
Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome

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Abstract

Intradialytic hypotension (IH) is a frequent complication of hemodialysis (HD) and is associated with increased patient mortality and cardiovascular events. We studied IH to determine its variability, correlates, and clinical impact in 13 outpatient HD facilities. Blood pressure was captured by machine download. IH was defined as >30 mmHg decrease in systolic blood pressure to <90 mmHg. Risk factors were assessed by logistic regression and hospitalization by Poisson regression. Time to death and first hospitalization were assessed using Kaplan–Meier analysis in patients completing >20 HD treatments. We studied IH in 44,801 treatments (Tx) in 1137 patients. IH was frequent (17.2% of treatments) and highly variable by patient (0–100% Tx) and dialysis facility (11.1–25.8% Tx). 25.1% of patients had no IH (0% Tx) and 16.2% had IH on >35% Tx. Increased IH frequency was associated with age, female gender, diabetes, Hispanic origin, longer end stage renal disease vintage, higher body mass index, higher ultrafiltration volume, the second and third weekly Tx, lower pre-HD systolic blood pressure, higher difference between prescribed and achieved post-HD weight, and higher dialysate temperature. Dialysis facility was an independent predictor of IH frequency. Patients with >35% IH treatments had poorer survival ($P = 0.036$), and more frequent and longer hospitalization ($P = 0.04$, $P = 0.002$, respectively) than patients without IH. In conclusion, IH frequency was highly variable, associated with individual facilities, patient and treatment characteristics, and correlated with mortality and hospitalization. Identifying practice patterns associated with IH coupled with routine reporting of IH will facilitate medical management and may result in the prevention of IH, decreased mortality, and decreased hospitalization.

Key words: Blood pressure, hemodialysis, hypotension, intradialytic hypotension

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INTRODUCTION

Intradialytic hypotension (IH) is reported to occur during approximately 5% to 30% of hemodialysis (HD) treatments (Tx)^{1–4} and has been associated with increased

patient mortality, access failure, and cardiovascular events.^{5–9} Despite this significant impact, IH is not routinely reported or aggregated in US HD facilities. This lack of categorized reporting makes it difficult to assess the overall frequency and impact of IH and may hinder routine medical management. Investigations of IH etiology have primarily focused on the patient factors associated with the development of hemodynamic instability, blood pressure (BP) variability, and specific interventions to prevent and treat IH.^{10–18} Despite the multiplicity of reports, the majority of studies reflect a relatively limited number of HD treatments in a small number of dialysis facilities and do not provide insight into the overall incidence of IH in the broader HD population. Additionally, there is a paucity of data regarding the variation in IH frequency in individual patients or between dialysis facilities. The purpose of this study was to determine the variability of IH in individual patients and outpatient dialysis facilities, the patient and treatment factors associated with IH, and the impact of IH on patient outcomes including hospitalization and mortality.

METHODS

We prospectively evaluated the epidemiology of IH in 13 outpatient Renal Research Institute (RRI) HD facilities in five US states (New York 4, Connecticut 3, Michigan 2, Illinois 1, North Carolina 3) between March 2011 and July 2012. The data collection was part of an ongoing quality improvement initiative with data feedback to the patients' caregivers as part of their normal clinical care. These activities are covered under patients' informed consent for treatment and do not qualify as "human research."

IH was defined as an intradialytic decrease in systolic BP (SBP) by more than 30 mmHg to a level of less than 90 mmHg. Multiple episodes of IH during the same HD treatment were considered as one IH episode, and the HD treatment was considered to have had an IH event (IH treatment). BP was measured approximately every 30 minutes during dialysis, captured by direct machine download (iCare system, Fresenius Medical Care NA, Waltham, MA, USA) and stored in a database. Patient demographics, treatment parameters, laboratory data and clinical outcomes were obtained from the RRI clinical data warehouse. All treatments with available intradialytic BP data were included for data analysis.

