Safety and parents’ acceptance of ultrasound contrast agents in children and adolescents – contrast enhanced voiding urosonography and contrast enhanced ultrasound

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Abstract

Aims: To evaluate the safety of the contrast enhanced voiding urosonography (ceVUS) and contrast enhanced ultrasound (CEUS) in children and adolescence and to receive data about parents’ acceptance of intravesical and intravenous application of sulfur hexafluoride. Material and methods: In this prospective, single centre study conducted over a 1 year study period, parents of 56 children (f/m=32/24; mean age 3.1 years; range 3 weeks - 15.9 years) with ceVUS and of 30 children (f/m=15/15; mean age 10.5 years; range 2 months - 17.7 years) with CEUS agreed to be included. A standardized telephone survey about the acceptance of the parents during and after the procedure as well as the adverse events (AE) were conducted within three days of the examination. Results: The parents would agree with the use of both ceVUS and CEUS as a diagnostic tool again in 96% (54/56) or 100% (30/30) of the cases, respectively and 92.9% (52/56) would prefer ceVUS to voiding cystourethrography (VCUG). In addition, 83.3% (25/30) would prefer CEUS to CT and 73.3% (22/30) would prefer CEUS to MRI. AE were reported in 3.6% after ceVUS (2/56; skin rash, mild fever) and in 3.3% after CEUS (1/30; vomiting). AE were subacute and self-limited. Conclusions: The vast majority of parents prefer ceVUS and CEUS to VCUG, CT or MRI because of the safety profile of the contrast agent and diagnostic accuracy.

Keywords: child; Sulphur Hexafluoride; contrast-enhanced ultrasonography; contrast-enhanced voiding urosonography; survey

Introduction

Contrast enhanced voiding urosonography (ceVUS) and contrast enhanced ultrasound (CEUS) are adjunctive techniques to conventional ultrasound. These techniques are radiation free imaging modalities, which are important especially for children [1]. Using ceVUS and CEUS modalities as alternatives to radiography, fluoroscopy or CT, one can reduce the radiation exposure during childhood or the need for sedation which is necessary in time consuming MRI examinations [2-4].

CeVUS and CEUS have a diagnostic efficiency comparable to conventional imaging methods. Studies demonstrated that ceVUS has a sensitivity of 57-100 % and specificity of 85-100 % in comparison to voiding cystourethrography (VCUG) [5]. In addition, a study showed that 96.2 % of the parents would prefer ceVUS for further examinations [6]. CEUS has almost equal sensitivity and specificity in comparison to MRI or CT and is superior to fundamental B-mode sonography dependent on the indication [7,8]. Until now there is no study evaluating the acceptance of parents for CEUS examinations in their children.

For ceVUS the ultrasound contrast agent (UCA) is applied intravesically and for the CEUS examination the
UCA is applied intravenously [9]. The UCA SonoVue® (Bracco Imaging, Italy) is approved in Europe for the intravenous application in children since 2017, but the intravenous application is only possible with off-label use. Whereas, in the USA Lumason® (=SonoVue) is also approved for intravenous use since 2016 [1]. SonoVue® consists of stabilized sulfur-hexafluoride microbubbles [10] and is well tolerated [11,12]. Intravenously applied SonoVue® is eliminated by micturition whereas intravesically applied SonoVue® is eliminated by the lungs [10]. In consequence, SonoVue® can also be used in case of renal failure [9].

There are few studies evaluating the risks of intravesical or intravenous use of SonoVue® in children. In intravesical use the minority of children shows adverse events caused by catheterisation, mostly minor or moderate and non-serious events [6,13,14]. In intravenous use few paediatric cases showed adverse events, mostly minor or moderate. There were only two cases of serious adverse events in children reported in the literature up to now [15,16].

The aim of this study was to evaluate parents’ acceptance of contrast enhanced sonography in their children and to ask if they would prefer ceVUS to VCUG or CEUS to CT or MRI for a possible next examination. Furthermore, this study was designed to evaluate the safety profile of SonoVue®.

