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Intra-Dialysis Hypotension in Patients Undergoing Hemodialysis

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Introduction: Intra-dialysis hypotension occurs in 20- 55% of hemodialysis sessions. We aimed to define the prevalence and impact of pre-dialysis blood pressure, inter-dialysis weight gain, vasodilator agents, and characteristics of dialysis, serum calcium, and adjusted calcium, sodium, and albumin levels on intra-dialysis hypotension.

Materials and Methods: In an observational prospective study, 44 hemodialysis cases aged 4.8-25 years were evaluated in 552 dialysis sessions. A decrease in the mean arterial blood pressure \geq 10 mm Hg was defined as intra-dialysis hypotension. The characteristics of the patients were compared between cases and those without intra-dialysis hypotension.

Results: Intra-dialysis hypotension was noted in 61.4% of the cases and 24.6% of the dialysis sessions. The duration of hemodialysis, weight gain between dialysis sessions, using vasodilator medications, serum sodium and adjusted calcium levels were compared between IDH + and IDH - cases. No significant differences were found in these variables between the 2 groups ($P > 0.05$ for all). Intra-dialysis hypotension was significantly more prevalent in cases with normal versus high systolic and diastolic blood pressure ($P=0.014$ and $P=0.005$ respectively). Intra-dialysis hypotension was significantly more frequent in girls, anuric patients, and patients with a history of transplantation ($p=0.022$, 0.011 and 0.008 respectively). A significantly lower serum albumin concentration was found in cases with intra -dialysis hypotension ($P=0.021$).

Conclusions: Intra-dialysis hypotension is a common complication of hemodialysis and is more prevalent in girls, normotensive patients, subjects with lower serum albumin concentrations, cases with a history of transplantation, and anuric patients.

Keywords: Hemodialysis; Blood Pressure; Hypotension; Serum Albumin; Serum Calcium.

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Introduction

Intra-dialysis hypotension (IDH), a potentially important cause of hypo-perfusion injury which can result in poor outcomes, occurs in 20- 55% of hemodialysis sessions [1].

There is no evidence-based consensus for definition of intradialytic hypotension. The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines has defined IDH as a decrease in either systolic BP (SBP) \geq 20 mmHg or mean arterial pressure (MAP) \geq 10 mmHg as well as the presence of associated symptoms [2].

The mean arterial pressure is calculated as $[(2 \times \text{diastolic BP}) + \text{systolic BP}] / 3$ [3]. As the data of symptoms and interventions are often unavailable in large databases, various IDH definitions have been presented. However, these definitions have some weak points [2]. For example, Chesterton et al [3] defined IDH as systolic blood pressure (SBP) \leq 100 mmHg even in the absence of symptoms, or a fall in SBP $>$ 10% of the pre-dialysis readings. Excessive ultrafiltration rate, left ventricular dysfunction, reduced cardiac output, reduced vascular tone, effects of low calcium and sodium

concentrations in dialysis solutions, and bio-incompatible dialyzer membranes are suggested in pathogenesis of IDH [4]. Few studies have investigated the prevalence of IDH [5]. This entity can potentially result in serious complications such as cardiac or cerebral ischemia [5]. In uremia, the heart is prone to ischemia because of a low coronary flow reserve due to the high prevalence of coronary artery disease [6]. Therefore, early diagnosis and management of IDH is crucial and needs more attention in the clinical setting.

As this clinical situation is common and can potentially affect the perfusion of vital organs such as the heart and kidney, every research in this field may be valuable. Studies that focus on defining possible factors significantly associated with increased occurrence of intra-dialysis hypotension may help clinicians to avoid severe symptomatic hypotension by repeated monitoring of blood pressure during dialysis in more susceptible patients.

The aims of our study were to determine the prevalence of IDH, both symptomatic and asymptomatic, and to assess the impact of dialysis characteristics as well as clinical and serological factors on the occurrence of IDH.

Materials and Methods

An observational prospective study was designed to assess the occurrence of IDH in 44 cases receiving hemodialysis (HD) during a one-month period. Written consent was obtained from patients or their parents. The research followed the tenets of the Declaration of Helsinki. The patients were placed on hemodialysis from 1 to 128 (49.2±38.4) months before the study. IDH was defined as a (MAP) ≥ 10 mmHg [2].