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc, Cary, NC). Mean, standard deviation and 95% confidence intervals were calculated for continuous variables; frequency, 95% confidence intervals and

percent were calculated for categorical variables. Continuous variables were compared by Student t test between groups. Predictors of IH were investigated with logistic regression. We built both unadjusted and adjusted models; for the latter we employed a generalized form of mixed effects models with patient-specific random effects. This adjustment takes into account the intra-patient variability in patient parameters. Time to death and time to first hospitalization were modeled by Kaplan–Meier analysis. For time to event analysis, we analyzed up to 7 months of follow-up and included only patients with more than 20 recorded treatments. Unadjusted Poisson regression was used to compare total number of hospital admissions and number of hospital days. Further, relationships between IH, and time to death and first hospitalization were evaluated using Cox proportional hazard model adjusted for risk factors for IH, which were significant in the aforementioned logistic regression. Please note: this analysis did not include some lab variables such as hemoglobin, serum sodium, serum K, and albumen that have been reported associated with IH. Significance was defined as a two-sided P value < 0.05.

RESULTS

We studied 44,801 treatments in a total of 1137 patients as part of an ongoing quality improvement initiative. Patient demographics and treatment parameters are shown in Table 1. IH was common (present in 17.2% of all treatments) and was highly variable by patient (between 0% and 100% of all treatments), facility (11.1–25.8% of all treatments) and calendar treatment date (6.8–26.9% of all treatments on a specific calendar date i.e., mm/dd/yyyy). The majority of patients (75.1%) had one or more episodes of IH (facility range: 63.0% to 84.8% of facility patients had ≥1 IH episode) and 25.1% of patients had no episodes of IH (zero frequency: IH on 0% of their Tx; facility range: 15.2–37.0% patients with 0% IH Tx). In 58.8% of patients, IH occurred in 1% to 35% (moderate frequency) of their Tx (facility range: 50.4–73.7% patients with 1–35% IH Tx) and 16.2% of patients had IH on >35% (high frequency) of their Tx (facility range: 10.3–33.0% patients with >35% IH Tx) (Table 2).

Over and above patient-related factors, individual dialysis facilities were independently associated with the frequency of IH (expressed as % of treatments affected with IH), both without and with adjustment for patient-specific random effect (this adjustment takes into account intra-patient variability in patient parameters; Table 3;

Table 1 Patient demographics (N = 1137)

	Mean	Range between facilities
Number of patients (N)	1137	
Patients (N) per facility	87.5	24–175
Age (years)	61.94 (15.78)	55.4–68.4
Race		
Black (%)	51.4	5.3–72.0
White (%)	44.0	8.6–87.1
Hispanic (%)	11.5	0–29.1
Male (%)	53.5	47.1–64.8
Diabetic (%)	56.2	41.8–64.8
Vascular access		
AVF (%)	60.7	48.9–79.4
AVG (%)	22.1	7.4–37.5
Catheter (%)	16.4	7.2–27.2
Vintage (years)	4.51 (4.26)	2.95–7.89
BMI (kg/m ²)	29.0 (8.8)	26.7–32.0
Pre-dialysis SBP (mmHg)	145.5 (20.1)	140–155
Treatments with IH (%)	17.2	11.3–25.8
Sodium gradient (mmol/L) ^c	-1.26 (2.75)	0–2.0
Post weight – EDW (kg)	0.62 (5.1)	0–2.2
Blood flow (mL/min)	428 (46.8)	390–488
Dialysate flow (mL/min)	680.0 (68.9)	629–762
Treatment time (min)	216.3 (29.8)	201–232
spKt/V	1.58 (0.29)	1.47–2.00
Dialysate sodium (mmol/L)	137 (1.1)	136–138
Dialysate potassium (mmol/L)	2.2 (0.35)	2.0–2.4
Dialysate bicarbonate (mmol/L)	35.4 (1.1)	35.0–37.0
Dialysate temperature (Celsius)	36.5 (0.39)	36.2–36.9

