher predialysis BP (1.04, 90%CI: 1.03-1.05) and higher phosphorus level (1.38, 90%CI: 1.07-1.76). The risk decreased 24.4% for each additional antihypertensive drug taken by the patient. **Conclusions:** The odds of hypotension occurrence decrease throughout dialysis sessions of the week. Minimizing modifiable risk factors may decrease IDH episodes.

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## Introduction

Intradialytic hypotension (IDH) is a very serious clinical problem. It is one of the most frequent complications in renal replacement therapy which diminishes patient's quality of life, and increases mortality in the dialyzed population. Organ damage may be due in part to episodic tissue hypoxia, including myocardial stunning, ischemic damage to the white matter

of the brain, and perhaps disruption of the gastrointestinal barrier against endotoxins with increased inflammation [1, 2]. Key modifiable determinants of hemodialysis (HD) induced myocardial stunning are ultrafiltration volume and intradialytic drop in blood pressure (BP). Patients with thrice-weekly HD have higher predialysis weights and ultrafiltration rates at the first compared with subsequent dialysis sessions of the week. This is caused by the longer interdialytic interval before the first dialysis session of the week, which results in a higher interdialytic weight gain (IDWG). Greater IDWG implies the need for more rapid fluid removal because dialysis time is essentially fixed for individual patients.

These variations in fluid status over the week may have major consequences for BP dynamics before and during the individual dialysis sessions. So we decided to collect hemodynamic data repeatedly for each HD patient during one month.

## Materials and Methods

### *Study Design*

The criteria to be eligible for the study were: participants with >18 years of age, medically stable, an HD schedule of 3 times weekly for 4 hours and for more than 2 months. Since BP may fluctuate more widely immediately after dialysis therapy initiation due to dry weight probing and medication titration, we excluded patients on HD therapy for less than 2 months.

Patients entered the cohort between September and October, 2012. In total, the analytical cohort consisted of 41 unique patients. Laboratory parameters were measured monthly according to the organization protocol; all processing was conducted at a single clinical laboratory. Dialytic session data were recorded on a session-to-session basis. Patients were dialyzed on either a Monday-Wednesday-Friday or Tuesday-Thursday-Saturday schedule. Monday and Tuesday were defined as the first; Wednesday and Thursday, as the second; and Friday and Saturday, as the third sessions of the week. Data were analyzed separately for the first, second, and third sessions of the week. BP was measured with the patient in the seated position using automated oscillometric devices immediately before, after, and during all treatment sessions. Target weight was evaluated clinically (peripheral edema, signs of pulmonary congestion, intra- and extradialytic BP course, and muscle cramps) and by (changes in) the cardiopulmonary radiologic aspect. Excess weight at the start of dialysis was defined as the difference between predialysis weight and target weight. The prescribed ultrafiltration volume was calculated by adding the estimated intradialytic fluid intake (usually 500-750 mL) to the excess weight. However, for all analyses, the exact ultrafiltration volume as delivered by the dialysis apparatus was used. Dialysis hypotension was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) definition: a drop in BP  $\geq$  20 mmHg in systolic BP or  $\geq$  10 mmHg in mean arterial pressure; the presence of symptoms of end organ ischemia; and an intervention carried out by the dialysis staff. Hypertension was defined as BP >140mmHg systolic or >90mmHg diastolic. Heart failure was defined as left ventricular ejection fraction <50%.

### *Dialysis Settings*

All patients were dialyzed with synthetic hollow-fiber dialyzers, Elisio™ – 15H, 17 H or 21H (Nipro). All the sessions consisted of standard HD using standard dialysis solutions. Standard bicarbonate concentrations were adjusted if necessary (30-35 mmol/L). Two needles were used in all patients with an arteriovenous access. Blood flow ranged from 300-450 mL/min. Dialysate flow was 500 or 700 mL/min. Blood flow and dialysate flow were kept constant throughout the study period in individual patients. All patients were dialyzed with a constant ultrafiltration rate. Dialysate temperature was 35.5°C or 36.0°C and was kept constant during the study period for individual patients. Patients received a light meal and 2 cups of coffee or tea during treatment. Dialysis settings were identical for the first, second, and third sessions of the week. Individual treatment characteristics were not changed in the course of the study.

