Possible Role of Increased Sodium Gradient on Intradialytic Hypertension Phenomenon

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Abstract

**Background:** Intradialytic hypertension is poorly understood neglected complication of hemodialysis. Better understanding of the pathogenesis of this phenomenon will lead to better management of this complication.

**Aim of Work:** To detect the frequency of intradialytic hypertension among Hemodialysis patients in Assiut University dialysis unit and the role of increased sodium gradient on this phenomenon.

**Patients and Methods:** A cross-sectional study included 200 hemodialysis patients in Assiut University Dialysis Unit was conducted between January 2017 and Mars 2017. Intradialytic hypertension was defined as an increase in systolic BP >10 mmHg from pre to post dialysis. Patients were subjected to detailed history and careful examination. Pre and post hemodialysis blood pressure were measured. Pre dialysis plasma sodium was measured and Sodium gradient was calculated as: Dialysate sodium (dNa)-pre hemodialysis plasma sodium (pNa).

**Statistical Analysis:** Statistical analysis of data was performed using SPSS version 23. To compare between patients we use student’s t-test for unpaired normally distributed data, Mann-Whitney test for medians, and \( \chi^2 \) test for categorical data.

**Results:** 60 patients (30%) had intradialytic hypertension. The intradialytic hypertensive patients had lower predialytic plasma Na and higher Na gradient compared to the control group. Mean predialytic Na sodium and Na gradient in the case group were 132.66 and 7.33 respectively, while 137 and 2.7 in the control group respectively.

**Conclusion:** The frequency intradialytic hypertension in our center was 30%. Intradialytic hypertension is strongly associated with increased sodium gradient.

**Key Words:** Dialysis sodium gradient, Intradialytic hypertension, Hemodialysis.

Introduction

HEMODIALYSIS is one of the modalities of renal replacement therapy for End Stage Renal Disease (ESRD) patients. The most common expected response to a Hemodialysis treatment (HD) is a decrease in systolic Blood Pressure (BP) of about 10-15mm Hg with BP reduction more steeply during the first hour and then decreasing more slowly for the remaining duration of the session [1]. However, a notable subgroup demonstrating increases in BP during the treatment. This increase in BP during hemodialysis, termed Intradialytic Hypertension (IDH) [2]. There are multiple definitions for IDH, but, to date, there is no standard definition. An increase in Systolic BP (SBP) >10 mmHg from pre to post dialysis is one of the most popular definitions [3]. Prevalence may differ from study to another. Observation studies in the 1990s demonstrated that hypertension during dialysis occurs in ≈5% to 15% of patients [4]. In another study it reached 28.4% [5]. In a cohort of more than 100,000 hemodialysis patients followed for more than 5 years, a mean systolic BP reduction of 14mm Hg represented the group with the best survival [6]. The highest mortality occurred in patients with either any rise in systolic BP or a 30mmHg reduction in systolic BP [6]. This impor-
tant study demonstrated the risk associated with intradialytic hypertension and the need to identify the pathogenesis of this phenomenon. The pathogenesis of intradialytic hypertension is complex and not yet fully understood. Several factors have been proposed to be involved in the pathogenesis of this phenomenon [7]. These factors are summarized in the Fig. (1) below.

Fig. (1): Pathogenesis of intradialytic hypertension.

SNS: Sympathetic Nervous System.
I.V.: Intravenous.
ESA: Indicates Erythropoietic-Stimulating Agent.

Intradialytic hypertension is neglected poorly understood complication of HD. Early identification and management of this complication will decrease the cardiovascular risks. Better identification of risk factors of IDH will lead to better management.

Aim of work: To detect the frequency of intradialytic hypertension among Hemodialysis patients in Assiut university dialysis unit and the role of increased sodium gradient on this phenomenon.

Patients and Methods

It is cross sectional study. The study included all ESRD patients in Assiut University Dialysis Unit (213 patients). Patients excluded from this study were patients with advanced heart failure, advanced liver cirrhosis, active severe infection, advanced hyperglycemia and advanced malignancy.

Subjects: 200 ESRD patients met inclusion and exclusion criteria. We used the definition (an increase in Systolic BP (SBP) >10mmHg from pre to post dialysis) to determine the intradialytic hypertensive patients from those without. After determination of patients with IDH (the case groups), 60 age and sex matched ESRD patients, whose blood pressure decreased with ultrafiltration, were taken as control group. Hemodialysis were performed on Fresenius 4008 and Gambro AK 95S HD machines, 2-3 times a week with a duration of 3 to 4 hours per session the blood flow rates ranged between 200 to 300ml/min, and the dialysate flow from 500 to 600ml/min. The dialysate sodium concentration (dNa) was 140mmol/L for all patients. Detailed history from the patients was taken especially: Age (years), gender, duration of dialysis, number of dialysis session per week, duration of dialysis session, number and type of antihypertensive drugs. Careful examination especially (BP, pulse, Jugular Venous Pressure (JVP), chest examination, lower limb examination for edema) was done. Study duration was from January 2017 and Mars 2017. Informed oral consent was taken from the patients. The study protocol was approved by the Local Ethics Committee in Faculty of Medicine, Assiut University.