AVF = arteriovenous fistula; AVG = arteriovenous graft; BMI = body mass index; EDW = estimated dry weight; IH = intradialytic hypotension; sodium gradient = dialysate sodium-serum sodium; SBP = systolic blood pressure.

data without adjustment not shown). Increased risk of IH was associated with greater age, female gender, presence of diabetes, Hispanic ethnicity, longer vintage, higher body mass index (BMI), larger ultrafiltration volume (UFV), HD on the second and third weekly treatment day, lower pre-HD SBP, higher difference between prescribed post-HD weight and actually achieved post weight (calculated as achieved minus prescribed post-HD weight), and higher dialysate temperature.

Mortality and hospitalization were analyzed in the subset of patients (N = 446) with more than 20 recorded treatments. In this subset, time at risk was computed from the 20th treatment through December 31, 2012. For the purpose of this analysis, patients were divided into three groups based upon IH frequencies: IH in 0% of treatments (zero frequency), IH in 1% to 35% of treatments (moder-

ate frequency), and IH in >35% of treatments (high frequency). In these 446 patients, mortality was 11.69 deaths per 100 patient-years, hospitalization rate was 1.24 per patient year, and hospitalization days per patient year was 9.31. Mortality rate, hospital admission rates, and number of hospital days were significantly higher in patients with a high frequency of IH (Table 4).

Survival analysis demonstrated a difference in survival between these three groups (P = 0.045; Figure 1). Patients with highly frequent IH had the poorest survival (P = 0.036 compared with patients with without IH (zero frequency: 0% of treatments). Survival did not differ between patients with zero and moderate IH frequency (Table 4). When compared with patients with a high frequency of IH, the adjusted hazard ratio of death was 0.45 (P = 0.20) in patients without IH (zero frequency), and

Table 2 Intradialytic hypotension (IH) by clinic

Facility	Number of patients	Number of treatments	Treatments with IH (%)	Patients with zero frequency IH (0% treatments; %)	Patients with moderate frequency IH (1–35% treatments; %)	Patients with high frequency IH (>35% treatments; %)
Facility 1	76	2,351	19.1	21.1	63.2	15.8
Facility 2	99	5,537	18.2	15.2	73.7	11.1
Facility 3	24	646	19.0	20.8	62.5	16.7
Facility 4	139	2,803	21.3	30.2	50.4	19.4
Facility 5	54	1,606	23.7	20.4	55.6	24.1
Facility 6	114	7,223	16.2	21.9	65.8	12.3
Facility 7	70	2,634	19.2	20.0	60.0	20.0
Facility 8	69	2,223	19.7	29.0	56.5	14.5
Facility 9	79	2,193	15.1	27.8	58.2	13.9
Facility 10	73	3,364	13.6	37.0	50.7	12.3
Facility 11	68	3,650	19.9	33.8	52.9	13.2
Facility 12	97	2,537	25.8	15.5	51.5	33.0
Facility 13	175	8,034	11.1	28.6	61.1	10.3
Total	1,137	44,801	17.2	25.1	58.8	16.2

0.40 (P = 0.08) in patients with moderate IH frequency, respectively. Hospitalization rate and number of days spent in the hospital were associated with the frequency of IH; patients without IH (zero frequency) experienced the

least and shortest hospitalizations (Table 4). When analyzing the time to first hospitalization, we observed a significantly shorter time to first hospitalization in patients with a high frequency IH (P = 0.039) (Figure 2).

