Improve Uremic Complications: How hemoperfusion helps?

Academic Perspective

Removal of uremic toxins: Where we are and what are the challenges & results sharing of the pilot study on protein bound uremic toxins removal

Prof. Vincenzo Panichi
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1. Uremic toxins and why it is dangerous

Uremic toxins could be classified according to molecular sizes and water solubility into three groups:

1) Free small water-soluble non protein-bound solutes (molecular weight [MW]500 Da) such as urea
2) Middle molecules (MW>500 Da) such as β2 microglobulin (B2MG)
3) Protein-bound solutes that are liposoluble with a protein binding capacity ranging from ~10 to near 100%

Among protein bound uremic toxins (PBUTs), indoxyl sulfate (IS) and p-cresyl sulfate are the most extensively evaluated with regard to their adverse cardio-vascular and renal effects. Publication reveals that the free serum levels of protein bound uremic toxins are associated with mortality in patients treated with hemodialysis. It has been suggested that PBUTs are likely to be a potential missing link in cardiorenal syndrome. Several mechanisms have been proposed, such as uremic toxins may induce systemic inflammation, oxidative stress and endothelial dysfunction, thus lead to cardiovascular disease. The best way to remove renal protein bound uremic toxins is renal transplantation.

2. Renal replacement therapies for uremic toxins

Potential therapeutic strategies to reduce IS and PCS levels in patients with CKD may involve:

1) Reducing gut synthesis
2) Gastrointestinal sequestration,
3) Reduced proximal tubular retention
4) Increased dialytic clearance

The removal of protein bound toxins by dialysis therapy is still difficult and less efficient than for non-bound solutes of similar molecular weight. Numerous strategies have been developed to increase dialytic clearance of protein-bound solutes. Prolonging dialysis treatment time with longer HD treatment session (8 hours) as compared to routine 4-h treatment has been associated to a better clearance of PBUT. Increase in dialysate flow (QD) and dialyzer surface (KoA) beyond standard dialysis practice is another way to optimize the clearance of the protein-bound toxins. Adding
convection seems to improve the removal of protein-bound toxins. Adsorption is considered a complementary mechanism for solute removal, due to the intrinsic capability of sorbents to bind molecules based on chemical affinity.

3. A pilot study from Italy

Study Design: Observational pilot non-randomized study.

Groups: HD alone (10 patients) vs HD+HA130-HP (7 patients).

Study period: 8 weeks. Hemoperfusion was performed twice a week during the first week and once a week in the following seven weeks.

Indicators: Pruritus score using the VAS (visual analogic scale), B2MG, Kt/V, p-cresol and indoxyl -sulphate levels (HPLC method) were evaluated at the beginning and at the end of the study.

Dialysis technique: Standard bicarbonate technique for all patients; Polysulphone hollow fiber of 1.7-1.9 sqm; Blood flow of 315±15 ml/min; Dialysate flow of 550±100 ml/min; Dialytic time of 225±15 min

Results:

1) Plasma beta2 MG varied from 32.94±10.45 to 32.71±11.65 in the study group and increased from 36±9 to 37.5±8.22 in the control group. (p= ns).

2) Urea Kt/V increased from 1.54±0.43 to 1.56±0.33 in the study group and varied from 1.53±0.48 to 1.45±0.51 in the control group (p=ns).

2) Indoxyl – sulphate and p-cresoldecreased significantly in treatment group, while it increased in control group.

Conclusion:

1) Dialysis adequacy should be no more based only on Kt/V urea but it should consider the kinetics of other retention solute that are associated with adverse clinical outcomes.

2) Preserve kidney function is of primary importance (avoid nephrotoxic agents, CKD conservative therapy, incremental dialysis schedule…).

3) Adsorption plus HD/HDF can be a good therapeutic option. Combination of upstream therapy (reduction in PButs intestinal production) and downstream strategies (renal replacement therapy) is the best approach.
Middle uremic toxins clearance by combining hemoperfusion with hemodialysis

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1. Uremic toxins and the complications
Some of the conditions which occur in maintenance hemodialysis (MHD) patients with a high incidence, resulting in a decline in their quality of life, include malnutrition, insulin resistance, pathological changes in the peripheral nervous system, renal osteodystrophy, left ventricular hypertrophy, refractory hypertension, chronic systemic inflammation and accelerated deterioration of residual renal function. Before the 1980s, low-flux dialysis was the main technology for extracorporeal blood purification in uremia treatment, which could hardly remove the middle and large molecule toxins and protein-bound toxins. After the 1980s, with developments in the research of dialyzer membranes and dialysis machines, high-flux dialysis and online -HDF were applied. Adsorption, which is considered a complementary mechanism for solute removal relies on direct binding of solutes to membranes or sorbent materials contained within a cartridge. It can be applied both alone and in combination with other blood purification techniques. An important characteristic of sorbent materials is minimizing unwanted molecules loss, which is frequently encountered using other extracorporeal blood purification techniques.