Blood pressure was measured 10 minutes before, during, and immediately after each dialysis session by the auscultation method with applying a suitable cuff size that covered at least half to 2/3 of the upper arm length. During the dialysis sessions, blood pressure was checked every hour or whenever symptoms suggestive of hypotension appeared.

Dialysis was conducted by bicarbonate-based dialysis solutions containing 217 gr/L of sodium and 6.4gr/L of calcium. The temperature of the dialysis solutions was maintained at 37 °C

during dialysis. In case of symptomatic IDH, 5% hypertonic sodium chloride solution \pm normal saline was used. If IDH occurred in the last hour of dialysis, a 50% hypertonic glucose solution was usually administered.

Dialysis was done with the Fresenius 4008 (Germany), AK95 (Switzerland), or AK96 (Switzerland) dialysis machines using a low flux dialyzer (R3-R5 and low-flux Polysulfone membranes). The blood flow rate was adjusted at 100-300 cc/min. On the day of dialysis, patients on vasodilator antihypertensive medications (calcium channel blockers and hydralazine) were advised to use their drugs after dialysis to prevent IDH.

Normotension, prehypertension, and hypertension were defined as systolic or diastolic blood pressure < 90 percentile, $= 90-95$ percentile, and > 95 percentile for age, gender and height respectively [7]. In patients > 18 years, normal blood pressure, prehypertension, and hypertension ranges for systolic blood pressures (SBP) were defined as < 120 mmHg, 120-139 mmHg, and ≥ 140 mmHg, respectively. A diastolic blood pressure (DBP) < 80 mmHg, 80-89 mmHg, and ≥ 90 mmHg were considered normal pressure, prehypertension, and hypertension, respectively [8].

Non-hypertensive cases were considered as subjects with systolic and diastolic blood pressure in the normal or prehypertension ranges [7]. The types of the dialysis regimens were either conventional (three 4-hour sessions per week) or non-conventional (dialysis sessions not obeying this schedule) [9]. Adequate inter dialysis weight gain (IDWG) and increased IDWG were considered as a weight gain $\leq 5\%$ and $> 5\%$ of the total body weight between dialysis sessions (inter-dialysis), respectively [10].

Descriptive statistics included mean \pm SD for continuous variables and percentage for categorical variables. The normality of the variables was checked with one sample Kolmogorov-Smirnov test. All variables had a normal distribution. Dialysis characteristics, IDWG, pre-dialysis BP, time from onset of dialysis, use of antihypertensive medications

with vasodilator effects, serum calcium, adjusted calcium, sodium, and albumin levels were compared between cases with IDH (IDH+) and those without (IDH-). Chi square (for categorical variables) and independent T tests (for continuous and dependent variable) were applied for data analysis. P values <0.05 were considered significant.

Results

The patients were 58-300 (204.9 ± 60) months old. Intra-dialysis blood pressure changes were evaluated in 44 HD cases during 552 dialysis sessions (Table 1) in a one -month period. Table 1 and 2 present the details of enrolled subjects and the systolic blood pressure status (normal blood pressure, prehypertension, and hypertension) before, during, and after dialysis. Eight cases (18.2%) were hypertensive during and after dialysis. The main symptoms of IDH in our cases were muscle cramps, irritability, vomiting. Skin mottling was also noted in small children. Intra-dialysis hypotension was reported in 136 of 552 (24.6 %) dialysis sessions and in 27 cases (61.3%).

High systolic and diastolic blood pressure were seen in 17 (38.6%) and 15 cases (34.1%), respectively. As a suggested policy, patients were recommended not to take anti-hypertensive drugs with vasodilator effects on the morning of dialysis. Totally, 22 (50%) cases were hypertensive and vasodilator drugs were prescribed for 16 (72.7%) of them. The prevalence of IDH was compared between the two groups (Table 3).

A high systolic and diastolic BP versus non-hypertensive conditions was significantly more common in IDH- compared with IDH+ cases (P=0.005 and 0.014 for systolic and diastolic blood pressure, respectively) (Table 3). Occurrence of IDH was not significantly different based on types of IDWG, weekly dialysis schedule, administration or no consumption of vasodilator drugs in inter-dialysis period (P > 0.05 for all).

