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REVIEW

Safety of contrast-enhanced ultrasound in children for non-cardiac applications: a review by the Society for Pediatric Radiology (SPR) and the International Contrast Ultrasound Society (ICUS)

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Abstract The practice of contrast-enhanced ultrasound in children is in the setting of off-label use or research. The widespread practice of pediatric contrast-enhanced US is primarily in Europe. There is ongoing effort by the Society for Pediatric Radiology (SPR) and International Contrast Ultrasound Society (ICUS) to push for pediatric contrast-enhanced US in the United States. With this in mind, the main objective of this review is to describe the status of US

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contrast agent safety in non-cardiac applications in children. The five published studies using pediatric intravenous contrast-enhanced US comprise 110 children. There is no mention of adverse events in these studies. From a European survey 948 children can be added. In that survey six minor adverse events were reported in five children. The intravesical administration of US contrast agents for diagnosis of vesicoureteric reflux entails the use of a bladder catheter. Fifteen studies encompassing 2,951 children have evaluated the safety of intravesical US contrast agents in children. A European survey adds 4,131 children to this group. No adverse events could be attributed to the contrast agent. They were most likely related to the bladder catheterization. The existing data on US contrast agent safety in children are encouraging in promoting the widespread use of contrast-enhanced US.

Keywords Children · Ultrasound contrast agent · Adverse event · Contrast-enhanced ultrasound

Introduction

Children are considerably more sensitive to ionizing radiation than adults [1–4]. Thus there is ongoing emphasis on reduction of radiation dose, in particular regarding CT. However, an alternative altogether radiation-free diagnostic imaging option is contrast-enhanced US, which is safe and reliable in a wide range of patients, including children. Contrast-enhanced US uses biocompatible US contrast agents to improve the diagnostic property of a US image. US contrast agents do not contain radioactive material or dye and do not damage the kidney. Contrast-enhanced US is conducted with equipment that is relatively low-cost and widely available and the procedure does not require sedation. Because US contrast agents often improve the accuracy of an initial US diagnosis, they may reduce the need for CT and other unnecessary diagnostic procedures.

A considerable body of scientific literature describes the increasing use of contrast-enhanced US in children to diagnose a range of medical abnormalities with a high degree of accuracy and an extremely low rate or absence of contrast-related adverse events [5–7]. Although in the United States pediatric contrast-enhanced US is generally used off-label or in research settings, its clinical use is relatively widespread in Europe and other parts of the world [5, 8–12]. Therefore most contrast-enhanced US advances in pediatrics are being made in Europe.

The Society for Pediatric Radiology (SPR) and the International Contrast Ultrasound Society (ICUS) recognize the imperative of reducing radiation-based diagnostic imaging in children and supporting the appropriate use of contrast-enhanced US as a safe and effective alternative imaging option for children. The two organizations prepared this technical paper following an ICUS professional society briefing on Sept. 11, 2012, with Center for Drug Evaluation and Research (CDER) staff at the Food and Drug Administration (FDA), at which participants expressed interest in further investigation of contrast-enhanced US as a potential radiation-free diagnostic imaging option for children.

Background

The largest single contributor to medical radiation exposure in the United States is CT [13]. Although CT can be an important diagnostic option for some patients, its growing use is considered a public health concern by the National Cancer Institute [13]. Another important diagnostic imaging option is MRI, which, like contrast-enhanced US, is radiation-free. Nonetheless MRI has several drawbacks that are of particular concern in children. One MRI contrast agent, gadolinium, can increase a child's risk of nephrogenic systemic fibrosis, presenting potentially heightened concerns in newborns and infants because their kidneys have not reached full maturity [14]. In addition children often require sedation when undergoing MRI [15, 16].

Since the late 1990s, US contrast agents have been increasingly used in children to enhance US images and improve their diagnostic reliability [5, 6, 17, 18]. Factors contributing to the growth of pediatric contrast-enhanced US include: (1) the availability of stabilized commercial US contrast agents, (2) the development of advanced US imaging equipment for use with US contrast agents, (3) the greater ease of performing US on a child's smaller body size and more favorable tissue composition as compared with an adult, (4) the relatively low cost and widespread availability of US equipment and (5) growing public concern about the increasing utilization of radiation-based diagnostic imaging, especially in children [3, 4].

The use of pediatric contrast-enhanced US has lagged in the United States compared to Europe, perhaps because of the relatively lower emphasis on US in the overall diagnostic imaging scheme, the less widespread use of US by pediatric subspecialists and the general use of sonographers rather than pediatric radiologists to perform US scans. In addition, pediatric contrast-enhanced US is often non-cardiac and the FDA has not approved an US contrast agent for non-cardiac imaging in the adult population [5]. The level of health insurance reimbursement also might play a role in this difference.