### *Data Collection and Description*

Information on demographic characteristics (age, gender, dialysis vintage) and comorbid conditions (diabetes, hypertension, heart failure) were obtained from the clinical electronic medical record. Laboratory

values (parathyroid hormone, phosphorus, calcium, and hemoglobin) were relative to the month of study. Dialytic session characteristics (predialysis BP, ultrafiltration volume, and excess weight at HD start) were collected at each dialysis session. Prescribed antihypertensive medications were also considered and were not changed for the purposes of the study.

The number of IDH episodes in 12 consecutive HD sessions was recorded for each patient. The responsive measures included saline administration or premature cessation of dialysis.

#### Statistical Analysis

Quantitative variables were described by the mean and the standard deviation. The distribution of categorical variables was represented by proportions.

The model considered was a logistic regression model for repeated binary observations (repeated measures or longitudinal data), estimated by the generalized estimation equations method assuming an unstructured working correlation matrix (to account for the correlation among repeated binary observations, i.e., intra-patient or within-subject dependence).

The independent variables considered were gender, age, dialysis vintage, diabetes, hypertension, heart failure, number of antihypertensive drugs taken by the patient, hemoglobin, parathyroid hormone, calcium and phosphorus level, predialysis BP, ultrafiltration volume, interdialytic weight gain and dialysis session of the week.

Because of the large number of these variables, simple (bivariate) regression models were fit first with each variable as independent and the significance of the corresponding estimated parameter was checked at the 10% significance level. The variables with nonsignificant estimated parameters were excluded, which led to a fitted model including dialysis session of the week, age, predialysis BP, number of antihypertensive drugs and phosphorus level.

## Results

### Cohort and Treatment Characteristics

Overall, 41 Caucasian patients underwent a total of 492 dialysis treatments, during which 3 qualifying BP measurements were recorded. Characteristics are listed in table 1.

Mean age was 65.9 years, most ages range between 60 and 80 years, with only a few lower than 50 years. All patients were dialyzed by arteriovenous fistula and 58.5% were prescribed antihypertensive medications with a maximum of 4 drugs. Patients taking 1 (19.5%) or 2 drugs (22%) were the most frequent.

### BP Metric

An important proportion of patients had hypotension on each session (table 2). In fact, this proportion ranged from 22% to 48.8% (nearly half the patients) and was above 30% half of the sessions analyzed. Note also that the largest proportion occurred on the first session of the week (session 1, 4 and 10) with the exception of the third week where it occurred on the second day.

Table 3 displays the information concerning quantitative time-dependent variables in each dialysis session. The most important conclusion is the fact that values were larger on the first

**Table 1.** Patient characteristics

Variable	
Age (years)	65.9 ± 13.1
Male gender	23 (56.1)
Dialysis vintage (months)	46 [4-388]
Diabetes mellitus	11 (26.8)
Hypertension	26 (63.4)
Heart failure	10 (24.4)
Number of antihypertensive drugs	1.2 ± 1.2
Hemoglobin (g/dl)	11.5 ± 0.62
Parathyroid hormone (pg/ml)	300.8 ± 153.6
Calcium (mg/dl)	8.8 ± 0.38
Phosphorus (mg/dl)	4.8 ± 1.2

Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation

dialysis session than on the other two days of the week and that values on the second day were larger than those on the third, although the differences were smaller.

IDH occurred 63 times (a proportion of 38.4%), 55 times (33.5%) and 42 times (25.6%) on the first, second and third day respectively. Consequently, hypotension occurrence was larger on the first day and also decreased throughout the week.

The fitted logistic regression model (table 4) shows that hypotension occurrence was positively affected by age, dialysis session of the week, the phosphorus level and predialysis BP and negatively by the number of antihypertensive drugs taken by the patient.

