Clinical factors associated with intradialytic hypotension. A single-center study.

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Abstract

Introduction: Intradialytic hypotension (IDH) is a frequent complication during hemodialysis sessions and increases the risk of thrombosis of arteriovenous fistulas, myocardial stunning, and death, among others. The objective of the present study was to identify the risk factors associated with IDH in an observational study of a cohort of Mexican subjects on hemodialysis.

Methods: 1344 intermittent hemodialysis sessions were evaluated and attended in a single center from September to November 2013. IDH was defined as a decrease in systolic blood pressure ≥20 mmHg or a decrease in mean arterial pressure ≥10 mmHg, accompanied by clinical symptoms or the need to reduce or suspend the ultrafiltrate (UF) during the session. In addition to other clinical variables, exposure to the hourly UF rate was recorded by investigators and the appearance or not of IDH.

Results: 112 patients were included, with a median age of 57 years (interquartile range [IQR] 42-67); 66 cases (59%) were women. The frequency of IDH events was 5.4% (73 events), 76 subjects (68%) did not have any hypotensive events, and nine subjects (8%) had more than 2 IDH events. In the group with IDH, the pulse pressure was 77 versus 65 mmHg in the group without IDH; the UF/hour/weight rate was 13.3 versus 10.9 ml/kg/hr, respectively (P<0.001). In the multivariate analysis, age (Odds Ratio [OR]=1.029), ultrafiltrate volume (OR=1.005), and pre-hemodialysis pulse pressure (OR=1.029) were independently associated with IDH (P<0.001).

Conclusions: The factors associated with IDH were older age, higher ultrafiltration rates, and higher pre-hemodialysis pulse pressure.

Keywords:

MESH: Hypotension; Renal Dialysis; Ultrafiltration; Declining Rate Filtration; Kidney Failure, Chronic; Renal Insufficiency, Chronic.
Intradialytic hypotension (IDH) is the most common acute complication of patients with advanced chronic kidney disease undergoing hemodialysis treatment [1]. There is no universal definition of IDH, but most authors define it as a decrease in systolic blood pressure ≥20 mmHg or a decrease in mean arterial pressure ≥10 mmHg accompanied by clinical symptoms or the need to decrease or discontinue ultrafiltration (UF) during the hemodialysis session [2]. IDH occurs in 6% to 17% of hemodialysis sessions [3] and can be associated with interruption of the procedure, noncompliance with dialysis prescription goals, inability to achieve an appropriate fluid balance, increased risk of thrombosis of the arterial fistulovenous, higher frequency of ischemic events in the cerebral, mesenteric or coronary vasculature and directly to death during hemodialysis [4]. IDH is the result of an inadequate cardiovascular response to the reduction in blood volume during UF throughout the hemodialysis procedure, generally associated with a high rate of UF in short periods in predisposed patients [5]. Several clinical factors and those related to dialysis prescription are known to increase the risk of IDH events:

1. High rates of UF are associated with low redistribution of fluid from the extracellular compartment. During a typical hemodialysis session, the volume of ultrafiltered fluid that is primarily removed from the intravascular space is offset by redistribution of interstitial fluid to the intravascular space from the peritoneal phase, a phenomenon known as "vascular refilling." This refilling can decrease the actual removal of plasma volume by up to 20% [6]. Some authors have suggested that a low rate of vascular refilling uncoupled from intravascular space volume loss during the hemodialysis session is the leading cause of IDH. The causative factors of low vascular refilling rates are total interstitial fluid volume, serum albumin, and predialysis urea nitrogen [7]. Several studies on IDH have focused on the rate of total UF during sessions and have omitted the search for variables associated with vascular refilling, which are essential to understanding the phenomenon of IDH. Flythe et al. published that high rates of UF were associated with higher overall and cardiovascular mortality in 1,846 subjects on chronic hemodialysis. In this study, the UF kg/h rate was proportionally and directly associated with higher mortality. Patients with UF rates between 10 and 13 mL/kg/h had higher overall mortality, especially those with congestive heart failure, and rates >13 mL/kg/h were associated with higher mortality, regardless of the presence of heart failure. However, the UF rate explains only 40% of the IDH events reported in the series [7]. In another study, I. Akhmouch et al. described that subjects with IDH had more significant interdialytic weight gains (2875 g versus 2475 g) and a higher frequency of UF/hour rates of 800 mL/h (68% versus 43%) than those without IDH [8]. On the other hand, other underscribed variables could better explain the hypotension phenomenon since high rates of UF/hour or high interdialytic gains occur in only slightly more than 50% of IDH events.

