Disclosure of Interest

RUJKHANA SHROFF

No interest conflicts to declare

The details of each Disclosure of Interest are available at the Invited Speakers’ desk (located in the Registration Area).
Potential advantages of convective therapies for children

Rukshana Shroff
Great Ormond Street Hospital
London, UK
Outline

- Benefits of HDF vs conventional HD in children
  - Focus on growth and nutrition
  - a nocturnal in-centre HDF programme

- Survey of HDF practice across the EU

- Research study – effects of HDF vs HD on growth and cardiovascular outcomes in children
HDF – clearance by diffusion and convection
Advantages of HDF

1. Clearance of uraemic solutes across a wide molecular weight range

2. Biocompatibility

3. Hemodynamic stability
Growth on HDF

Fischbach et al, NDT 2010
Growth failure is a common end point of multiple CKD-related abnormalities:
- Malnutrition – anorexia and reduced energy intake
- Cachexia - protein energy wasting - due to chronic inflammation and inadequate dialysis

35 - 50 % of children with ESRD grow up to become short adults (final height <3rd centile)
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

Fischbach et al; NDT, 2010
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/
- mean: 10.4 cm/y

NOTE:
- High convective volume
- Daily HDF
Dialysis efficiency & tolerance

- Mean weekly $Kt/V_{\text{urea}} = 10$
  - dialysis dose $\sim 35\%$ 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)

- $\beta_2$ microglobulin $13.5 \pm 3.5$ mg/L
# Diet and medications

<table>
<thead>
<tr>
<th></th>
<th>Start of daily HDF (n=12)</th>
<th>After 1 year on daily HDF (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td>Restricted</td>
<td>Free (water, salt, proteins)</td>
</tr>
<tr>
<td><strong>Antihypertensive</strong></td>
<td>10/12 (&gt;2 drugs/patient)</td>
<td>2/12 (1 drug/patient)</td>
</tr>
<tr>
<td><strong>drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>12/12</td>
<td>4/12</td>
</tr>
<tr>
<td><strong>chelators</strong></td>
<td></td>
<td>(only on dialysis free day)</td>
</tr>
<tr>
<td><strong>Phosphate</strong></td>
<td>12/12</td>
<td>1/12</td>
</tr>
<tr>
<td><strong>chelators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post dialysis</strong></td>
<td>6 to 15 min</td>
<td>No post-dialysis recovery time</td>
</tr>
<tr>
<td><strong>recovery time</strong></td>
<td></td>
<td>No sleep disturbances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved school attendance</td>
</tr>
</tbody>
</table>
Figure 6. Estimated SAN-stdKt/V versus age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatments given 3 times/wk by Tom et al. (10) and one using 6-times/wk hemodiafiltration 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
  - suppresses endogenous GH secretion
- Minimises inflammatory cytokine release
- ? Removal of somatomedin and gonadotropin inhibitors by HDF
- ? reverses rhGH resistance

Schaefer et al, NDT 2010
HDF in an in-centre nocturnal dialysis programme

- $n = 7$ children

- Convective volume per session was $> 30$ liters

Thumfart T, Muller D et al; Ped Nephrol 2014
Nocturnal HD vs HDF x 3/wk

- Kt/V
- Phosphate
- iPTH
- MAP
Survey of HD / HDF practice across the EU
Survey on current dialysis practice across Europe

Q2 On average, how many children per year receive:

47 responses

HD – 210 children
HDF – 125 children
ESPN/ERA-EDTA registry ~145 children on HDF across Europe
Q3 How do you decide whether to use HD OR HDF?

Answered: 43  Skipped: 4

- kt/v urea: 7
- to achieve optimal (dry) weight: 4
- to improve serum phosphate levels: 9
- all of the above: 22
- none of the above: 3
- Other (please specify): 11
Q5 If you do NOT perform HDF in your unit, is this because of (tick all that apply):

Answered: 19  Skipped: 28

- Lack of appropriate machines: 8
- Lack of infrastructure for 'ultra...': 2
- Concerns that HDF is more expensive: 6
- Nurses and doctors are no...: 4
- You do not believe that HDF...: 7
- You think that HDF is not...: 
- Any other reasons...: 

Other reasons...
Q6 If you do NOT perform HDF in your unit, for HD do you use:

Answered: 24 Skipped: 23

Q8 If you use high flux membranes for HD, what level of purity in the dialysate do you achieve:

Answered: 24 Skipped: 23

- 'pure' ..............ie bacterial count <100CFU/ml and Endotoxin level <0.25EU/ml
- 'ultrapure'.....ie bacterial count <0.1CFU/ml and Endotoxin level <0.03EU/ml
In centres that do HDF

**Dialysis Machines**
- Fresenius
  - 4008  \( n = 7 \)
  - 5008  \( n = 15 \)
- Gambro
  - AK200UltraS  \( n = 6 \)
  - Artis  \( n = 2 \)

**Dialysers**
- Fresenius
  - FX CorDix  \( n = 15 \)
  - Optiflux  \( n = 1 \)
- Gambro
  - Polyflux  \( n = 5 \)
- Nipro  \( n = 1 \)

**Technique**
- Pre-dilution  \( n = 2 \)
- Post-dilution  \( n = 17 \)
Convective volume achieved

Q18 In POST-dilutional HDF what is the convective volume you AIM for?
Answered: 13  Skipped: 34

Q19 In POST-dilutional HDF on average, what is the convective volume ACHIEVED (expressed as L/m² BSA)?
Answered: 15  Skipped: 32
Cardiovascular outcomes with HDF

Hazard Ratio

0.0
0.2
0.4
0.6
0.8
1.0
1.2

lowflux HD
< 15.5 L
15.5-20.3 L
> 20.3 L

p=0.016

Cumulative Survival

p=0.002

Cardiovascular Survival

HDF (≤17.4 L)
HDF (>17.4 L)
High-flux HD

Survival Probability

Log-ranking p-value: 0.010

Follow-up (months)

HD
OL-HDF

450
367
318
284
232
200
179
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

Nested cohort study within:
- Cardiovascular Comorbidity in Childhood CKD (4C) study
- International Pediatric Hemodialysis Network
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
Cardiovascular outcomes

Cardiovascular measures

• Carotid intima media thickness
• Aortic pulse wave velocity

1. Markers of bone metabolism
   Calcium, phosphate, PTH, 25-hydroxyvitamin D and FGF-23
   Bone-specific alkaline phosphatase, collagen telopeptides

2. Markers of inflammation and oxidative stress
   IL6, IL-10, high-sensitivity CRP, TNF-α
   GDP, AGE
   Changes in intradialytic plasma endotoxin levels

3. Markers of clearance
   β2 microglobulin, cystatin C

4. Others
   Hepcidin-25, ADMA
Nutrition and growth outcomes

- Anthropometry and Tanner staging
- Nutritional measures - Albumin, normalized protein catabolic rate (nPCR)
- Satiety factors - Leptin, ghrelin (aceyl & des-aceyl), cholecystokinin
- Endogenous GH production, IGF-1 and IGF-BP
- Adiponectin
- Resting energy expenditure

Quality of life measures
Post-dialysis recovery time, school and college attendance, physical activity and sleep pattern
Summary

- HDF in children is not widely practiced across Europe
- HDF improves growth (but only shown in nocturnal and daily HDF programmes)
- Ongoing study to examine effects of HDF on growth and cardiovascular outcomes
Thank you!

Rukshana.Shroff@gosh.nhs.uk