Table 1. Characteristics of 44 hemodialysis patients who participated in the study

Variable	Characteristics	(Number/%)
Age group	≤ 18 years	(12 /27.3)
	>18 years	(32 /72.7)
Gender	Male	25 (56.8)
	Female	19 (43.2)
History of Tx*	Yes	9 (20.5)
	No	35 (79.5)
Urine output status*	Anuria	11 (29.7)
	Non anuria	26 (70.3)
Mean systolic blood pressure (mmHg)	Normal	17(38.6)
	Pre HTN	10 (22.8)
	HTN	17 (38.6)
Mean diastolic blood pressure (mmHg)	Normal	19(43.2)
	Pre HTN	10 (22.7)
	HTN	15 (34.1)
Main etiologies of CKD †	VUR ‡	24 (54.5)
	Glomerulopathies	8 (18.2)
	Idiopathic	8 (18.2)
	Stone diseases	3(6.8)
	Cystinosis	1(2.3)
Dialysis regimen	Conventional regimen §	18 (40.9)
	Non-conventional dialysis	26 (59.1)
Dialysis sessions/month	Conventional regimen ¶	234 sessions ¶ (42.4)
	Non-conventional regimen #	318 sessions # (57.6)

*Transplantation **) Urine output status in 7 cases were not clear and patients were not sure about complete anuria, so they didn't include in the classification). †) Chronic kidney diseases. ‡) Vesicoureteral reflux. §,) Three 4-hour session in week. ||) Dialysis time > or < 12 hours /week. ¶) 18 cases ×13 dialysis sessions. #) Eleven cases with 13 sessions of 3-hour /month (143 sessions) , 10 cases with 9 sessions of 4-hour /month (90 sessions) and 5 cases with 17 sessions of 4-hour /month (85 sessions) which indicated a total 318 sessions .

The mean ±SD serum sodium, calcium, and adjusted calcium levels were not significantly different between IDH+ and IDH- patients (P > 0.05 for all).

Table 2. Changes in systolic blood pressure in different stages of hemodialysis

Pre-dialysis stage (N / %)
Total number (44/100) Normal ranges ¹ (17/ 38.6) Prehypertension ranges ² (10 /22.8) Hypertension ³ (17/ 38.6)
Intra dialysis stage (N/%)
Total number (44/100) No hypotension episode (17/ 38.6) Intra dialysis hypotension (27/ 61.4) Persistent hypertension ± IDH (8/18.2)
Immediately post dialysis (N/%)
Total number (44/100) Normal or prehypertension ranges (31/70.4) Persistent hypertension (8/18.2) Hypotension (5/ 11.4)

*This table focuses on SBP changes because they were more prominent, but always systolic and diastolic BP changed parallel. †) Systolic BP <90 percentile for age, gender and height in age group ≤18 year, and <120mmHg in patients >18 years. ‡) Systolic BP =90-95 percentile for age, gender and height in age group ≤18 year, and 120-139 mmHg in patients >18 years. §) Systolic BP > 95 percentile for age, gender and height in age group ≤18 year and ≥140mmHg in patients >18 years

Longer times from onset of dialysis were found in IDH⁻ versus IDH⁺ patients (Figure 1). Additionally, a lower mean systolic and diastolic BP was found in IDH⁺ cases (the minimum systolic and diastolic BPs was 80 and 40 mmHg in IDH⁺ cases and 100 and 60 mmHg in IDH⁻ patients, respectively (Figures 2 and 3). In addition, lower serum albumin concentrations were detected in IDH⁺ cases (Figure 4). According to Table 3, IDH was significantly more prevalent in girls, non-hypertensive cases, patients with a history of transplantation, subject with a lower serum albumin levels, and anuric patients versus (P= 0.022, 0.005, 0.008, 0.021, and 0.011, respectively). The dialysis regimen was conventional in 18 (40.9%) cases including 10 of 27 patients with IDH (37.03%). It means that about 60% of all cases and about 2/3 of cases with IDH had non-

conventional dialysis regimens. The mean frequency of IDH episodes in patients with two 4- hour dialysis sessions/week and three 3-hour dialysis sessions /week (non - conventional regimen) was 5.14 and 10 episodes/ month, respectively.

The mean episodes of IDH in cases with conventional dialysis (three 4-hour dialysis sessions /week) were 6.8 episodes/ month. The majority of IDH⁺ patients had non-conventional dialysis regimens (62.9%), and 20% of IDH⁺ cases with a conventional dialysis regimen experienced hypotension in all dialysis sessions (Flow chart A).