Measurements:

Pre- and Post-HD blood pressure were measured. These values were obtained by using a sphygmanometer after the patient was at rest for 5min in a supine or sitting position in mid-week dialysis in two successive weeks.

Weight, height were measured for case and control group. Body Mass Index (BMI) was calculated as weight/height$^2$ (kg/m$^2$).

Predialytic plasma Sodium concentration (pNa): A blood sample was collected before the midweek dialysis session and pNa was measured using Diestro 103 AP V3. The dNa concentration was determined using the online conductivity measurements on the Gambro AK 95S HD machines and Fresenius 4008.

Sodium gradient was calculated as: dNa-pre-HD pNa.

Statistical analysis of data:

Statistical analysis of data was performed using SPSS Version 23, word processing data base and statistics programs. Continuous data were expressed as mean ± SD or median and interquartile range. Comparisons between patients were performed using student's $t$-test for unpaired normally distributed data, Mann-Whitney test for medians, and $\chi^2$ test for categorical data.

Results

Our study included 200 patients; 60 patients (30%) had intradialytic hypertension.
The demographic and clinical data of the studied patients:

Table (1): Showing patient demographics involving the two groups collectively:

<table>
<thead>
<tr>
<th></th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>46.28 (14.8)</td>
<td>44.52 (13.1)</td>
<td>0.491</td>
</tr>
<tr>
<td>Number of males</td>
<td>36</td>
<td>36</td>
<td>0.574</td>
</tr>
<tr>
<td>Weight in Kg</td>
<td>64.88 (15.466)</td>
<td>67.34 (15.76)</td>
<td>0.390</td>
</tr>
<tr>
<td>Height in cm</td>
<td>161.8±9</td>
<td>162±8</td>
<td>0.723</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.7±4.16</td>
<td>25.5±5.2</td>
<td>0.452</td>
</tr>
</tbody>
</table>

*: Data are expressed in mean ± standard deviation, while sex as a categorical data is expressed in counts.

Table (2): Comparison of different demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialytic plasma Na</td>
<td>132.66±3.87</td>
<td>137±2.46</td>
<td>.000</td>
</tr>
<tr>
<td>Na gradient</td>
<td>7.33±3.9</td>
<td>2.710±2.4</td>
<td>.000</td>
</tr>
</tbody>
</table>

*: Data are expressed in mean (standard deviation), while sex as a categorical data is expressed in counts.

Clinical signs volume overload in each group:

In the case group; the percentage of patients who had clinical signs volume overload (as lower limb edema and raised Jugular Venous Pressure (JVP)) was 70.0% which much more than the control group 10% as shown in Fig. (4). The difference between the two groups according to Chi 2 test was statistically significant with p-value 0.000.
Antihypertensive drug intake:

In the case group; 44 patients (73.3%) on antihypertensive treatments which was much more than control group (34 patients (56.7%). The difference between the two groups according to Chi squared test was statistically significant with \( p \)-value 0.042.

In case group, the most common drugs received by the patients were Calcium Channel Blocker (CCB) (55%) followed by bisoprolol (30%). In control group, the most common drugs received by the patients were CCB (43%) followed by the ARBs (21.7%).

<table>
<thead>
<tr>
<th>No antihypertensive drug</th>
<th>Antihypertensive drug</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Percentages</td>
<td>26.7%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Control Group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>Percentages</td>
<td>43.3%</td>
<td>56.7%</td>
</tr>
</tbody>
</table>

Table (5): Types and percentages of antihypertensive drugs in all patients and in each group.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall frequency</th>
<th>Case frequency</th>
<th>Controls frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB</td>
<td>59 (49.17%)</td>
<td>33 (55%)</td>
<td>26 (43.3%)</td>
</tr>
<tr>
<td>ARBs</td>
<td>27 (22.5%)</td>
<td>14 (23.3%)</td>
<td>13 (21.7%)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>24 (20%)</td>
<td>18 (30%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Other beta-blocker</td>
<td>9 (7.5%)</td>
<td>4 (6.7%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>Alpha methyl dopa</td>
<td>9 (7.5%)</td>
<td>6 (10%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8 (6.67%)</td>
<td>7 (11.7%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>ACEIs</td>
<td>5 (4.17%)</td>
<td>5 (8.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>1 (0.8%)</td>
<td>1 (1.7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Number of antihypertensive drugs:

The number of antihypertensive drugs received by the patients with IDH was more than that received by patients without IDH. This was statistically significant according to independent-samples Mann-Whitney test (non-parametric test as the number of drugs is not normally distributed according to Kolmogorov-Smirnov) with \( p \)-value 0.012.

