Hands-on Ultrasound Session

CONTRAST ENHANCED VOIDING UROSONOGRAPHY [ceVUS]

Organized by:

Kassa Darge, MD, PhD
Professor of Radiology and Surgery
Perelman School of Medicine, University of Pennsylvania
John W. Hope Endowed Chair and Chief
Division of Body Imaging, Dept. of Radiology
The Children’s Hospital of Philadelphia (CHOP)
Philadelphia
Part – 1

ORAL PRESENTATIONS

Susan BACK, MD
University of Pennsylvania

Jeanne CHOW, MD
Harvard University

Kassa DARGE, MD, PhD
University of Pennsylvania

Zoltan HARKANYI, MD, PhD
Heim Pal Children’s Hospital, Budapest

Aikaterini NTOULIA, MD, PhD
Kings’ College London
1. US contrast agents: not FDA approved for children
2. No financial disclosure
Objectives

How to do

Hands-on in vitro demo
US contrast agents

- Selection for off-label use:
  - Optimized for intravesical use
  - Intravesical dose known
- Add to pharmacy formulary

- **Lumason®** [Bracco, Italy]
  - *Gas:* sulphur hexafluoride
  - *Shell:* phospholipid
  - [SonoVue®]
  - **DOSE:** 0.5% - 1% of bladder filling volume

- **Optison®** [GE Healthcare, USA]
  - *Gas:* perfluorocarbon
  - *Shell:* albumin
  - **DOSE:** 0.1% - 0.5% of bladder filling volume
US Contrast Administration

- Bladder catheterization
  - Standard sterile technique
  - Empty bladder

- Mode of contrast administration:
  - **INFUSION**
    - NaCl saline
    - 3-way-stop-cock
    - 20 ml syringe with normal saline
    - Homogenous contrast distribution
    - Ease of handling

- INJECTION
  - NaCl injection/infusion
  - Partial filling
  - Contrast direct injection
  - NaCl flash

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
US Modality

- Dedicated contrast modality
  - Low mechanical index [MI]
  - Other technical features:
    - Color overlay
    - Background subtraction
    - Dual presentation
    - Optimized for specific contrast agent(s)

www.pedrad.org
US Scan: BLADDER

- Sonographic monitoring of bladder filling
- Fast injection of a small bolus of NaCl
- Optimal bladder filling:
  - Homogenous distribution
  - No acoustic shadowing
  - Visualization of bladder base
  - Visualization of retrovesical space
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑ speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑ MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent
US Scan: BLADDER

- Absence of adequate and/or homogenous distribution of microbubbles
  - Normal saline container: Glass!
  - Injection angle 90° and ↑speed
  - Normal saline flash missing
  - Low or high US contrast agent dose
  - US scan parameters incorrect [↑ MI]
  - US contrast vial usage duration
  - Preceding study with intravenous x-ray, CT or MR contrast agent

Pitfalls
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑ speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑ MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent
US Scan: BLADDER

- Absence of adequate and/or homogenous distribution of microbubbles
  - Normal saline container: Glass!
  - Injection angle 90° and ↑speed
  - Normal saline flash missing
  - Low or high US contrast agent dose
  - US scan parameters incorrect [↑MI]
  - US contrast vial usage duration
  - Preceding study with intravenous x-ray, CT or MR contrast agent
Absence of adequate and/or homogenous distribution of microbubbles

- Normal saline container: Glass!
- Injection angle 90° and ↑speed
- Normal saline flash missing
- Low or high US contrast agent dose
- US scan parameters incorrect [↑MI]
- US contrast vial usage duration
- Preceding study with intravenous x-ray, CT or MR contrast agent
US Scan: KIDNEYS

- Supine, prone or both
- Sitting, standing
- Alternating scan right/left
- Dual modality useful
Background subtraction
- Excessive
- Incomplete

Dual modality
- Grayscale resolution ↓

US Scan: KIDNEYS

Pitfalls
US Reflux Grading

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
US scan: URETHRA

- Suprapubic
- Transperineal
Part – 1

Case Demonstration: ceVUS in Daily Practice

The Children’s Hospital of Philadelphia

Susan BACK, MD

University of Pennsylvania

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Female
4-month old
Fever, 4 days

Urine culture
E. coli positive

Ultrasound:
kidney + bladder
VCUG

Antibiotic
Nitrofurantoin
1. VCUG

IPR 2016: contrast enhanced Voiding UroSonography *Hands-on Session*
1. VCUG

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Female
4 months
Fever, 4 days