2. Cardiovascular disorders. Hemodialysis patients show a high rate of cardiovascular mortality compared to the general population [4]. However, atherosclerotic disease is not the leading cause of death in these patients. One of the potential contributing factors to mortality is the phenomenon of myocardial stunning during hemodialysis sessions, especially in those subjects with IDH. Burton et al. reported a 64% frequency of subclinical myocardial damage detected by serial echocardiography in 70 subjects treated with chronic hemodialysis. In this study, myocardial stunning was associated with age, UF volume, IDH rate, and cardiac troponin T concentrations. In addition, an increased risk of death was identified in patients with elevated and decreased troponin T levels. In the ejection fraction during hemodialysis compared with that observed at rest [4]. Therefore, it has been proposed that better adherence to interdialytic weight gain could reduce the rate of UF, IDH episodes, myocardial stunning, and cardiovascular mortality in the medium term. Some hemodynamic parameters observed in echocardiography could be closely associated with IDH. A study in chronic hemodialysis patients reported that left ventricular dysfunction measured by echocardiography and atrial natriuretic peptide were not different in subjects with IDH versus those without hypotension, except for two echocardiographic parameters: the ratio of velocities between the two ventricular filling waves early and late left at the level of the mitral valve during diastole (E/A ratio) <1 and decreased diastolic flow propagation velocity, both of which were found to be present in 89% of subjects with IDH [9].

3. Autonomic neuropathy. Arteriolar vasoconstriction in response to UF is mediated by autonomic nervous system activity that increases peripheral vascular resistance and arterial pressure. In some patients, this vasoconstrictor response is due to the excessive production of vasodilators [10]. One of the proposed vasodilators is adenosine, which is released by vascular endothelial cells and myocytes in response to tissue ischemia, causing vasodilation and depression of myocardial function [10]. Another factor associated with poor vasoconstriction is a low release of vasopressor proteins during vascular refilling. In patients with recurrent IDH, chromogranin A determination increases to a lesser degree during hemodialysis events. Chromogranin A is a cosecreted protein with catecholamines, and its low release suggests abnormalities in the autonomic response secondary to several factors, including chronic hyperkalemia [11]. Chang MH et al. measured nerve conduction velocities in...
subjects on chronic hemodialysis to identify the presence of polyneuropathy and determined heart rate variability to assess the autonomic nervous system. They found that the frequency of polyneuropathy was similar in subjects with IDH and those with hemodynamic stability. However, heart rate variability was significantly decreased in IDH subjects, suggesting that a low chronotropic cardiac response during UF might be associated with IDH events [2].

4. Diabetes mellitus. There is evidence that diabetes contributes to IDH through alterations in autonomic tone. Nakamoto et al. described that subjects with diabetes mellitus on chronic hemodialysis had a more significant decrease in cardiac output and mean arterial pressure during hemodialysis without increased peripheral vascular resistance in response to intravascular volume change [12].

5. Dialysis fluid temperature. This parameter is relevant to maintaining hemodynamic stability. Nicholas et al. performed serial echocardiograms during the dialysis session in 10 chronic hemodialysis subjects with recurrent IDH (>30% IDH in monthly sessions) alternately exposed to different dialysis fluid temperatures. Subjects exposed to a temperature of 37°C had better myocardial stunning and less hemodynamic stability than those exposed to a 35°C exposure [13,14]. Several of the factors discussed may be relevant in the clinical assessment of patients in chronic hemodialysis, and these could predict the appearance of IDH, the prevention of IDH has been focused on the development of electronic devices or software programs installed in the hemodialysis machine, which monitors hemodynamic variables in real-time intending to stop UF before the appearance of IDH. In the authors’ experience, several of these devices are rarely used in daily clinical practice, and their reported usefulness could be linked, in some cases, to conflicts of interest. There is little information on the clinical variables commonly used related to the physiopathogenic factors mentioned, which could be helpful as a tool in the prescription of UF to prevent the appearance of IDH. Additionally, some studies have suggested that the Hispanic race [2] has a higher risk of IDH events. Therefore, an observational study was carried out to identify the individual risk factors related to each hemodialysis session with the appearance of IDH events in a cohort of Mexican subjects.

Materials and methods

Study design
The present study is observational, cross-sectional and analytical.

