Hemodiafiltration: a superior dialysis modality for children?

Rukshana Shroff
Great Ormond Street Hospital for Children
London, UK

Effectiveness of RRT modalities

McFarlane, Seminars in dialysis, 2009

No benefit from increased urea clearance

HEMO study, NEJM, 2002
**Outline**

- Mechanisms of hemodiafiltration (HDF)
- Theoretical advantages of HDF vs HD
- Clinical benefits of HDF vs conventional HD
  - lessons from adult studies
  - focus on growth and nutrition
- Research study – effects of HDF vs HD on growth & cardiovascular outcomes in children

**Mechanisms of HD vs HDF**

<table>
<thead>
<tr>
<th>Conventional hemodialysis</th>
<th>Hemodiafiltration</th>
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<tbody>
<tr>
<td>Only diffusion</td>
<td>Diffusion + convection</td>
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**Requirements for HDF**

1. High-flux membrane
2. Large quantities of IV quality fluid (‘ultrapure’ dialysate) as replacement fluid
3. Machines with accurate UF control systems
1. Dialysis Membranes

Solute clearance depends on its mol wt

Characteristics of high-flux membranes

1. Flux - Measure of ultrafiltration capacity
   Low flux: Kuf <10 mL/hr/mm Hg
   High flux: Kuf >20 mL/hr/mm Hg

2. Permeability - Measure of the clearance of β2-microglobulin (= middle mol wt solutes)
   Low permeability: β2-microglobulin clearance <10 mL/min
   High permeability: β2-microglobulin clearance >20 mL/min

3. Efficiency - Measure of urea (= low mol wt solute) clearance
   Low efficiency: KoA <500 mL/min
   High efficiency: KoA >600 mL/min
2. Substitution fluid to drive UF

‘Ultrapure’ water for HDF

- Preparation
  - Sterilized + RO
  - Mix with concentrates
  - Ultrafiltration
  - Ultrafiltration

- Microbiological quality:
  - CFU/ml
  - <0.25

- Application in dialysis
  - Ultrafiltration of dialysate fluid in low-flow HD with synthetic membranes
  - Dialysis fluid in all forms of HD & HDF

- Infusion solution in HDF & HF
  - <0.03
Replacement of substitution fluid - pre-dilution vs post-dilution HDF

**Post-dilution HDF is superior**

1. Requires ½ vol of replacement fluid compared to pre-dilution
2. More efficient removal of low mol wt solutes
3. Risk of high hematocrit and filter clotting
4. Pre-dilution is only useful if low blood flows or hemodynamically unstable patient

**Determinants of convective clearance:**

1. membrane properties
   - flux (KuF)
   - surface area
2. UF rate (depends on bl flow rate)
3. treatment time
Advantages of HDF

1. Clearance of uraemic solutes across a wide molecular weight range
2. Biocompatibility
3. Hemodynamic stability

1. Clearance on HDF vs HD

[Bar chart showing clearance of different substances in HDF vs HD]
**β₂ microglobulin clearance**

- HDF achieves 70 – 78% reduction in β₂ microglobulin (vs 40 – 50% with high-flux HD)
  
  Thomas et al, Semin Dialy, 2009

- No signs of amyloidosis after 8 yrs on HDF (vs 100% pts on HD have amyloid by 13 yrs)
  
  Canaud et al, NDT, 1998

- 82% reduced incidence of carpal tunnel syndrome and 67% reduced incidence of erosive arthritis
  
  Dember et al, Semin Dialy, 2006

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**Predialysis β₂m levels correlate with mortality (HEMO Study)**

For every 10 mg/l increase in predialysis β₂M there is a 11% increase in the relative risk of death

Cheung et al, JASN 2000

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**Other middle molecules cleared by HDF**

- Parathyroid hormone
- Inflammatory cytokines (IL-6, IL-8, IL-12)
- Homocysteine
- Guanidine
- Polyamines
- Appetite suppressants (leptin, cholecystokinin, tryptophan)
- Complement factor D
2. Reduced inflammation and oxidative stress

1. reduces inflammation (↓ TNFα, IL-6, IL-8, IL-12)
2. suppresses oxidative stress (↓ reactive oxygen species and superoxide)
3. improves antioxidant capacity
4. reduces generation of AGEs

Mechanisms
1. Biocompatible membranes
2. "Ultrapure" dialysate
3. Removal of cytokines