Although commercially available US contrast agents are not approved for use in children, the off-label use of drugs in this population is widespread. A European survey revealed the rate of pediatric prescription of off-label drugs to be 39% and a recent review of the international literature on the same topic put the rate of off-label drug use in children at about 49% [19, 20]. A study in the United States taking a sample of data from the 2001–2004 National Ambulatory Medical

Care Surveys found that 62% of outpatient pediatric visits included off-label prescribing [21]. Another study that evaluated 1-year data from the Pediatric Health Information System, which contains inpatient data from 36 nonprofit tertiary care pediatric hospitals in the United States, discovered that at least 1 drug was used off-label in 78.7% of patients [22]. There was one exception with regard to approved use of US contrast agent in children, namely Levovist® (Bayer-Schering, Berlin, Germany). This galactose-based, air-filled US contrast agent was approved in a few European countries for intravenous (IV) and intravesical use in children; Levovist®, however, is no longer marketed and has been replaced by a second-generation US contrast agent, SonoVue® (Bracco, Milan, Italy), which contains lipid/sulfur hexafluoride [5, 6].

Independent professional societies have established guidelines and recommendations for the safe and appropriate use of contrast-enhanced US in children. The European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) first incorporated pediatric contrast-enhanced US in its 2008 updated clinical practice guidelines and recommendations for contrast-enhanced US [23]. The organization's current guidelines also address pediatric contrast-enhanced US [24]. In addition, the European Society of Paediatric Radiology (ESPR) Uroradiology Task Force and the European Society of Urogenital Radiology (ESUR) Paediatric Working Group promulgated recommendations for pediatric contrast-enhanced US imaging, primarily for intravesical administration, in 2008 and 2012 [25, 26]. At the 2013 ESPR meeting recommendations specifically for intravenous contrast-enhanced US in children were to be presented. These guidelines and recommendations underscore the significance of pediatric contrast-enhanced US as an established diagnostic option in infants, children and adolescents.

In addition, since 2011 major steps have been taken to facilitate the appropriate use of pediatric contrast-enhanced US in the United States. In 2011 the Society for Pediatric Radiology established a contrast-enhanced US task force with the mandate to raise awareness of pediatric contrast-enhanced US and to promote contrast-enhanced US research among pediatric radiologists in North America. The task force's web site (www.pedrad.org) contains comprehensive information and cases on pediatric contrast-enhanced US. In addition, it conducted for the first time in 2013 in the USA pediatric contrast-enhanced US workshops during the annual meetings of both the SPR and the American Institute of Ultrasound in Medicine (AIUM). The task force is also responsible for communicating with and supporting the FDA on issues related to pediatric contrast-enhanced US. The task force is collaborating closely with the International Contrast Ultrasound Society, which recently created a board position dedicated to pediatric contrast-enhanced US and elected a task force member to fill the position.

Clinical applications

Three routes of US contrast agent administration have been described in children: intravenous (IV), intracavitary and oral. IV administration is typically used for characterization and detection of solid organ pathology, analogous to established IV uses in adults [6]. Intracavitary contrast-enhanced US utilizes catheterization and includes intravesical administration for diagnosis of vesicoureteric reflux (VUR) and contrast-enhanced genitography for evaluation of ambiguous genitalia and cloacal malformations, both pediatric-specific indications [5, 17, 18, 27]. Oral US contrast agent administration has only been described in one study involving the diagnosis of gastroesophageal reflux [28]. The procedures, uses and safety of IV and intravesical contrast-enhanced US in children are described below.

IV applications

IV contrast-enhanced US is a potentially important medical imaging option for children. It is diagnostically reliable and completely radiation-free and uses US equipment, which is less expensive than CT or MRI and is portable and widely available. In addition, IV contrast-enhanced US does not require the sedation of children and aligns with the growing implementation of pediatric point-of-care US [3, 4, 29, 30]. The potential uses of IV contrast-enhanced US in children, including therapeutic purposes, have been described [31, 32].

IV contrast-enhanced US

The IV contrast-enhanced US procedure used in children is basically the same as the procedure used in adults, although the US contrast agent dose is modified for age as well as type of US contrast agent and the indication [6]. There are no official pediatric-specific recommendations regarding IV contrast-enhanced US dosage for non-cardiac applications. This is expected to change soon with the publication of guidelines by the ESPR task force. The package insert of the first-generation US contrast agent (Levovist®), which is no longer available, had pediatric IV dose recommendations in one or two European countries where the US contrast agent had been approved for use in children as part of mandatory regulatory approval in adults.

Clinical examples

Two clinical examples illustrate the value of IV contrast-enhanced US for rapidly establishing a reliable diagnosis, avoiding burdening diagnostic testing or biopsy, and guiding appropriate therapy in children. Both examples coincidentally involve 14-year-old boys treated at a major medical center in Canada. One of the boys collapsed while playing rugby

(Fig. 1). His initial US scan showed a focal hypoechoic mass in the pancreatic body/tail; however, upon IV administration of an US contrast agent, the contrast-enhanced US image showed hypervascularity of the mass in the arterial phase, with rapid washout classic for a neuroendocrine tumor (Fig. 1). The diagnosis was confirmed at surgery. The second boy sought medical care in connection with right flank pain. The initial US image showed an apparent incidental liver mass, indeterminate on baseline scan (Fig. 2). After US contrast agent administration, a sequence of frames in the arterial phase of contrast-enhanced US showed stellate vessels and centrifugal filling of the mass, classic for a benign and insignificant growth, focal nodular hyperplasia, which required no further confirmation or therapy. In both instances, IV contrast-enhanced US rapidly confirmed the diagnosis for these children without further testing or exposure to ionizing radiation.