2. HD+HP 130 - OUR EXPERIENCE
Method
A total of 36 patients, who underwent routine hemodialysis, were assessed in this study. Follow up period from May 2019 until may 2020

Group 1: 17 patients, underwent HD + HP- individualized treatment
Group 2: 10 patients, underwent HD with high flux dialyzer
Group 3: 9 patients, underwent HD with low flux dialyzer

When looking at the difference between the 3 groups on the laboratory and clinical variables (Vascular approach, BMI, Hb, EPO, Fe, TIBC, Albumin, PO4, PTH, Ca), we can conclude that at the starting point of measurement there are no differences between research groups.

Results
After the treatment, Differences between experimental and control groups were not observed on the following variables: Gender, BMI, Vascular Approach, Hb, EPO, Fe, PTH, Ca. Significant differences between control groups were observed for: patient age, HD length, TIBC, albumin, and PO4. Phosphorus levels were significant lower in the HD+HP group than in the control group. (p<0.01). Significant higher levels of TIBC and albumin were noticed in the HD+HP group (p<0.05).

Within the HD+HP group, PO4 is significantly lower after the follow up period compared to baseline. (significance of difference = 0.000) and PTH is significantly lower after the follow up period compared to baseline (significance of difference = 0.016).

Conclusion
1) HD+HP was superior to HD in regularly eliminating middle and large molecule uremic toxins accumulated in the body.
2) These findings suggest a potential role for HD+HP in the treatment to improve the quality of life and survival rate of MHD patients.
Hemoperfusion combined with hemodialysis for long-term dialysis complications: Single center experience from Greece

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1. Demographic and clinical characteristics

4 patients were included in the HP therapy, they were: Male; Over 50 yrs; Stable (no active infection, no hepatic disease); On HDF x3/week; With high vintage and secondary hyperparathyroidism. The Main reason for starting combined blood purification therapy was uremic pruritus.

2. Adsorption therapy protocol

- HP apparatus (HA-130) in series with / before dialyzer
- 2 hours HD+HP, QB: 250ml/min; 2-2.5 hours HDF, QB: 350ml/min
- 14 000 IU UFH in the HP apparatus
- UFH according to ACT values

HP was applied once a week for the first month, then once a month from Jan. 2020 to Jun. 2020.

3. Results

1) All the patients reported clinical improvement of itching (Moderate → mild/ no itching), and Kt/v.
2) There is no change of Albumin in these patients
3) For the PTH level, one patient remained stable, and one patient showed a decrease. Two patients had high PTH level (above 1000), which may be because of the reduction of paricalcitol dose for one patients, and tertiary hyperparathyroidism for another patient.
4) The level of Ca++ and P remained unchanged. Change of liver function (SGOT, SGPT) and blood count (WBC, PLT) remained in normal range.

4. Conclusion

The experience from the use of combined HP+HDF treatment in our center so far is rather positive in:
1) Biocompatibility and no adverse effects (hemodynamic instability, hemorrhagic diathesis, allergies)
2) Hemodialysis adequacy : not negatively affected
3) Clinical improvement of itching
Clinical practice of hemoperfusion for dialysis patients

Dr. Sandra Derkevica
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2. Hemoperfusion experience sharing

Case 1: 47 years old woman (Maintenance IHD for 8 years, 12 hrs/week)
- Primary arterial hypertension, hypertensive nephropathy; High uremic toxin concentration (urea - 43.6, P - 2.48, Kt/V – 0.98); Severe itching complaints (VAS=8) + severe hypertension
- 2 hours for each HA130 session every 2 weeks. No improving of complaints during the first year. After 16 months – HP treatment was intensified to every week.
- Pruritus disappear after 3 months (19 months after HP was started). PTH decrease was 16% after 6 months of HP+HD every week. Kt/V increase noticed after 6 months on HP.