Chronic low-grade exposure to endotoxins

- Chronic inflammation
- Anorexia, poor nutrition and growth, catabolism, loss of lean body mass – cachexia
- Anaemia – poor ESA response
- Risk of atherosclerosis

Malnutrition – inflammation – atherosclerosis complex

Improved anaemia control on HDF

<table>
<thead>
<tr>
<th>Hemoglobin values and need for transfusions</th>
<th>HD (12 months)</th>
<th>HDF (12 months)</th>
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<tbody>
<tr>
<td>Hb g/dl</td>
<td>7.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Number of transfusions for the whole group</td>
<td>32 (mean 5)</td>
<td>12 (mean 2)</td>
</tr>
<tr>
<td>Membrane</td>
<td>Cuprophane</td>
<td>Polyacrylonitrile</td>
</tr>
<tr>
<td>Duration (sessions)</td>
<td>3x5 h</td>
<td>3x3 h</td>
</tr>
</tbody>
</table>

Fischbach et al; Ped Nephrol 1984
3. Hemodynamic stability

1. Fewer intra-dialytic hypotensive episodes
2. Higher UF better tolerated by patient
3. Reduced post-dialysis fatigue
4. Overall better BP control

Mechanisms:
1. Cooling of dialysate
2. Removal of vasodilating mediators
3. High Na content of infusion fluid

Reduced risk of intra-dialytic hypotension on HDF

- Blood returning to the patient is cooler during o-HDF than HD - enhanced energy loss within the extracorporeal system
- In the patients’ circulation the mean blood temperature is lower during o-HDF than HD

Cardiovascular and survival advantage of HDF vs HD
1. Dutch HDF Study: CONTRAST

2. Turkish HDF Study: High vs Low Efficiency HDF

3. Spanish HDF Study: High vs Low Efficiency HDF

Switching 8 patients from HD to HDF prevents one death / year

OK E; Kircelli F; Turkish Online Haemodiafiltration Study; NDT 2013
On-line HDF provides better overall and CV survival only when high convective volumes are achieved.

Cochrane review - 2015

- Convective dialysis had no significant effect on all-cause mortality (11 studies, 3396 participants: RR 0.87, 95% CI 0.72 to 1.05; I(2) = 34%).
- Convective dialysis significantly reduced cardiovascular mortality (6 studies, 2889 participants: RR 0.75, 95% CI 0.61 to 0.92; I(2) = 0%).
- Effects on nonfatal cardiovascular events & hospitalisation are inconclusive.
- Unreliable due to limitations in study methods and reporting.

Criticism
- Studies on HDF and HF were included under ‘convective therapies’
- Studies with different end-points were combined, and some were underpowered to examine CV or all-cause mortality.

Regression of LVH on daily HDF

Fischbach et al; NDT 2004
Growth on daily HDF

- Height SDS
  - start: -1.5 ± 0.3
  - end: +0.2 ± 1.1
  - target height relative to mid-parental height: +0.3

- Height velocity
  - before daily HDF: 3.8 ± 1.1 cm/y
  - first year of daily HDF: 14.3 ± 3.8 cm/y
  - mean: 10.4 cm/y

NOTE:
- High convective volume
- Daily HDF

Growth study in children

- 15 children on daily HDF; mean age: 7.3 (2.8 – 16.7 yrs)
- 7 converted from PD & 5 from 3/week HD
- Vascular access: fistula (n=13) & catheter (n=4)
- Pre-dilution HDF; Qb & Qd adjusted to achieve a Kt/Vurea ≥1.4 per session x 18 hours per week

Dialysis efficiency & tolerance

- Mean weekly Kt/Vurea ≥10
  - dialysis dose ~ 35% GFR
- Phosphate: 1.39 (1.65 - 0.63) mmol/l
  - despite high protein intake (>2 g/kg/day)
  - 2/15 child on chelators
- CRP – normal in 13/15 (2 children had chronic infections)
- β2 microglobulin 13.5 ± 3.5 mg/L
**Dialysis dose and growth**

Figure 4. Estimated SGR (kg/m²/yr) versus age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatment given 5 times/wk by Ten et al. (10) and one using 3-times/wk hemodialfiltration by Fischbach et al. (11).