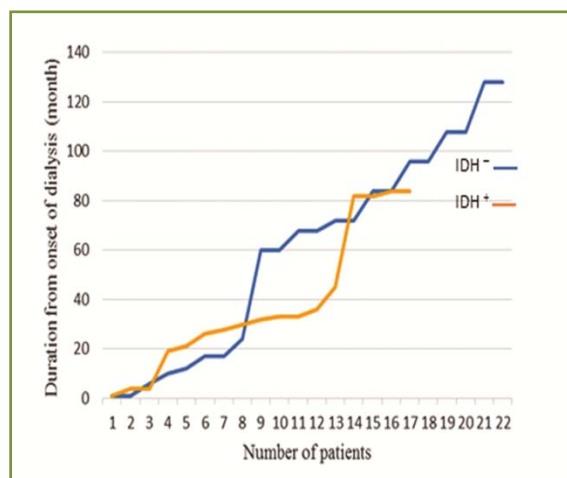


Figure 1. Duration from onset of dialysis in IDH⁺ compared with IDH⁻ cases

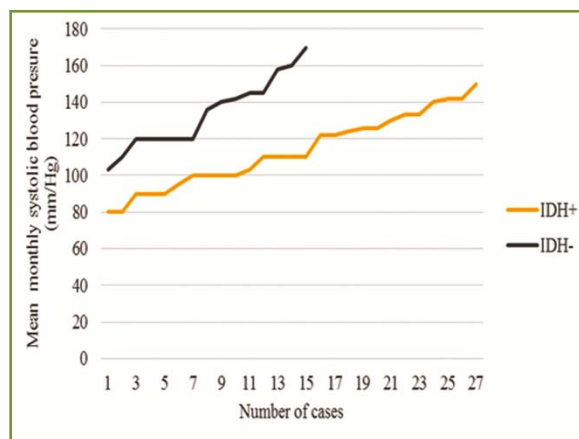


Figure 2. Mean monthly systolic blood pressure in IDH⁺ and IDH⁻ group

Table 3. Comparing clinical and dialysis characteristics, and serologic parameters in IDH⁺ with IDH⁻ cases

Variable	IDH ⁺ , N (%) [*] 27(61.4)	IDH ⁻ N (%) 17(38.6)	P-value	Value or t [†]	df
Age group[‡]					
≤ 18 years	13(48.15)	11(64.7)	0.283	1.154	1
>18 years	14(51.85)	6(35.3)			
Mean ±SD[§] (month)	201.8±64.9	204.2±49.9	0.9	0.126	42
Gender					
Male	8(29.6)	11(64.7)	<u>0.0221</u>	5.23	1
Female	19(70.4)	6(35.3)			
History of transplantation [‡]	9(33.3)	0			
Yes	18(66.7)	17(100)	<u>0.008</u>	7.124	1
No					
Urine output status [‡]					
Non anuria[†]	10(45.5)	1(6.7)	<u>0.011</u>	6.423	<u>1</u>
Anuria	12(54.5)	14(93.3)			
Systolic blood pressure status [‡]					
Non-hypertensive	21(77.8)	6 (35.3)	<u>0.005</u>	7.941	<u>1</u>
Hypertensive	6(22.2)	11(64.7)			
Diastolic blood pressures status [‡]					
Non-hypertensive	22(81.5)	7(41.2)	<u>0.014</u>	6.039	1
Hypertensive	5(18.5)	10 (58.8)			
weekly dialysis schedules [‡]					
Conventional (3 four-hours sessions/week)	10(37)	8 (47.1)	0.5	1.154	1
Non-Conventional (<or>than 12 h /week)	17(63)	9 (52.9)			
inter-dialysis weight gain [‡]					
Adequate(≤5% of body weight)	16(59.2)	11 (64.7)	0.718	0.131	1
Increased(>5% of body weight)	11(48.8)	6 (35.3)			
Using vasodilator drugs [‡]					
yes	6(60)	10(83.3)	P=0.221	6.133	<u>1</u>
No	4(40)	2(16.7)			
Time from onset of dialysis [‡]					
≤1 year	5(22.7)	3(17.7)	0.697	0.152	1
>1 year	17(77.3)	14(82.3)			
Time from starting dialysis	60±42.4	37.9±6.8	0.072	-1.853	37
(month)					
Mean Systolic blood pressure ^E	113.25±2	134.7±18.5	<u>0.001</u>	3.571	42**
(mm/Hg)					
Mean Diastolic blood pressures	66.5±1.8	86.5±1.4	<u>0.0001</u>	3.899	42*
 mm/Hg)					
Serum hemoglobin levels	9.5±2.3	10.5±2.3	0.217	1.257	35
(mg/dl)					
Serum calcium levels (mg/dl)	8.46±1.07	8.8±0.98	0.287	1.081	35
Serum sodium levels (meq/L)	138.5±2.6	139.5±3.04	0.29	1.073	35
Serum albumin concentration (mg/dl)	3.35±0.51	3.88±0.33	<u>0.021</u>	2.569	16
Adjusted Serum calcium levels ^E (mg/dl)	8.6±1.3	8.76±0.74	0.732	0.349	16