Table (6): The median and interquartile range of antihypertensive drugs received by each group.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with IDH</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Patients without IDH</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Number of dialysis sessions:

The percentage of dialysis sessions number was as in Fig. (4), with percentage of 3 sessions per week was 93%. No significance difference between the two groups according to Chi squared test with \( p \)-value 0.57.

Correlation:

Correlation between different quantitative variables is shown in Table (7). From the table, the following data can be concluded:
- There is moderate significant positive correlation between age and Body Mass Index (BMI) with correlation coefficient 0.374 and \( p \)-value 0.000.
- There is strong significant negative correlation between predialytic sodium and sodium gradient with correlation coefficient –0.999 and \( p \)-value 0.000.

Table (7): Correlation between different quantitative variables.

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI</th>
<th>Predialytic Na</th>
<th>Na gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation</td>
<td>.374**</td>
<td>–.142-</td>
<td>.141</td>
</tr>
<tr>
<td>( p )-value</td>
<td>.000</td>
<td>.121</td>
<td>.124</td>
</tr>
<tr>
<td>BMI</td>
<td>Correlation</td>
<td>.086</td>
<td>–.089-</td>
</tr>
<tr>
<td>( p )-value</td>
<td>.350</td>
<td></td>
<td>.333</td>
</tr>
<tr>
<td>Predialytic Na: Correlation</td>
<td>–.142-</td>
<td>.806</td>
<td>–.999-**</td>
</tr>
<tr>
<td>( p )-value</td>
<td>.121</td>
<td>.350</td>
<td>.000</td>
</tr>
<tr>
<td>Na gradient: Correlation</td>
<td>.141</td>
<td>–.089-</td>
<td>–.999-**</td>
</tr>
<tr>
<td>( p )-value</td>
<td>.124</td>
<td>.333</td>
<td>.000</td>
</tr>
</tbody>
</table>

Discussion

In our study, the frequency of IDH was 30% which is high. Prevalence may differ from study to another due to variation in the definition of IDH, increased number of old age patients in the study due (increased arterial stiffness with age) and lastly, some researchers enrolled patients who recently commenced hemodialysis (dry weight not reached). In one recent cohort study, the prevalence of intradialytic hypertension was 21.3 per 100 treatments [8]. The prevalence of persistent intradialytic hypertension was 8 per 100 patients [8]. This latter finding demonstrated that IDH may be a transient phenomenon. Nongnuch et al., did a prospective audit of 531 patients and found a prevalence of 18% [9]. Another cross-sectional study involving 190 chronic hemodialysis patients in the Western
positive Na+ balance in some hemodialysis patients, patients can lead to increased sodium gradient a
presence of a stable set point for pNa has beneficial
former studies
plasma and higher Na gradient compared to the
Na gradient between the IDH patients and control
group. In HD patients, sodium (Na+) balance depends on dietary salt intake during
the interdialytic period and removal of sodium
during HD treatment [11]. Na+ gain during the
interdialytic period should be removed during HD
treatment so that a neutral Na+ balance can be
maintained. In HD, Na is removed by convection
diffusion. A dNa higher than the plasma sodium
concentration (pNa) → diffusion of Na from dialysate to the patient → positive Na+ balance during
HD treatment → thirst and increased interdialytic
water consumption → increased IDWG → volume
overload which is one of the most important factor
contributing to the pathogenesis of IDH [10,12-14].
Also, none osmotic accumulation of Na in subcutaneous
space and other organs, increased Na stores
may affect inflammatory and cardiac fibrotic process via vascular endothelial growth factor [15].
Also Na deposition in arterial smooth muscle may
lead to increased vascular stiffness [15] which in
turn lead to increased peripheral vascular resistance
and blood pressure. Multiple studies have demonstrated
that each HD patient has a unique remarkably
stable osmolar 'set point' for pNa [16]. The
presence of a stable set point for pNa has beneficial
implications to the Na and body fluid control and allows the calculation of the sodium gradient (NaG)
[17]. Therefore, the use of a fixed dNa for all HD
patients can lead to increased sodium gradient a
positive Na+ balance in some hemodialysis patients,
which highlights the benefit from dNa individual-
ization to maintain neutral Na+ balance [16].