Materials and methods

The prospective study was approved by the local internal Ethics Review Board.

Patient Selection

Over a one-year study period, 55.4 % (56/101) of the parents of all ceVUS examinations and 54.5 % (30/55) of the parents of all CEUS examinations could be interviewed. The other parents or legal guardians rejected the participation in the survey because of time constraints or no interest.

Before ceVUS and also before CEUS examinations the parents were informed about the aim and asked to participate in the study. All legal guardians were informed about the off-label use of SonoVue®, procedures and alternative imaging modalities for ceVUS and CEUS. Alternative procedures, such as VCUG, CT and/ or MRI were explained in detail including information about advantages and disadvantages of these methods. Some parents were familiar with the alternative imaging modalities due to prior examinations. Their informed written consent was obtained prior to the examination. Their knowledge about the procedures as well as the advantages and disadvantages were not analysed.

Exclusion criteria included patients aged >18 years, a known sensitivity of sulfur hexafluoride or other components of SonoVue®, cardiopulmonary disorders [17], acute urinary tract infection for ceVUS or the lack of informed consent of the legal guardians.

Ultrasound was performed by two certified paediatric radiologists with experience in CEUS for more than ten years (each >300 ceVUS, >100 CEUS). The indication for ceVUS or CEUS was made in an interdisciplinary consultation in coordination with the legal guardians.

ceVUS examination

CeVUS was performed using a 9-3 MHz convex probe on a ZS3 ultrasound machine (Mindray, China). Baseline pre-contrast ultrasound of the urinary tract (bladder, ureter, kidneys) was conducted in supine and prone position. Afterwards, the bladder was catheterized under standardized aseptic conditions using a 6 CH feeding tube with two lateral eyes (B. Braun, Germany). One urine tube was sampled for laboratory examination and the bladder was emptied. Then, the catheter was linked to a three-way stopcock; one line (direct way) was connected to the UCA and the other to the saline solution bag. SonoVue® was always prepared in accordance with the manufacturer’s recommendations and applied in a sterile manner. 0.1 ml of SonoVue® was applied into the bladder. After the administration of the UCA the bladder was filled with prewarmed saline solution by drop infusion (70 cm table height) until the estimated age-related maximum bladder capacity was reached or the child started to micturate. Under real-time ultrasound guidance the distribution of the UCA in the bladder was observed and the retrovesical and proximal ureters as well as the ureteropelvine junction and the kidneys were examined continuously during filling and voiding. During voiding the urethra was explored by perineal positioned probe. Filling and micturition were repeated up to four times in each patient (minimum two times). To minimize destruction of the bubbles, the mechanical index was turned to a level maximum of 0.10.

CEUS examination

For UCA administration application in the cubital vein was preferred. In small infants, other positions (e.g. scalp veins) were used. Baseline pre-contrast ultrasound examination was tailored to the specific clinical query 9-3 MHz probe on a ZS3 ultrasound machine (Mindray, China) or a 6-1 MHz convex abdominal probe ACUSON S2000 (Siemens Healthineers, Germany). The amount of SonoVue® was calculated using the formula 0.1 ml x age in years as mentioned in the ESPR guidelines [18]. SonoVue® was always prepared according to the manufacturer’s recommendation and applied in a sterile manner in the direct way of a three-way cock. Single UCA
dose was administered with a repeated dose if necessary. Each contrast bolus was followed by a saline bolus of 10 ml. The average amount of administered SonoVue® was 1.4 ml ± 0.9 per patient. During the contrast-specific examination mode the mechanical index was turned to a low level (0.04 - 0.10) to minimize ultrasound related disruptions of microbubbles.