Scenery
The study was carried out in the “El Refugio” Clinic hemodialysis medical unit of the Fresenius Medical Care group in Mexico. The study period was from September 1, 2013, to November 30, 2013. The study ended the data collection phase on January 23, 2014.

Participants
Patients older than or equal to 18 years old who received renal replacement therapy with hemodialysis for three months or more were included. Treatments carried out for at least 180 minutes were analyzed.

Variables
The dependent variable was the presence of IDH. Variables such as age, type of vascular access, treatment time in the hemodialysis program, concomitant diseases, urea reduction ratio, kt/V, hemoglobin, serum ferritin, serum albumin, serum calcium, serum phosphorus, serum sodium, serum potassium, weight, interdialytic gain, UF rate, and IDH symptoms.

Data sources/measurements
The investigators took the variables from the institutional clinical file. IDH was defined as a decrease in systolic blood pressure ≥20 mmHg or a decrease in mean arterial pressure ≥10 mmHg accompanied by clinical symptoms or the need to reduce or stop ultrafiltrate during the session.

Biases
The data were guarded at all times by the principal investigator with appropriate guidelines and records to avoid possible interviewer, information, and memory biases. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period mentioned above were recorded during hemodialysis sessions. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once the patients’ agreement was verified.

Study size
The sample was probabilistic. The prevalence of the IDH event was considered 20% as a risk factor and 5% as an unrelated factor, a difference of 15%, which implies an odds ratio of 4 to 1. The confidence level was 95%, and the statistical power was 80%. This estimate resulted in the analysis of 75 sessions (m’) with the occurrence of the IDH event. In most of the reviewed studies, significant variability in IDH was found, with an average frequency of 12%. To have 75 hemodialysis sessions with IDH, in this study, the frequency of IDH was 5.4%, so the sample size was adjusted to 1,388 hemodialysis sessions with the following equations:

\[
m’ = \frac{Z_a \sqrt{(r + 1)PQ + Z_p \sqrt{P_1Q_1 + P_2Q_2}}^2}{r \delta^2}
\]
\[ m = \frac{m'}{4} \left( 1 + \sqrt{1 + \frac{2(r + 1)}{rm'}} \right)^2 \]

\[ N = (r + 1)m \]

**Quantitative variables**

Inferential descriptive statistics were used. The results of central tendency were expressed as the means or medians and those of dispersion in standard deviation or interquartile range depending on the data distribution.

**Statistical analysis**

Depending on the variables, the factors associated with intradialytic hypotension were compared between groups using the t test, chisquare test, and Fisher’s exact test. A multivariate logistic regression analysis was performed, assigning the appearance of IDH as the dependent variable. The model with the best goodness of fit was selected, including clinical variables such as age, sex, diabetes mellitus, weight gain between sessions, UF rates per hour, systolic blood pressure, diastolic pressure, and pulse pressure.

**Results**

**Participants**

A total of 112 patients entered the study. The diagram of the participants is presented in Figure 1.

![Figure 1. Diagram of study participants.](image)

**Characteristics of the study population**

There were 66 women (59%). Age 57 years (IQR 42-67). The length of stay in the dialysis program was 5 years (IQR 3-7). There were 48 patients with diabetes mellitus (43%) and 6 with ischemic heart disease (5.4%). Vascular access with arteriovenous fistula occurred in 58 cases (52%), with tunneled catheter in 37 cases (33%), and temporary catheter in 17 cases (15%). Table 1 presents the descriptive clinical characteristics of the population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, (g/dL)</td>
<td>10.3  (9.0-11.3)</td>
</tr>
<tr>
<td>Albumin, (g/dL)</td>
<td>3.6   (3.4-3.8)</td>
</tr>
<tr>
<td>Ferritin, (mg/dL)</td>
<td>68    (21-265)</td>
</tr>
<tr>
<td>Calcium, (mg/dL)</td>
<td>9.5   (8.9-9.9)</td>
</tr>
<tr>
<td>Phosphorus, (mg/dL)</td>
<td>5.4   (3.7-6.8)</td>
</tr>
<tr>
<td>Sodium, (mEq/L)</td>
<td>138   (136-139)</td>
</tr>
<tr>
<td>Potassium, (mEq/L)</td>
<td>5.3   (4.5-5.6)</td>
</tr>
<tr>
<td>Urea-URR, (%)</td>
<td>74    (71-77)</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.6   (1.5-1.7)</td>
</tr>
<tr>
<td>Erythropoietin use, (%)</td>
<td>55    (51%)</td>
</tr>
<tr>
<td>Use of antihypertensives, (%)</td>
<td>36   (31%)</td>
</tr>
<tr>
<td>Pre-dialysis MAP, (mmHg)</td>
<td>97    (± 16)</td>
</tr>
<tr>
<td>Dialysis MAP, (mmHg)</td>
<td>94    (± 16)</td>
</tr>
<tr>
<td>Predialysis PP, (mmHg)</td>
<td>69    (± 22)</td>
</tr>
<tr>
<td>Post-dialysis PP, (mmHg)</td>
<td>64    (± 20)</td>
</tr>
</tbody>
</table>