Agarwal et al., reported that intradialytic hyperten-
sion may be a sign of over hydration and achieving
dry weight may lead to a normal decrease in BP
during hemodialysis session and achievement of
a more normal interdialytic ambulatory BP [18].
Another study reported Similar findings using
Bioimpedance Spectroscopy (BIS) measurements,
where it was found that the ECW: TBW ratio before
and after hemodialysis session was greater in those
with IDH when compared with those who experi-
enced intradialytic hypotension [9]. Cirit et al.,
evaluated seven hypertensive chronic hemodialysis
patients who had marked cardiac dilatation and
whose blood pressure rose with further ultrafiltration
[19]. The patients were treated with repeated
good ultrafiltration to decrease their dry weight,
and cardiac function was monitored. Complete or
partial normalization of blood pressure (without
the need for antihypertensive agents) was achieved
for all patients. Echocardiographic parameters,
also improved. The authors explained that fluid
overload → cardiac dilatation. Removal of excess
fluid by ultrafiltration → improvement of cardiac
output and RAAS activation → BP. In our study,
the percentage of patients with IDH who had clinical
signs of volume overload, like lower limb
edema, raised JVP and puffiness, was 70.0% while
the percentage of control patients who had clinical
signs of volume overload was 10%. This was
statistically significant compared to control group.
But more accurate methods are needed to evaluate
the volume status of the patients like bioimpedance
spectroscopy.

In a previous study, participants with intradia-
lytic hypertension were older, they received a
greater number of antihypertensive drugs [7]. Eft-
imovska-Otovic et al., found that; older age, lower body mass index, borderline hyponatremia, higher
sodium gradient were the clinical characteristics
of patients with intradialytic hypertension [12].
In our study, the patients with IDH were older, but
there was no statistically significant difference
compared to the control group. They had lower
body mass index, but there was no statistically
significant difference compared to the control
group. The patients with IDH, 44 patients (73.3%)
on antihypertensive treatments which was much
more than control group (34 patients (56.7%). This
was statistically significant according to Chi² test
with p-value 0.042. The number of antihypertensive
drugs received by the patients with IDH was more
than that received by patients without IDH. This
was statistically significant difference according
to independent-samples Mann-Whitney with $p$-value 0.012. The greater need for antihypertensive drugs is logic as they did not reach dry weight.

**Conclusion:**
The frequency intradialytic hypertension in our center was 30%. Intradialytic hypertension is strongly associated with increased sodium gradient.

**Recommendations:**
- Regular checkup of serum sodium to individualize dialysate sodium as possible.
- Dry-weight reduction must be considered an initial approach in IDH patient.

**References**

دور زيادة التدرج في الصوديوم بين سائل الغسيل الكلوي ودم المريض في ظاهرة إرتفاع ضغط الدم الشرياني أثناء جلسات الاستئصال الدموي

تم إجراء دراسة مقطوعة على 200 مريض من مرضى الفشل الكلوي بوحدة غسيل الكلى بمستشفى جامعة أسيوط لتقييم مدى إنتشار ظاهرة إرتفاع ضغط الدم الشرياني أثناء جلسات الاستئصال الدموي في مستشفى الجامعة ومعرفة العلاقة بين زيادة تركيز الصوديوم في سائل الغسيل الكلوي وهذه الظاهرة. وقد تم استبعاد المرضى الذين يعانون من مراحل متاخرة من الفشل الكلى، مراحل متاخرة من القلب، مراحل متاخرة من السرطان أو الزيادة المفرطة للجلوكوز بالدم. وقد تم أخذ التاريخ المرضي وإجراء الفحص الطبي على جميع المرضى، وقد تم قياس الضغط قبل بدء جلسة الاستئصال الدموي وبعد الانتهاء من الجلسة لتحقيق من تشملهم تلك الظاهرة. التعريف المستخدم في الدراسة هو زيادة الضغط الإنتقائي > 100 مم زئبق بعد جلسة الغسيل الكلوي مباشرة من مدي قبل بدء الجلسة. وقد تم قياس تركيز الصوديوم في دم المريض قبل البدء في جلسة الاستئصال الدموي، وتم حساب التدرج في الصوديوم بين تركيز الصوديوم في سائل الغسيل الكلوي وتركيزه في دم المريض. أظهرت الدراسة أن نسبة حدوث هذه الظاهرة كانت 20٪، وأن أهم الأسباب المؤدية لهذه الظاهرة هو زيادة التدرج في الصوديوم بين تركيز الصوديوم في سائل الغسيل الكلوي وتركيزه في دم المريض. وينص بالمتابة الدورية لتركيز الصوديوم بدم المريض على ضبط تركيز الصوديوم في سائل الغسيل الكلوي لكل مريض على حدة.