*) Number/percent. †) Value for chi square and t for independent tests. ‡) Chi square test. §,) Mean± standard deviation ||) Independent T test. ^{†)} in 7 cases periods of presence and absence of urine output were reported, so they were not included as cases with anuria or without anuria. In 7 cases patients were not sure about anuria or non-anuria.#) exact time from onset of dialysis were not available in 7 cases. **) In 2 cases the systolic and diastolic BP in some HD sessions in pre-dialysis stages were not available, so they didn't included in measurement of mean systolic and diastolic BP values.

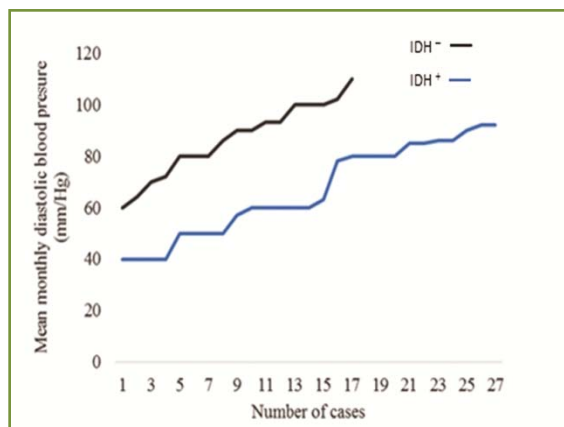


Figure 3. Mean monthly diastolic blood pressure in IDH⁺ and IDH⁻ cases

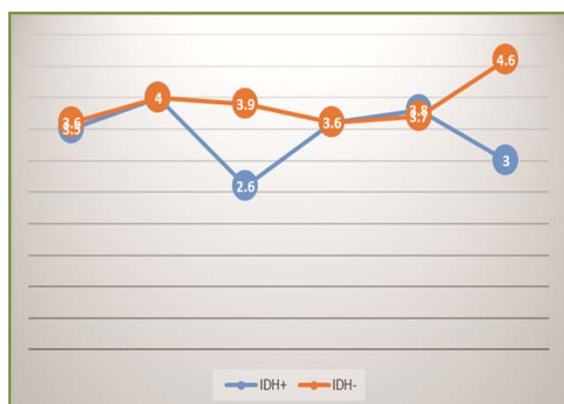


Figure 4. Serum albumin concentration in IDH⁺ versus IDH⁻ cases

Discussion

Vasoactive agents including vasopressin, nitric oxide, Endothelin 1, and adenosine have been proposed to play a part in the pathogenesis of IDH. Adults prone to IDH have an imbalance between nitric oxide (vasodilator substances and endothelin 1 (vasoconstrictor agent) [11]. A review of the literature underlines some dialysis characteristics as factors contributing to increased risk of IDH, shorter dialysis sessions [12], higher ultrafiltration rates [13], and relatively higher dialysate temperatures [14]. However, conventional HD has been recommended as a policy to reduce IDH [12]. Our findings did not show any significant difference in the occurrence of IDH in patients who underwent conventional versus those who

received non- conventional HD. ($p = 0.5$) (Table 3).

The Importance of preserving residual renal function (RRF) after the initiating of dialysis has been shown in different studies. RRF significantly contributes to better small solute and middle molecular uremic toxins clearance, fluid balance, and better phosphorus control. A strong inverse relationship has been reported between RRF and cardiac hypertrophy [5].