**Anabolic effect of daily HDF**

- Stimulates appetite - removal of circulating satiety factors (leptin, cholecystokinin, tryptophan)
- Correction of metabolic acidosis. Acidosis can:
  - activate the ubiquitin-proteosome pathway & increase protein degradation
  - suppress endogenous GH secretion
- Minimises inflammatory cytokine release
- ? Removal of somatomedin and gonadotropin inhibitors by HDF
- ? reverses rhGH resistance

**Paediatric HDF in Europe**

144 cases of HDF in children in 2013 (~12% of all HD cases)

ESPN/ERA-EDTA registry
Potential limitations for setting up HDF

1. HDF machine
   - newer machines can all do HDF

2. Water quality
   - one time installation cost, then 1-3 monthly monitoring
   - must use ultrapure water with all high flux membranes

3. Staff training
   - provided by Fresenius / Gambro

4. Costs
   - €40 /patient/month more than HD

5. No paediatric data
   - We need a study!

The effects of HDF vs conventional HD on growth and cardiovascular markers in children

3H (HDF, Hearts and Height) study

Hypothesis

Children on HDF compared with HD have improved:

- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life
Primary outcome measures:
- Change in carotid artery intima-media thickness (cIMT) standard deviation score (SDS)
- Change in height SDS

Secondary outcome measures:
- For nutritional status
  - Body mass index SDS
  - Markers of appetite regulation and nutritional status
- For cardiovascular status
  - 24-hour mean arterial BP SDS
  - Left ventricular mass index
  - Pulse wave velocity SDS
  - Biomarkers of cardiovascular disease
- Quality of life (QoL) questionnaires

Inclusion and exclusion criteria
- Inclusion criteria:
  - All children 4 - 20 years age undergoing HDF in paediatric dialysis centres (incident and prevalent patients)
  - Age-matched HD patients
  - Prevalent HDF and HD patients must achieve a single pool Kt/v>1.2 in the month preceding recruitment
- Exclusion criteria:
  - if living donor kidney transplant is planned within 6-months

Study design
- 1:1 study design
- Recruitment for 2 years, follow-up minimum 12-months

Numbers needed
- 150 children (75 in each study arm)

Standard prescriptions for HDF and HD
- Aim for target convection volume of 12-15L/m² (post-dilution)
- Dialysate purity equivalent in HD & HDF
- Fresenius dialysers
Recruitment to date

- 173 children from 19 centres in 10 countries
- Full data available in 152 children

Demographics

- Age at study entry
  - Mean 13.5 ± 4 years
  - Median 15.5 years
- 69 males (49%)
- Previous RRT
  - Incident 89 (63%)
  - Previous dialysis 53 (PD 31, HD 13, both PD & HD 9)
- Time on dialysis (before start of study)
  - Median 39.5 (range 1 – 158) months
- Failed Transplants returning to dialysis 30 (21%)

Centres with HD and HDF

[Graph showing the number of centres with HD and HDF]
**HD vs HDF patients - Age**

p = 0.78

**HD vs HDF – previous RRT**

p = 0.14

**HD vs HDF – Access type**
**SWITCH study**

**Hypothesis**
HDF is associated with less inflammation and endothelial dysfunction compared to HD

**To compare:**
Low flux HD vs high flux HD vs HDF
3-months on each modality

**Recruitment:**
Istanbul (n = 9), London (n = 13) & Toronto (n = 5)

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**Conclusion**

- HDF is a superior dialysis modality in adults
  PROVIDED high convective clearance is achieved

- Mechanisms:
  - Improved clearance across a wide mol wt range
  - Reduced inflammation
  - Hemodynamic stability

- Studies in children are under way

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**Thank you!**

**Collaborators:**

A. Bayazit (Adana); C. Stefanidis & V. Askiti (Athens); B. Spasovjevic (Belgrade); S. Stephens (Birmingham); W. Hayes (Bristol); S. Hegde (Cardiff); S. Habbig (Cologne); R. Buescher (Essen); K. Ažukaitis, D. Borzych-Dužalčka, C. Schmitt & F. Schaefer (Heidelberg); S. Çalışkan, N. Canpolat, & S Emre (Istanbul); S. Mir (Izmir); B. Ranchin (Lyon); M. Shenoy (Manchester); K. Vondrák (Prague); M. Fischbach (Strasbourg); S. Picca (Rome); R Nemic, C. Licht (Toronto); M. Litwin (Warsaw).