**Table 2.** Hypotension occurrence

Session	Hypotension	
	n	%
1 (First day, week 1)	15	36.6
2 (Second day, week 1)	15	36.6
3 (Third day, week 1)	10	24.4
4 (First day, week 2)	13	31.7
5 (Second day, week 2)	12	29.3
6 (Third day, week 2)	11	26.8
7 (First day, week 3)	15	36.6
8 (Second day, week 3)	16	39.0
9 (Third day, week 3)	9	22.0
10 (First day, week 4)	20	48.8
11 (Second day, week 4)	12	29.3
12 (Third day, week 4)	12	29.3
Total	160	32.5

**Table 3.** Predialysis BP, ultrafiltration volume and excess of weight at HD start on each dialysis session of the week

	First HD of week	Second HD of week	Third HD of week
Predialysis BP (mmHg)	143.8 ± 28.9	137.6 ± 28.6	134.9 ± 28.4
Ultrafiltration volume (L)	3 ± 0.98	2.6 ± 0.99	2.4 ± 0.85
Interdialytic weight gain (Kg)	2.7 ± 1	2.4 ± 1	2.3 ± 0.93

Values are given as mean ± standard deviation

**Table 4.** Logistic regression estimation results

Variable	Parameter estimates				Odds ratios	
	Estimate	Wald		90% CI	Ratio	90% CI
		statistic	p-value			
Intercept	-9.678	29.49	0.000	]-12.61,-6.75[	0.000	]0.000,0.001[
Age	0.030	4.27	0.039	]0.006,0.053[	1.030	]1.006,1.055[
First session	0.462	3.87	0.049	]0.076,0.848[	1.587	]1.079,2.335[
Second session	0.376	2.95	0.086	]0.016,0.736[	1.456	]1.016,2.087[
Number of anti-hypertensive drugs	-0.280	5.22	0.022	]-0.481,-0.078[	0.756	]0.618,0.925[
Phosphorus level	0.318	4.48	0.034	]0.071,0.566[	1.375	]1.073,1.761[
Predialysis BP	0.038	57.12	0.000	]0.029,0.046[	1.038	]1.030,1.047[

## Discussion

One of most relevant findings of this study is the decreased risk of hypotension along each session in a three weekly HD regimen. The odds of hypotension occurrence on the first session of the week were 1.59 times those of the third session, nearly a 60% increase, and could achieve 2.335, more than twice the odds on the third session. Surprisingly, the risk of hypotension was not related with ultrafiltration or IDWG. Comparing the second and third dialysis session, the odds of having hypotension was 1.5, a 50% increase, and they could achieve 2.087, twice the odds on the third session. Furthermore, the odds of hypotension occurrence on the first session of the week were 1.09 times those of the second one, a 9% increase, and the increase could achieve 11.9%.

A previous prospective observational study conducted to compare the hemodynamics of first versus subsequent HD sessions of the week, involved 124 Dutch patients and 789 US patients followed during 3 months [3]. The US cohort showed significantly higher rates of dialysis hypotension (15.6%, 17.7%, and 17.2% of treatments at the first, second, and third sessions of the week, respectively) than the Dutch cohort (7.4%, 6.6%, and 7.2% of treatments at the first, second, and third sessions of the week, respectively) [3]. The frequency of dialysis hypotension was more pronounced on the first treatment of the week in Dutch study population. In the US cohort, contrary to this finding, fewer hypotensive episodes occurred on the first HD day compared to the second and third HD days.

It is important to note first that the definition of IDH in this study - decrease in systolic BP (SBP) <30 mm Hg in combination with SBP decrease to <90 mm Hg - can be a potential explanation for the lower IDH rates in comparison to our study and the literature [2, 4, 5].

Age, gender and proportion of patients with diabetes were similar in our cohort and in the Dutch study population which may explain the similar results concerning frequency of hypotension brought about by the first dialysis session of the week. This is reflected in other European studies showing a trend for a reduction in the frequency of IDH episodes as the week progressed [6].