**Adverse event monitoring**

During the examination and until 30 min thereafter, all children with ceVUS and CEUS were observed for any perineal skin or mucosal tissue reaction, generalized hypersensitivity or anaphylactoid reactions. Parents were instructed to monitor their children for three days and to inform their family doctor or paediatrician in the case of any adverse events (AE).

**Telephone survey**

Three days after the examination the parents were contacted for a standardized telephone survey. At first, parents were asked if they would be willing to repeat the examination with the same procedure (ceVUS or CEUS) if necessary. Secondly, they were asked if they would prefer VCUG to ceVUS for the next time or if they would prefer CT or MRI to CEUS. Furthermore, the parents were asked about a list of possible AE. For ceVUS these were skin rash, pruritus, wheals, fever, urinary tract infection, respiratory problems and for CEUS these were skin rash, pruritus, wheals, fever, respiratory problems, taste disorders, vomiting and pain.

**Statistical analysis**

Descriptive statistics was used to report the results.

**Results**

**CeVUS**

All ceVUS examinations were of diagnostic quality and answered all diagnostic questions. No child needed further imaging diagnostics such as VCUG following ceVUS. In the study, the indications for ceVUS were assessment of vesicoureteric reflux (VUR) (fig 1), bladder rupture or urogenital malformation as recommended in the guidelines of the ESPR/ESUR [19]. Patient characteristics for both groups are shown in Table I.

![Fig 1. In a 2-month-old female baby, diagnosed with hydronephrosis during fetal ultrasonography and postnatal positive urethral sign, the ceVUS showed high grade reflux (IV) with dilated and elongated ureter](image)

<table>
<thead>
<tr>
<th></th>
<th>ceVUS (n=56)</th>
<th>CEUS (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (f/m)</td>
<td>32/24</td>
<td>15/15</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>3.1 year</td>
<td>10.5 year</td>
</tr>
<tr>
<td>Age range</td>
<td>3 week – 15.9 year</td>
<td>2 month – 17.7 year</td>
</tr>
<tr>
<td>Weight (mean)± SD</td>
<td>40.8 ± 24.8 kg</td>
<td>40.8 ± 24.8 kg</td>
</tr>
<tr>
<td>Dose (mean) of SonoVue® ± SD</td>
<td>0.1 ml</td>
<td>1.4 ± 0.9 ml</td>
</tr>
</tbody>
</table>

ceVUS, contrast-enhanced voiding urosonography; CEUS contrast-enhanced ultrasonography; SD, standard deviation

For ceVUS 96 % (54/56) of the parents would repeat ceVUS if necessary and 4 % (2/56) of the parents refused ceVUS for further examinations. The main reason reported for rejection was the stress children are put under due to catheterisation which is needed also in the alternative examination VCUG. Concerning CEUS examination, 100% (30/30) of parents would agree with performing CEUS again. ceVUS was favour to VCUG by 92.9% (52/56) parents. The main reported reason was in 84.6% (44/52) of cases the lack of radiation exposure. Two parents preferred VCUG to ceVUS because they felt VCUG is less complicated and less stressful for their child. In one case, every further examination with catheterization was refused and in another case the parents did not give any statement.

AE after ceVUS were reported by the parents in 3.6 % (2/56) of the cases. These events were mild fever and skin rash, which each occurred once and were both self-limited.

**CEUS**

After CEUS the therapy of one child could be finished, one child needed a change in the therapy and 86.7 % (26/30) needed a follow-up. For 93.3% (28/30) of the children CEUS was adequate. Two children needed MRI and an endoscopic retrograde cholangiopancreatography
(ERCP) for further imaging diagnostics, because the imaging of the questioned structure was not high quality. One structure was a case with necrotizing areas in the pancreas. Within the CEUS examination it was possible to detect a homogenous distribution of the microbubbles in the organ though the imaging of the entire pancreas was superimposed by air. Consequently, necrotizing pancreatitis could not be excluded by CEUS, and MRI was indicated for further strategies by the clinicians. The other case was a tumour within the main biliary duct which was suspected in an outside MRI, performed without diffusion weighted imaging and contrast application. During the CEUS examination, no suspect tumour could be identified and ERCP was necessary which excluded intraluminal pathology.