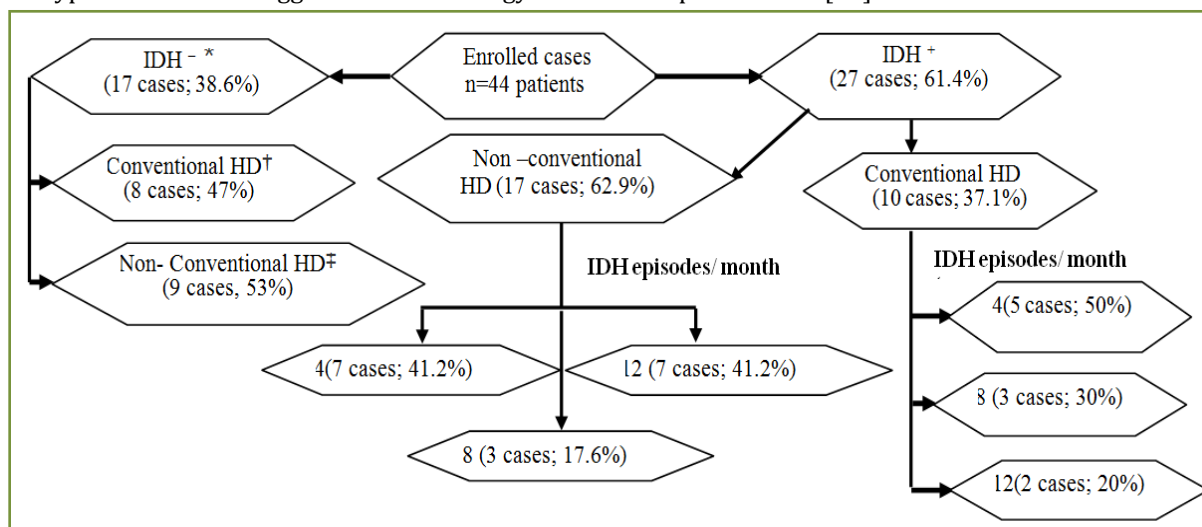
The results of our study are consistent with the findings of a newly published study [5] reporting a significant association between the occurrence of IDH and female sex and absence of RRF.

Contrary to our cases, in this study, the patients with IDH had a higher pre dialysis systolic BP compared with those without IDH ($P=0.01$). The authors also found that the occurrence of IDH was strongly associated with a lower body height and higher ultrafiltration volume.

Although IDH was significantly more prevalent in female patients, patients with a history of renal transplantation, those with lower serum albumin levels, and anuric cases in our series, the frequency of IDH episodes per month was not significantly different. The frequency of IDH episodes was 7 ± 3.54 episodes/month for girls and 7.78 ± 3.64 episodes/month for boys ($P=0.609$). In patients with a history of renal transplantation, IDH was reported in 5.77 ± 2.9 dialysis sessions, whereas it was found in 8.44 ± 3.6 dialysis sessions in those with no history of renal transplantation ($P=0.06$). Patients with no RRF (cases with anuria) had 6.8 ± 3.29 episodes of IDH, while 7.66 ± 0.39 episodes of IDH were reported in non- anuric cases ($P=0.589$). In adults, the ultrafiltration profiling has a positive effect on prevention of IDH [15], while no benefits compared to a constant ultrafiltration rate have been reported in pediatric patients [16].

The data of adult patients [17] have shown positive effects and improved hemodynamic stability by administrating bicarbonate buffers. In our cases despite using bicarbonate buffers for HD, IDH was a common problem and was reported in 29.3% of the HD sessions. Avoidance

of hypocalcaemia is suggested as a strategy to prevent IDH [18].



Flow chart A. Dialysis regimens in enrolled cases and number of IDH episodes in patients with conventional and non-conventional dialysis regimens

In our series, serum calcium and adjusted calcium <8.4 mg/dl (hypocalcemia) were reported in 40.9% and 60% of the IDH positive and 33.3% and 37.5% of the IDH negative patients, respectively (P= 0.641 and 0.343, respectively).