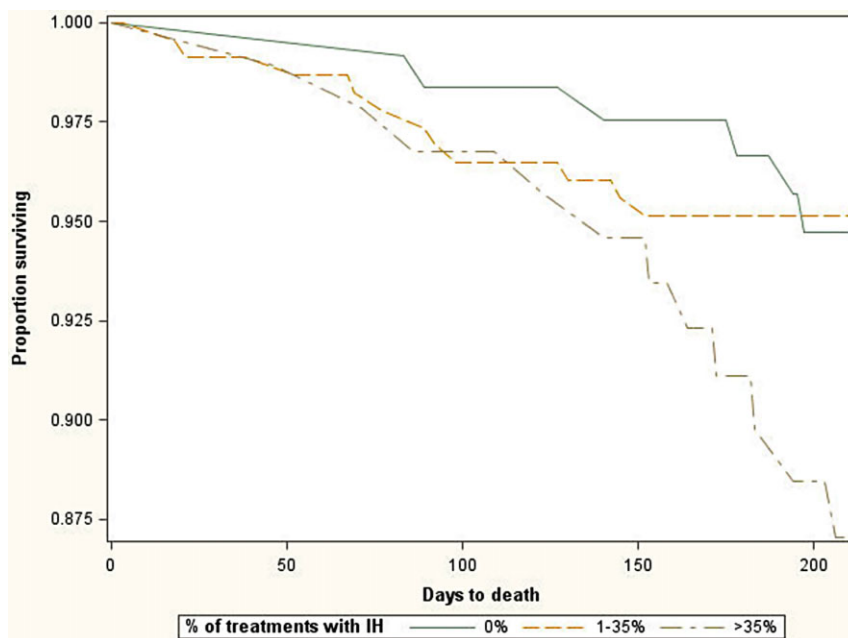


Figure 1 Time to death (N = 446). Patients with no (0%) treatments (zero frequency) with intradialytic hypotension (IH) had longer survival than patients with 1% to 35% (moderate frequency) or with >35% (high frequency) of treatments with IH (log-rank test; P = 0.045).

Table 3 Correlates of intradialytic hypotension (IH) by logistic regression

	Odds ratio	95% lower CI	95% upper CI	P value
Age (years)	1.020	1.014	1.025	<0.0001
Male	0.628	0.541	0.729	<0.0001
Race = White	1.027	0.870	1.212	0.7569
Diabetic	1.375	1.179	1.604	<0.0001
Hispanic	1.391	1.084	1.786	0.0095
Vintage (years)	1.046	1.029	1.062	<0.0001
Catheter	1.170	0.961	1.424	0.1187
BMI (kg/m ²)	1.013	1.004	1.023	0.0058
Shift				
Midday	0.894	0.763	1.047	0.1638
Evening	0.767	0.618	0.951	0.0155
Tx day				
Second tx day of the week	1.065	1.004	1.129	0.0356
Third tx day of the week	1.121	1.057	1.189	0.0001
Pre-HD SBP (mmHg)	0.986	0.985	0.988	<0.0001
Ultrafiltration volume (L)	1.309	1.251	1.369	<0.0001
Treatment time (h)	1.080	0.997	1.170	0.0609
Dialysate temperature (Celsius)	1.077	1.011	1.147	0.0209
Achieved minus prescribed post weight (kg)	1.020	1.010	1.031	0.0002
Dialysate sodium (mmol/L)	1.015	0.950	1.084	0.6593
Dialysate potassium (mmol/L)	0.948	0.797	1.127	0.5447
Facility 3	0.889	0.558	1.414	0.6185
Facility 4	1.087	0.819	1.443	0.5651
Facility 5	1.387	1.024	1.879	0.0346
Facility 6	0.906	0.684	1.201	0.493
Facility 7	1.032	0.734	1.450	0.8582
Facility 8	1.031	0.704	1.510	0.8745
Facility 9	0.859	0.606	1.218	0.3934
Facility 10	0.746	0.514	1.081	0.1212
Facility 11	1.078	0.746	1.556	0.6896
Facility 12	1.333	1.007	1.763	0.0446
Facility 13	0.618	0.458	0.833	0.0016

Odds ratio with IH as outcome by treatment with adjustment for random patient effect (for 1 unit change in the predictor variable). Reference = non-White, non-diabetic, female gender, treated in Facility 1 and 2, treated in the morning, and treated on the first tx day of the week.
 CI = confidence interval.