Case 2: Man, 28 years old
- Toxic kidney damage; Severe peripheral neuropathy, difficulty walking
- HA 130 + HD – 2 times per month
- Kt/V increased by 11.2% after 12 months; No positive effect on PTH concentration; Significantly improved walking ability

Case 3: Man, 63 years old
- Obstructive nephropathy, maintenance IHD for 2 years (from 2017); Low Kt/V, high phosphorus
- HA130 from April 2019, added to HD 2 times per month
- PTH decreased by 24.4% after 3 months and by 55.3% after 9 months
- No change on dialysis regime or orally medications (active vitamine D). Kt/V increased by 51% after 12 months on HP (No increase after 6 month)

Data summarization (n=5)

<table>
<thead>
<tr>
<th></th>
<th>Before HP</th>
<th>3 months later</th>
<th>6 months later</th>
<th>% changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea, mmol/l</td>
<td>28.32 (43.6 – 19)</td>
<td>28.42 (42.3 – 148)</td>
<td>22.38 (32.3 – 143)</td>
<td>Decrease 2.6% (n=1)</td>
</tr>
<tr>
<td>Creatinine, mmol/l</td>
<td>826 (1045 – 535)</td>
<td>807 (1159 – 620)</td>
<td>891 (1151 – 504.7)</td>
<td>Decrease 44% (n=1)</td>
</tr>
<tr>
<td>Phosphorus, mmol/l</td>
<td>2.25</td>
<td>2.41</td>
<td>2.3</td>
<td>Decrease 31.2% (n=1)</td>
</tr>
<tr>
<td>PTH, pg/ml</td>
<td>506.6</td>
<td>338.3</td>
<td>287.6</td>
<td>Decrease 35.6% - 62.5% (n=3)</td>
</tr>
<tr>
<td>Total protein, g/l</td>
<td>71.5</td>
<td>70.6</td>
<td>72.5</td>
<td>No changes</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>38.7</td>
<td>39</td>
<td>39.7</td>
<td>No changes</td>
</tr>
</tbody>
</table>

3. Conclusion
1) HA 130 hemoperfusion has been proven to be effective in pruritus relieve in ESKD patients.
2) HA 130 hemoperfusion added to MHD treatment improved uremic toxins – urea and PTH - removing.
3) There may be other uremic toxins removed and symptoms of ESKD and HD complications relieved with HA 130 adding to HD. This would require additional research and observations.
Discussion Session

Moderated by Prof. Vincenzo Panichi
Director of UOC Nephrology and Dialysis, Versilia Hospital, Italy

1. Which patients can we choose to do hemoperfusion treatment?
Dr. Alma Mutevelić-Turković, BiH: Patients in younger life age or middle life age; Patients with high value of phosphate or PTH, or clinical symptoms such as pruritus, refractory hypertension; Patients waiting for transplantation.
Dr. Sandra Derkevica, Latvia: Patients with severe uremic complaints, such as itching, high PTH, insufficient Kt/V.
Prof. Halima Resić, BiH: We choose patients with renal osteopathy.
Dr. Dimitris Petras, Greece: We start with patients with less than 10 years of dialysis treatment, and patients waiting for kidney transplantation.

2. What’s the treatment regimen of HA130 for ESRD patients?
Dr. Dimitris Petras, Greece: Once a week for one month, then once every month. Duration is usually 2.5 h. We use LMWH for anticoagulation. No adverse events were observed. Blood flow is 250ml/min then speed up to 350 ml/min.
Prof. Halima Resić, BiH: We treat patients 4 times monthly first, then changed to 1-2 times/month after the complication relieved. For refractory hypertension, we treat patients once per week lasting for 8 weeks, and then gradually changed to once per month. For CKD it is once per week lasting for 12 weeks, then once per month.
Dr. Sandra Derkevica, Latvia: We start with 2 times a month for 6 months. We do HP for 2h. We use routine anticoagulation. No adverse effects were observed. The routine blood flow rate is 270-350ml/min.
Dr. Alma Mutevelić-Turković, BiH: We used individualized frequency first. Then we changed to once a week for 2 week, then once /2 week, then once a month for a longer period. The duration of treatment is 4 hours with HD. We use same anticoagulant dose as regular HD treatment. No adverse effects such as allergic reaction were observed. 2 clotting were observed at first, but didn’t repeat anymore.

3. How to evaluate the HP efficacy for ESRD patients?
Dr. Alma Mutevelić-Turković, BiH: Clinical and laboratory data before and after HP; Clinical aspect; Questionnaire about sleep quality.
Dr. Sandra Derkevica, Latvia: Clinical symptoms such as pruritus; Lab test (PTH change, Kt/V change)
Prof. Halima Resić, BiH: Quality of life such as sleep quality; Clinical symptoms; lab test of uremic toxins.
Dr. Dimitris Petras, Greece: Lab test of PTH, b2-mg; Clinical symptoms; Questionnaire.