14 months later

Ultrasound:
kidney + bladder

IMAGING
2. US
IPR 2016: contrast enhanced Voiding UroSonography *Hands-on Session*
Female

Fever, 4 days

GW

20 months later

Contrast enhanced voiding urosonography [ceVUS]
IRP 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

Tissue
64%
C 55
Pen
M10.06

Contrast
52%
C 50
Gen
M10.06

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

Tissue
69%
C 55
Pen
M10.06

Contrast
53%
C 50
Gen
M10.06

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

Tissue 64%
C 55
Pen M10.06

Contrast 50%
C 50
Res M10.06

Left 6.0 cm

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

Contrast Low MI
51%
Dyn R 50
P Low
CRes

Left
ceVUS
IPR 2016: contrast enhanced Voiding UroSonography *Hands-on Session*
ceVUS PRONE IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
ceVUS

**Contrast Low MI**
- 50%
- Dyn R 50
- P Low
- CRes

**IPR 2016**: contrast enhanced Voiding UroSonography *Hands-on Session*
IPR 2016: contrast enhanced Voiding UroSonography *Hands-on Session*
Female
4 months
Fever, 4 days
20 months later
Follow-up ceVUS:
No resolution of grade 3 vesicoureteric reflux in lower moiety on the left
Continue antibiotic

Follow-up ceVUS
Part – 1

Intrarenal Reflux in ceVUS: Additional Detail

Heim Pal Children’s Hospital, Budapest, Hungary
Zoltan HARKANYI, MD, PhD
Clinical impact of intrarenal reflux

- IRR is the extension of reflux into the tubular system of the kidney
- Incidence of IRR is 1-10% in patients with UTI (documented by VCUG)
- Clinical significance: renal scarring
- Anti-reflux surgery and medical treatment can change the long term outcome

IRR = Intrarenal Reflux
Intrarenal reflux

cEVUS

VCUG

Controversial findings about IRR

- 276 patients with reflux grade III-V; age > 5 years
- 55 patients with IRR and 221 without
- Significantly decreased renal function in IRR group (51% vs. 30%) using DMSA scan

- High grade VUR patients, 33 with IRR and 27 without
- Follow up with DMSA for 18 and 36 months
- Prognosis not different for high-grade VUR with or without IRR

Kim SW et al. The clinical significance of intrarenal reflux in voiding cystourethrography (VCUG). Korean J Urol. 2010
- 50 patients with VUR and IRR; 9 treated conservatively, 41 operated
- Renal scarring was documented by DMSA
- VUR with IRR should be actively managed to decrease the chances of renal scarring
Clinical example
Clinical example
ceVUS IRR study: Our results

- 29 children, 18 girls, 11 boys
- Average age: 25 months
- 56 pelvi-ureteric units

**Indications for ceVUS:**
- Recurrent UTI ± pelvic dilatation
- Postoperative VUR
- F/U of VUR in children treated with antibiotics
- Renal developmental anomaly

- 27/29 IRR (5 cases bilateral IRR)

Courtesy Z. Karadi: Semmelweis Medical University

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Intrarenal reflux (IRR): Summary

- IRR easily detected on ceVUS
- ceVUS detects more reflux than VCUG thus potentially more IRR
- Use of Tissue Harmonic Imaging vs Contrast Specific Imaging may affect the sensitivity for the detection of IRR
- IRR mainly occur in reflux grades III-V
Part – 1

Aikaterini NTOULIA, MD, PhD

Kings’ College Hospital
London

Safety: ceVUS with intravesvesical contrast
Safety: US contrast agents

**Intravesical Bladder catheterization!**

Frequency of Symptoms after VCUG, RNC, and DRS in 61 Boys and 167 Girls

<table>
<thead>
<tr>
<th>Patients</th>
<th>VCUG (n = 100)</th>
<th>RNC (n = 100)</th>
<th>DRS (n = 28)</th>
<th>Total (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys and girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>32 (32.0)</td>
<td>37 (37.0)</td>
<td>11 (39)</td>
<td>80 (35.1)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>68 (68.0)</td>
<td>63 (63.0)</td>
<td>17 (61)</td>
<td>148 (64.9)</td>
</tr>
</tbody>
</table>