**Intradialytic hypotension**

A total of 1344 hemodialysis sessions were evaluated, with 12 sessions for each of the subjects included in the study. The prevalence of IDH was 73/1344 sessions (5.4%); 76 subjects in the sample had no hypotensive events during the period (68%). 19 had one hypotensive event during the period (17%), 8 had two hypotensive events (7%), and nine had ≥ 3 hypotensive events (8%). In slightly less than half of the IDH events, 36/73 cases (49%) did not report symptoms, although the change in blood pressure forced the modification of the prescribed dialysis treatment. The most frequent symptoms were cramps in 14/73 cases (18%), fainting in 3/73 cases (4%), and nausea in 2/73 cases (3%). No hospitalization, vascular access thrombosis, or death related to the hypotensive event was reported in the patients. Table 2 and Figure 1 summarize the hemodynamic, demographic, and dialysis prescription characteristics of each of the sessions studied; several clinical characteristics were different in the IDH group compared to the non-IDH group: older age (P= 0.02), female sex (P = 0.046), the presence of diabetes mellitus (P = 0.04), lower dry weight (P = 0.012), higher mean UF/hour rates (P < 0.001), higher mean UF rates adjusted for dry weight (P < 0.001), lower prehemodialysis diastolic pressure (P = 0.025), and higher predialysis pulse pressure. -hemodialysis (P < 0.001). There was no statistically significant difference with other variables, including time on dialysis, the presence of arteriovenous fistula, ischemic heart disease, systolic pressure, dialysis adequacy, hemoglobin, and other biochemical values.
Table 3 shows the best model of the multivariate analysis using logistic regression.

### Table 2. Clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Group without IDH n=1271</th>
<th>Group with IDH n=74</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>740 (59%)</td>
<td>52 (70%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Time on dialysis (Years)</td>
<td>5 (3-7)</td>
<td>5 (3-7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Arterio-venous fistula, n (%)</td>
<td>655 (52%)</td>
<td>35 (47%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>555 (44%)</td>
<td>45 (61%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>65 (5%)</td>
<td>7 (10%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Dry weight, (kg)</td>
<td>60 (54-70)</td>
<td>56 (53-66)</td>
<td>0.012</td>
</tr>
<tr>
<td>UF rate (ml/hr)</td>
<td>671 ± 233</td>
<td>789 ± 214</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP pre-HD (mmHg)</td>
<td>144 (123-151)</td>
<td>151 (123-151)</td>
<td>0.075</td>
</tr>
<tr>
<td>PD pre-HD (mmHg)</td>
<td>74 (67-85)</td>
<td>69 (51-77)</td>
<td>0.025</td>
</tr>
<tr>
<td>MAP pre-HD (mmHg)</td>
<td>99 (87-108)</td>
<td>97 (82-107)</td>
<td>0.620</td>
</tr>
<tr>
<td>PP pre-HD (mmHg)</td>
<td>65 (52-80)</td>
<td>77 (61-91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>URR</td>
<td>74 (71-77)</td>
<td>74 (73-79)</td>
<td>0.21</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.6 (1.5-1.7)</td>
<td>1.6 (1.5-1.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.9 (8.3-9.3)</td>
<td>9.3 (8.3-9.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.6(3.3-3.8)</td>
<td>3.6(3.3-3.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Ferritin (mg/dl)</td>
<td>66 (20-258)</td>
<td>41 (22-274)</td>
<td>0.06</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5 (8.7-9.9)</td>
<td>9.4 (7.6-9.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.3 (3.7-6.8)</td>
<td>5.9 (3.5-6.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>5.3 (4.5-5.5)</td>
<td>5.4 (4.4-5.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>138 (136-137)</td>
<td>137 (135-135)</td>
<td>0.10</td>
</tr>
</tbody>
</table>


### Discussion

This study is the first to demonstrate an independent association between increased prehemodialysis pulse pressure and the development of IDH events; until now, the opposite was known [14], taking into account population differences with a higher prevalence of diabetes mellitus in the present study (43% vs. 32%), a prolonged median time of hemodialysis (5 years) and notable differences in blood pressures between populations, with higher systolic figures and less use of antihypertensives (31% vs. 70%) in the present study, compared to what Davenport reports [14].