Hypocalcemia (adjusted serum calcium <8.4 mg/dl) was 1.6 times more common in IDH + cases; however, no significant difference in the mean adjusted serum calcium level was found between IDH+ and IDH - patients (P=0.732). In a study by Meredith DJ et al. [1], blood pressure changes were compared in 77 patients over 456 dialysis sessions using a post-dialysis symptom questionnaire. They found that 25% of the cases enrolled in the study who were apparently asymptomatic during dialysis (no complaints were reported to the staff during HD) reported symptoms in the questionnaire, while 64% had symptomatic hypotension requiring medical interventions. A 20% reduction in SBP from baseline or SBP <100 mmHg was commonly associated with symptoms requiring medical intervention. Inappropriate weight gain between dialysis sessions in HD cases makes blood pressure management difficult due to the need for using more ultrafiltration (UF) forces during dialysis sessions, which can potentially lead to

more episodes of IDH requiring administration of volume expander solutions to prevent serious complications of hypotension. The result will be suboptimal ultrafiltration and poor blood pressure control. To prevent this vicious circle, it is recommended that the weight gain between dialysis sessions should not to be more than 5% of the total body weight (a weight gain of 1 kg is optimal for a 20-kg patient). In our series, 6 (13.6%) and 18 (40.9%) cases had either no or an adequate IDWG, respectively. The prevalence of IDH in cases with adequate IDWG was about 60%, while it was 64.7% in those with increased IDWG (P=0.718). Eleven of 17 patients (64.7%) who did not experience IDH (IDH-) had adequate IDWG compared to 16 of 27 cases with IDH. Patients with adequate IDWG experienced 7.25±3.64 IDH episodes per month while 8±3.57 episodes/month were recorded in those with increased IDWG. (P=0.601). In fact, our findings suggest that adequate or increased IDWG has no significant impact on the occurrence of IDH episodes.

An extended study by Shoji et al. [19] revealed a significant correlation between decrease in systolic BP during HD with the following factors: duration from onset of dialysis, amounts of weight gain between dialysis sessions, applied

ultrafiltration rate based on the weight, dialysis induced hypovolemia, and serum albumin concentration. In contrast to systolic BP which affected by different factors, the fall in diastolic BP just showed a significant correlation with duration from onset of HD.

Bicarbonate based HD solutions improved cardiovascular stability; although relative alkalosis and subsequent hypocalcaemia increase risk of symptomatic IDH [9, 10]. It has been reported that IDH is more frequent in patients on long-term HD [20]. In our series, however, there was no significant difference between IDH⁺ cases who received HD from longer times versus those who did not (P=0.072).

One RCT study in 45 patients showed that 5% albumin was not superior to normal saline for the treatment of symptomatic hypotension in HD with a previous history of IDH [20], however, we found a significantly lower serum albumin concentration in IDH⁺ versus IDH⁻ cases (p=0.021), and all IDH⁻ cases had a serum albumin >3.5 gr/dl. Whether returning the serum albumin levels to normal values in IDH⁺ cases can prevent or decrease the IDH or not is a question that needs more investigations. Overall, our findings suggest that normotensive cases are more prone to developing IDH and thus need more attention during HD sessions; moreover, repeated BP measurements are required to diagnose symptomatic and asymptomatic IDH. In addition, as IDH was significantly more frequent in cases with lower serum albumin concentrations, maintaining the serum albumin level >3.5 gr/dl in cases who experience IDH may be effective in preventing this complication.

In our series, all IDH⁺ cases experienced an at least 10-mmHg decrease in both systolic and diastolic BP, resulting in a 10-mmHg decrease in MAP considering the formula used to measure MAP [3]; however, the exact values of MAP were not recorded and missed.

A decrease in SBP is always associated with a decrease in diastolic BP and vice versa. IDH⁻ cases either had no change in systolic and diastolic BP or the decrease in both systolic and diastolic BP was

less than 10 mmHg, indicating MAP changes < 10mmHg.

The main limitation of our study was that the symptoms of IDH and the exact MAP changes were not recorded. If the symptoms and MAP changes were recorded, we could assess whether there was any correlation between MAP change and symptoms. Further research is required to assess the correlation of BP changes (systolic, diastolic and MAP) with IDH symptoms and frequency of asymptomatic IDH.

Conclusions

Based on the results of this study, it can be concluded that the occurrence of IDH is common, even in patients dialyzed by bicarbonate dialysis solutions. It seems that IDH is significantly more prevalent in girls, anuric patients, those with a history of renal transplantation, and subjects with lower serum albumin concentrations; however, none of these factors has any significant impact on the number of IDH episodes in a month. Whether administering albumin to correct serum albumin levels in those with hypoalbuminemia decreases IDH or not is a question that should be supported by investigations focusing on changes in the occurrence or number of IDH episodes in patients with hypoalbuminemia.

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Conflict of Interest

Authors have no conflict of interests.

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