Type and Duration of Symptoms Reported in 228 Children after VCUG, RNC, and DRS

<table>
<thead>
<tr>
<th>Symptom or Duration</th>
<th>VCUG (n = 100)</th>
<th>RNC (n = 100)</th>
<th>DRS (n = 28)</th>
<th>Total (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
<td>29 (29.0)</td>
<td>35 (35.0)</td>
<td>11 (39)</td>
<td>75 (32.9)</td>
</tr>
<tr>
<td>Wetting</td>
<td>1 (1.0)</td>
<td>5 (5.0)</td>
<td>1 (4)</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5 (5.0)</td>
<td>3 (3.0)</td>
<td>1 (4)</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>Fever*</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (32.0)</td>
<td>37 (37.0)</td>
<td>11 (39)</td>
<td>80 (35.1)</td>
</tr>
</tbody>
</table>
## Safety: US contrast agents

<table>
<thead>
<tr>
<th>Studies</th>
<th>n</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levovist®</td>
<td>1062</td>
<td>17</td>
<td>1.6</td>
</tr>
<tr>
<td>SonoVue®</td>
<td>1889</td>
<td>37</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2951</td>
<td>54</td>
<td>1.8</td>
</tr>
<tr>
<td>European Survey</td>
<td>4131</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Grand total</strong></td>
<td>7082</td>
<td>54</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Adverse events

- **26** Dysuria
- **15** Transient macrohematuria
- **3** Abdominal discomfort/pain
- **2** Anxiety/crying
- **2** Urinary retention
- **1** Frequency
- **1** Blood/mucous discharge
- **1** Perineal irritation
- **1** Urethral pain
- **1** Urinary tract infection
- **1** Vomiting

**Most likely:** bladder catheterization
Safety: US contrast agents

- Prospective study
- Primary objective safety evaluation
- ONLY ceVUS with SonoVue®
- Comprehensive evaluation
- Follow-up after a week

- NO serious adverse events
- 37 (3.7%) patients minor events
- Self-limited adverse events
- Catheterization likely cause
- High safety profile!

Contrast-enhanced voiding urosonography with intravesical administration of a second-generation ultrasound contrast agent for diagnosis of vesicoureteral reflux: prospective evaluation of contrast safety in 1,010 children

Frederica Papadopoulou · Aikaterini Ntoula · Ekaterini Siomou · Kassa Darge


Hands-on Session
Safety: US scan agents

**Optison®**

- Only USA
- Current sites:
  1. Boston Children’s Hospital
  2. Children’s Hospital of Philadelphia
- Interim safety report:
  
  *No adverse events related to Optison®*
Part – 1

Comparison: ceVUS versus VCUG

Jeanne CHOW, MD
Boston Children’s Hospital
Harvard University

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Boston Children’s Hospital Experience

STUDIES

- 4/18/14-2/9/16
- 101 ceVUS studies
- 94 ceVUS and VCUG on the same day with ce VUS offered at no additional charge to families
Boston Children’s Hospital Experience

PATIENTS

- 94 patients
- 44 males, 50 females
- Average age 1.0 years
Boston Children’s Hospital Experience

METHODS

- Optison 0.15 ml in 250 cc saline
- Sterile catheterization
- Infused by gravity
- Cyclic study in children < 1 year old
- Filling to at least bladder capacity in older children
- Voiding around the catheter

- Study followed by a VCUG
Posterior urethral valves
Boston Children’s Hospital Experience

RESULTS

- 187 kidney units (one solitary kidney)

- Concordance
  166 kidney units or 89%

IPR 2016: contrast enhanced Voiding UroSonography *Hands-on Session*
Boston Children’s Hospital Experience

RESULTS

- Discordance
  - in 21 kidney units - 11%
    - ceVUS reflux only in 13 units
    - ceVUS reflux grade higher in 3 units
    - VCUG reflux only in 5 units
    - 8.6% ceVUS showed the presence of reflux or higher grade reflux than VCUG
Boston Children’s Hospital Experience
CONCLUSION

- ceVUS – VCUG
  - Concordance: 89%
  - Reflux only in ceVUS or higher grade: 8.6%
Part – 2
IN VITRO DEMONSTRATION AND HANDS-ON PRACTICE

In Vitro Demonstration of ceVUS:
What and How?

The Children's Hospital of Philadelphia
Kassa DARGE, MD, PhD
University of Pennsylvania

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
In Vitro Hands-On

- In vitro simulation
- US contrast preparation
- Visualization of microbubbles
Part – 2

IN VITRO DEMONSTRATION AND HANDS-ON PRACTICE

The Children’s Hospital of Philadelphia

Susan BACK, MD

Kassa DARGE, MD, PhD

Laura POZNICK, RDMS, AAS

Aikaterini NTOULIA, MD, PhD

University of Pennsylvania

University of Pennsylvania

Kings’ College London

IPR 2016: contrast enhanced Voiding UroSonography Hands-on Session
Thank you for your attention!