Indication for intravenous CEUS were trauma in 13.3% (4/30), inflammation in 30% (9/30) and focal lesions in 56.7% (17/30) of the liver (n=10), spleen (n=4), kidney (n=6) and pancreas (n=4) as recommended in the EFSUMB guidelines and position statements [1].

CT as an alternative to CEUS was refused by 83.3% (25/30) of the parents; 32% (8/25) of the parents answered that the reason for refusal was the radiation exposure. No one favoured CT over CEUS and 17% (5/30) did not give any statement. MRI as an alternative to CEUS was refused in 73.3% (22/30) of the cases; 45.5% (10/22) of the parents answered that CEUS was a more comfortable examination procedure than that of the MRI. Four parents preferred MRI and four parents did not give any statement. In these cases, no causes were reported.

After CEUS, a 13-year-old boy had a single event of vomiting 30 min after the examination (Table II). AE after CEUS occurred in 3.3% (1/30) of the cases.

**Discussion**

The majority of parents in this study agreed with the use of ceVUS and CEUS examination the next time if required. In addition, the parents preferred ceVUS or CEUS to VCUG, MRI or CT. One reason for that is presumably the comfortable imaging modality and the reduction of radiation exposure. Furthermore, the rate of observed AE was low with 3.6 % in the intravesical group and just one child in the intravenous group. AE were minor or moderate and no severe AE occurred. In the present study the most frequent indications for CEUS are oncological, traumatic or inflammatory questions. All children who had received a ceVUS did not need further diagnostic imaging (VCUG) and were therefore less exposed to ionizing radiation. Only in two cases a CEUS was followed by a diagnostic contrast enhanced MRI examination and an ERCP. All other children could be treated or followed up in a more gentle and radiation-free way.

To the best of our knowledge, there is no study evaluating the acceptance of parents after a CEUS examination of their children and there is only one study evaluating the acceptance of parents after ceVUS. This survey revealed that 96.2% of parents favour further radiation-free ceVUS examinations [6]. The acceptance in our study is comparably high (96%). All parents would do CEUS again, 83.3% refused the CT as alternative and 73.3% refused the MRI.

CeVUS has an equal or higher diagnostic sensitivity and specificity for VUR in comparison to VCUG

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Examination</th>
<th>Total (n)</th>
<th>Age</th>
<th>Gender</th>
<th>Dose of SonoVue*</th>
<th>Severity</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild fever</td>
<td>ceVUS</td>
<td>1</td>
<td>14 months</td>
<td>f</td>
<td>0.1 ml</td>
<td>minor</td>
<td>subacute</td>
</tr>
<tr>
<td>Skin rash</td>
<td>ceVUS</td>
<td>1</td>
<td>3 months</td>
<td>f</td>
<td>0.1 ml</td>
<td>minor</td>
<td>subacute</td>
</tr>
<tr>
<td>Vomiting</td>
<td>CEUS</td>
<td>1</td>
<td>13 years</td>
<td>m</td>
<td>1.3 ml</td>
<td>minor</td>
<td>subacute</td>
</tr>
</tbody>
</table>

ceVUS, contrast-enhanced voiding urosonography; CEUS, contrast-enhanced ultrasonography; f, female; m, male

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Fig 2. Hemangioma in a 4-month-old female preterm baby with native sonographic hypoechogenic lesion in the liver. After 0.3 ml of SonoVue® i.v. the lesion showed typical features of hemangioma with early peripheral nodular enhancement (a), followed by centripetal fill in (b). In the portalvenous phase the surrounding liver tissue shows hyperperfusion in comparison to liver tissue besides, 20 sec after contrast application the whole liver tissue was isoechogen (c). There was no wash out during 5 min of investigation.
In addition, CEUS has a sensitivity and specificity of up to 100% in low energy abdominal trauma in children [8]. In focal liver lesions, CEUS has a specificity of 98% and the interpretations correspond with the reference imaging in 85.3% of the cases [22]. Another study showed that CEUS has a diagnostic detection rate of 93% for the characterization of liver lesions and portal vein anomalies [7].