Table 4 Mortality and hospitalization in patients with ≥20 treatments^a

Percent of treatments with IH	Number of patients	Number of treatments	Deaths per 100 pt yrs	Hospital admissions per pt yr	Hospital days per pt yr
Zero (0%)	123	2460	8.90	1.10	8.90
Moderate (1–35%)	230	4600	8.9 (P = 0.999)	1.21 (P = 0.47)	9.02 (P = 0.725)
High (>35%)	93	1860	22.4 (P = 0.036)	1.5 (P = 0.04)	10.84 (P = 0.0002)
Total	446	8920	11.69	1.24	9.31

^aP values for comparison with patients with low IH frequency (<1% treatments).
 IH = intradialytic hypotension.

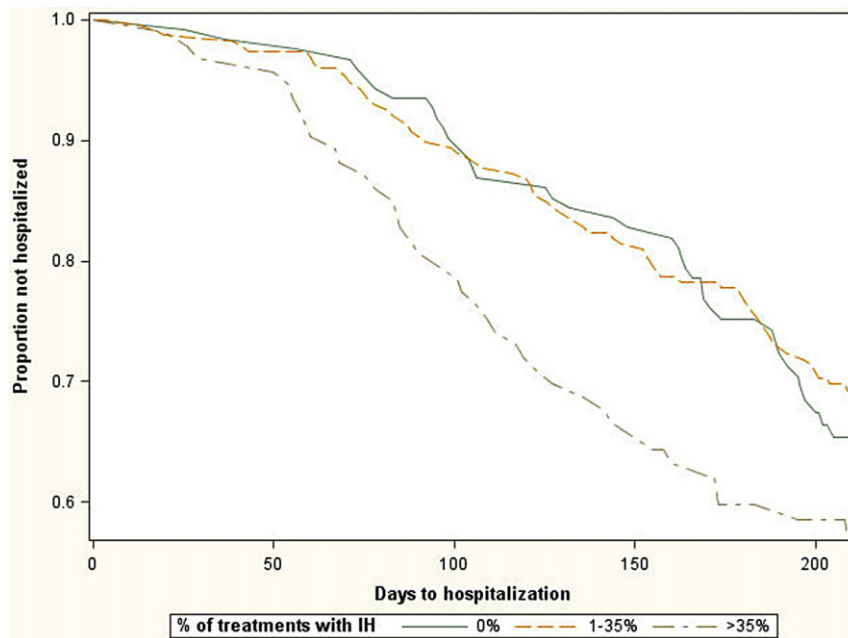


Figure 2 Time to first hospitalization (N = 446). Patients with >35% (high frequency) of treatments with intradialytic hypotension (IH) had a shorter time to first hospitalization than patients with 0% (zero frequency) or 1% to 35% (high frequency) of treatments with IH (log-rank test; P = 0.039).

DISCUSSION

IH is a frequent complication of HD therapy¹⁻⁴ with significant impact upon patient outcomes.⁴⁻⁹ In this study, IH was present in 17.2% of all treatments in a large sample size of 1137 patients with more than 44,800 treatments. This IH frequency is consistent with previous reports and emphasizes the clinical significance of the problem of IH. Shoji et al.⁶ reported an increased risk in mortality at 2 years in patients with a ≥ 40 -mmHg intradialytic fall in SBP during one HD treatment. Our data extend this observation by linking increased hospitalization, hospitalized days, and mortality to an increased frequency of treatments with IH episodes. Mechanistically, this is also consistent with reports linking IH with myocardial stunning and adverse outcomes.⁹