The increase in pulse pressure reflects the anatomical changes that occur in the arterial wall with aging when smooth muscle cells and elastin fibers are replaced by collagen, causing an increase in arterial stiffness and are closely associated with vascular calcification. In addition, fluid overload explains an increase in systolic blood pressure and a greater pulse amplitude before the hemodialysis session. The combination of age, increased pulse pressure, and UF rate were the main risk factors for IDH found in the present study. Additionally, some patients have an increased risk of suffering from IDH in more than 25% of the sessions. Consistently, in addition to the presence of diabetes mellitus, the increase in pulse pressure was greater in patients with recurrent IDH. In itself, the presence of diabetes has already been recognized as an important factor of IDH [15], but no data are found regarding pulse pressure. The difference between systolic and diastolic pressure could aggravate preexisting cardiovascular alterations; the increase in pulse pressure causes an increase in the afterload at the end.
of systole and decreases coronary perfusion during diastole, which, together with cardiovascular alterations such as left ventricular hypertrophy, exacerbates IDH events [16]. Other factors that may explain the increase in pulse pressure in patients with IDH are changes in the profiles of vasoconstrictor and vasodilator agents that occur intradialytically. Some vasoconstrictors that are increased during hemodialysis are angiotensin II, endothelin-1, and thromboxane A2 [17], whereas vasodilators that are increased are nitric oxide synthetase inhibitors, endothelin-1 asymmetric dimethylarginine, and adenosine [18]. Therefore, we can state that during the hemodialysis procedure, patients with IDH present a predominance of the action of vasodilator agents over vasoconstrictors, which causes a drop in peripheral resistance, and this can be reflected in wide pulse pressures that are maintained over time and a higher pulse pressure consecutive to the new treatment.

The prevalence of IDH episodes was 5.4%, similar to reports in Europe [1]. The United States of America typically has episodes with a higher prevalence of up to 17.2% [2]. Some differences in prevalence refer to different concepts to consider the presence of IDH; in some series, only the decrease in blood pressure is reported, without considering the presence of symptoms or modification in the UF prescription.

Weight was a protective factor for the presence of IDH since the constant interdialytic gain is probably attributed to a better nutritional status. In addition, subjects with greater weight may have a different vascular filling than patients with a lower weight. In this study, the ultrafiltration rate in the hour before the hypotensive events was 13.3 ± 3.6 ml/kg/h, which is consistent with the analysis published by Flythe [2], in which a rate >13 ml/kg/h is associated with the risk of death.

The present study has the limitations of observational studies. Additionally, there was no echocardiographic assessment to determine ventricular function, and these studies should possibly be addressed in the future.

### Conclusions

Risk factors associated with IDH events were age, ultrafiltration rate >13.3 mL/kg/h, and increased prehemodialysis pulse pressure. The prevalence of IDH events was 5.4%. There was no association between biochemical parameters, dialysis adequacy, and the presence of IDH events. The presence of diabetes mellitus and higher pulse pressure was associated with the presence of IDH events in >25% of the sessions.

### Abbreviations

IDH: Intradialytic hypotension.
UF: Ultrafiltration.

### Supplementary information

Supplementary materials have not been declared.

### Acknowledgments

Does not apply.

### Author contributions

Jesús Cisneros Carpintero: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
Ricardo Correa Rotter: Conceptualization, supervision, validation, visualization, and writing: revision and editing.
Juan Carlos Ramírez Sandoval: Formal analysis, Validation, Writing: review and editing.
All authors read and approved the final version of the manuscript.

### Financing

The authors provided research expenses. The laboratory studies were part of the normal institutional activity and were not expenses added to the institution or the patients.

### Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

### Statements

**Ethics committee approval and consent to participate**

It was not needed.

**Consent to publication**

This does not apply when images or photographs of the physical examination or radiography/tomography/MRI of patients are not published.

**Conflicts of interest**

The authors report having no conflicts of interest.
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References


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