To date, there are only few studies concerning the rate of AE in intravenous use of SonoVue® in children. There are some reports about complications during ceVUS. Our study showed AE after ceVUS in 3.6% of the children. Equally, a study with 1010 children showed minor AE in the intravesical use of SonoVue® in 3.7% of the cases and, as in our study, no severe AE occurred [14]. Further studies using ceVUS as an alternative method to VCUG showed no or few minor-to-moderate AE [6,13,21]. All the events were not caused by the contrast media itself but by the catheterization procedure.

In our study, only in one case self-limited vomiting was reported as a possible side effect after intravenous use of SonoVue®. A study of 40 paediatric patients and young adults showed comparable results: in 2.5% (2/79) applications AE occurred [23]. There are further studies which indicate that the intravenous use of SonoVue® in children has a low rate of AE [7,8,12,22,24]. There are only two cases of serious AE mentioned in the literature [15,16]. Our study showed a good safety profile of SonoVue® in children in intravesical and intravenous use in line with the existing literature. There are no reports about a possible correlation between the volume of SonoVue® and the observed rate of AE [15]. The recommended dose for SonoVue® for intravesical administration is 0.2 - 1.0% of the actual bladder filling [19]. Since there are no dose finding studies for the appropriate intravenous use of SonoVue® in children, we use 0.1 ml/year of life. Furthermore, a weight adapted dose of SonoVue® is often used (e.g. for infants 0.08 - 0.1 ml/kg body weight) [18]. The FDA recommended a dosage of 0.03 ml/kg body weight up to a maximum of 2.4 ml per injection followed by intravenous flush of 0.9% sodium chloride injection. Repeated application during a single examination is possible.

The advantages of the ceVUS and CEUS examination are equal or higher sensitivity and specificity in comparison to the standard routine imaging modalities, low level of AE, reduction of radiation and the acceptance of the parents for these ultrasound modalities. Furthermore, SonoVue® is not nephrotoxic, has no interaction with the thyroid gland, is not accumulating in the blood and is eliminated by the lung after intravenous application [10,25,26]. The main disadvantage of CEUS is the off-label use in children in most indications. AE such as hypersensitivity, headache, paraesthesia, dizziness, dysgeusia, blurred vision, flushing, hypotension, nausea, abdominal pain, rash, pruritus, back pain, chest discomfort, injection side reaction, feeling hot, chest pain, pain and fatigue are reported in adults; in children the list of AE is shorter (e.g. headache, disturbance of taste), most of them mild and temporary [11]. Considering all advantages, disadvantages and the acceptance by the parents in comparison to methods which need ionizing radiation or sedation one can see that there is a need for the approval of the intravenous use of SonoVue® in children.

The main limitation of the present study is the small sample size. That is why it is important to validate the obtained findings in a greater multicentre trial. Furthermore, the participation in the survey was optional. In this survey 44.6% of the parents in the ceVUS and 55.5% of the parents in the CEUS group refused participation. There is a likelihood of selection bias in the respondents. Parents supporting ceVUS or CEUS have possibly a higher propensity to respond. To underline the role of ceVUS and CEUS as an imaging modality for therapeutic decisions, a survey of the opinions of paediatricians would be helpful.

**Conclusion**

This prospective study demonstrates that ceVUS and CEUS are imaging modalities that are supported and preferred by parents. The survey underlines that AE are rare and mild. The parents’ acceptance is the consequence of the UCA safety and the diagnostic accuracy of ceVUS and CEUS in children.

**Conflict of interest:** none

**References**

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