Although the pattern of change in BP during HD has been previously reported,¹⁰ the high variability of IH frequency between facilities, independent of patient characteristics and treatment parameters, has been largely unappreciated, unreported, and not actively managed. This variability of IH frequency among outpatient facilities is likely the result of unrecognized variations in practice patterns and provides a fertile opportunity to improve patient outcomes. In particular, the facility level variation of IH frequency, given the association with

adverse patient outcomes,⁴⁻⁹ makes IH an attractive target for quality improvement initiatives. Numerous studies have evaluated potential therapeutic interventions to decrease IH. These include use of low-temperature dialysate,^{1,13,14} decreasing the ultrafiltration rate,^{11,12} longer and more frequent dialysis,^{11,15} the use of hemodiafiltration,¹⁶ means to lower interdialytic weight gain,¹¹ high dialysate calcium,¹⁹ biofeedback control of ultrafiltration and infusion²⁰, and adjustment of dialysate sodium.²¹ All these studies agree that IH has a high clinical impact and proposed multiple potential therapeutic interventions. However, IH is not consistently defined, regularly aggregated, or reported in US outpatient dialysis facilities. This lack of routine reporting limits the medical management of IH and often leaves attending nephrologists unaware of the frequency their patients experience IH. These gaps in reporting offer an enticing potential avenue to improve patient's clinical outcomes. We hypothesize that patient outcomes can be improved through active and routine reporting, tracking and treating of IH as part of ongoing clinical care and the facility quality improvement process. Further studies are necessary to determine whether such active reporting and routine assessment and management of IH will lead to improved patient outcomes, decreased hospitalization, and decreased cost of care.

Maduell et al.²² recently reported that the incidence of symptomatic IH was 679.2 episodes per 100 patient-years (~4.03% treatments) with online hemodiafiltration and 937.7 episodes per 100 patient-years (~6.01% treatments) with HD. Despite different IH definitions (our study did not capture symptomatic IH vs. non-symptomatic IH), one can speculate that these markedly lower rates of IH may contribute to the lower mortality rates for end-stage renal disease patients reported in Europe when compared with patients in the United States.²³

Most of the individual factors associated with IH frequency (increased age, female gender, diabetes, vintage, UFV, etc.; Table 3) were anticipated; however, the lower risk of IH on the first HD day of the week was unexpected. This may be related to the other adjustments including UFV in the model. Moreover, dialysis treatment time and dialysate sodium were not significantly associated with IH frequency. This lack of significance may relate to the limited range of treatment times (216.3 ± 29.8 minutes) and the relatively uniform prescribed dialysate Na (137 ± 1 mEq/L) in conjunction with multiple other factors included in the model.

This study is limited by its observational design, and hence can only provide aggregated measurements and associations. Moreover, patient symptoms were not collected. This limits comparisons with other studies that correlate outcomes with symptomatic IH rather than simply measured decreases in SBP. The associations between IH and mortality and hospitalization were limited by the relatively short follow-up time and limited number of deaths and hospitalizations. Additionally, limiting the subset analysis of mortality and hospitalization to patients with more than 20 recorded treatments may introduce bias because patients had to survive a minimum of 20 treatments, and therefore may have comprised a group of healthier patients. Lastly, the associations between IH and mortality and hospitalization may represent markers of patients' underlying disease state rather than IH per se as an independent causative factor.⁵ However, this limitation may be mitigated by previous reports linking IH to myocardial stunning; which suggests a potential causative role for IH in ongoing patient morbidity.⁹

CONCLUSION

IH is common and highly variable by patient and facility. The risk of IH was associated with demographic factors, presence of diabetes, longer dialysis vintage, higher BMI and UFV, failure to achieve prescribed target post-HD weight, a lower pre-HD SBP, and higher dialysate temperature. IH risk was independently associated with specific

dialysis facilities, suggesting an effect of practice patterns. IH frequency was also associated with mortality and hospitalization. Critical evaluation of facility practice patterns and potential modifiable risk factors coupled with routine standardized reporting of IH may reduce the frequency of IH and decrease patient mortality, hospitalizations, and cost of care.

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