Another prospective study evaluating 13 HD facilities in five US states also concluded for an increased frequency of IDH associated with HD on the second and third weekly treatment day [7]. Such result was unexpected for the authors without a possible explanation for this association.

A growing body of literature demonstrates unfavorable outcomes for the weekend interval in a three weekly session HD regimen. We evaluated for the first time the risk and not only the frequency and further found that IDH risk also decrease from the second to the third session of the week, with only one day of treatment interruption.

Results from the randomized frequent hemodialysis network trials showed that in the daily trial, the relative risk per dialysis session of IDH was lower with a six-times/week HD [8]. Daily dialysis therapies are characterized by improved treatment tolerability [9, 10] and reasonably lower risk of IDH. One might theorize that one day interval changes in multiple biochemical parameters and hemodynamic control raise the risk of IDH.

Finally and perhaps most important, our data extend this observation and identified other dialysis and patient-level risk factors associated with hypotension.

Our study showed that the odds of hypotension occurrence increased 3% for each additional year of age, and that the increase can achieve 5.5%. This finding was anticipated and consistent with previous reports [7, 11].

Our results also revealed that the odds of hypotension occurrence decrease 24.4% for each additional antihypertensive drug and that the decrease could achieve 38.2%. This finding is in contrast with a study evaluating 7890 HD sessions during a 1-week period in the Greater London area renal centers [12]. Concerning those patients prescribed antihypertensive agents had no impact on the frequency of IDH, regardless of whether they took or abstained from medication before dialysis.

Recent evidence suggests that angiotensin-converting enzyme inhibitors and calcium channel blockers may have an additional effect in preventing coronary artery disease, and both are protective against stroke, exerting cardioprotective effects that are independent of BP reduction. Knowing that hypotensive episodes are associated with accelerated ageing of arterial system, extensive calcification and stiffening of arterial walls [13], this contribution to cardiovascular outcomes may explain the positive effect of antihypertensive drugs.

The odds of hypotension occurrence, in our study, increased 3.8% for each predialysis BP additional mmHg and the increase could achieve 4.7%. The mechanism of this association is difficult to ascertain and probably complex.

These data are in line with a population-based study conducted to audit BP control and IDH during 1 week in 2193 patients, capturing 6579 HD sessions in London. It concluded that diabetic HD patients had higher BP, both before and after dialysis, associated with



greater IDWG and more frequent IDH [6], highlighting the role of higher BP in IDH episodes.

Hypertensive patients had a less compliant vasculature and accelerated endothelial dysfunction [12, 14]. In a recent cross-sectional analysis of 30 dialysis patients, endothelial dysfunction as measured by flow-mediated, endothelium-dependent vasodilation was independently associated with IDH [15].

In the same line of reasoning mineral metabolism disorders such as hyperphosphatemia, play a major role in pathophysiology of calcifications. Previous studies suggest that phosphorus itself has a detrimental hemodynamic effect [11, 15]. In our report the odds of hypotension occurrence increase 37.5% for each phosphorus level additional mg/dl and the increase could achieve 76.1%. This agrees with the literature, since strong correlations have been found between hyperphosphatemia and vascular calcification which causes increased arterial stiffness and contributes to IDH.

This retrospective cohort study enrolled only a small number of participants and followed a limited time course. Multicenter prospective randomized control trials could help circumventing these limitations.

### Conclusion

One of the main findings of this study, designed to compare the hypotensive events in a thrice-weekly HD regimen, is the decreased risk of IDH from first to second and from this to the last session of the week. Since hypotension is one of the most frequently encountered complications in HD, contributing to a significant morbidity and mortality, the widespread choice of thrice-weekly schedules in clinical practice, implies greater attention by the medical and nursing team to these events in the first 2 sessions of the week. This study also provides evidence of the role of modifiable risk factors like hypertension and hyperphosphatemia in intradialytic hypotensive episodes.

### Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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