Pre-clinical and clinical studies

A number of pre-clinical studies indicate the potential of IV contrast-enhanced US applications in children [31, 33]. These studies were published beginning in the late 1990s, and most are from the United States. They utilized IV contrast-enhanced US in various animal models to assess renal perfusion during urinary obstruction and pyelonephritis, testicular ischemia in testicular torsion, intratumoral blood flow and treatment response in neuroblastoma, abduction-induced hip ischemia and regional cerebral blood flow mapping for cerebral hyperemia [34–42]. The promising results of these studies prompted the projection of multiple pediatric diagnostic uses of IV contrast-enhanced US [31, 33].

Additional publications address clinical applications of IV contrast-enhanced US in children and are summarized in a recent review of pediatric IV contrast-enhanced US with second-generation US contrast agents [6, 43]. The main indications for pediatric IV contrast-enhanced US included various abdominal tumors and traumatic abdominal parenchymal injuries. Additional clinical reports describing air-containing US contrast agents focus on transcranial Doppler for cerebral arteriovenous malformations, Legg-Calvé-Perthes disease and splenic injury [44–46]. In addition, a number of IV contrast-enhanced US studies in adults for various indications included at least one child younger than 18 years [6].

Diagnostic comparison

Four studies have assessed IV contrast-enhanced US in children for non-cardiac indications. Doria et al. [47] used contrast-enhanced color Doppler US to evaluate the knees in 22 children with juvenile rheumatoid arthritis and found improved detection of active synovial inflammatory disease in subclinical cases. Another study evaluated the revascularization flow in Legg-Calvé-Perthes disease in 26 patients and demonstrated improved depiction of proximal femoral vascularity with contrast-enhanced power Doppler US [48]. Bonini et al. [49] studied postoperative liver transplantation complications in 30 children and compared it with other conventional modalities. IV contrast-enhanced US improved the diagnostic confidence and consequently resulted in reduction of more invasive imaging studies. The latest study in this group, by Valentino et al. [50], compared IV contrast-enhanced US with non-enhanced US and CT for evaluation of abdominal trauma in children [50]. With CT as the reference modality, the performance of contrast-enhanced US was better than non-enhanced US, and contrast-enhanced US had a sensitivity, specificity and negative and positive predictive values of 92.9%, 100%, 100% and 93.8%, respectively. In addition, a recent European survey on contrast-enhanced US in children included feedback from 30 centers using IV contrast-enhanced US [51]. The most common indications from the survey and the literature appear to be

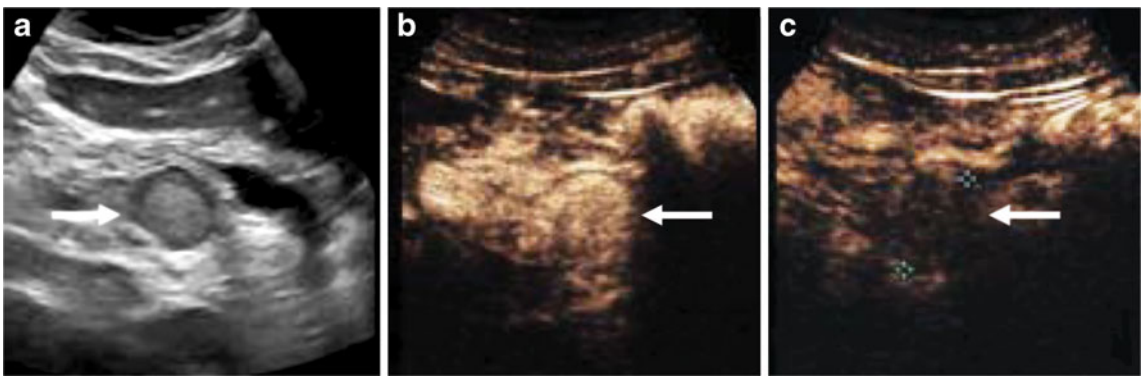

Fig. 1 Clinical example of contrast-enhanced US in a 14-year-old boy who collapsed playing rugby. **a** Baseline scan of the pancreas region shows a hypoechoic mass (*arrow*) in the pancreatic body/tail region in the center of the image. **b** Contrast-enhanced US in the arterial phase shows that the mass is hypervascular, appearing uniformly bright. **c** In the portal venous phase the contrast washes out with the mass appearing black. A neuroendocrine tumor was suspected and was confirmed at surgery. (Courtesy of S. Wilson, Calgary, Canada)

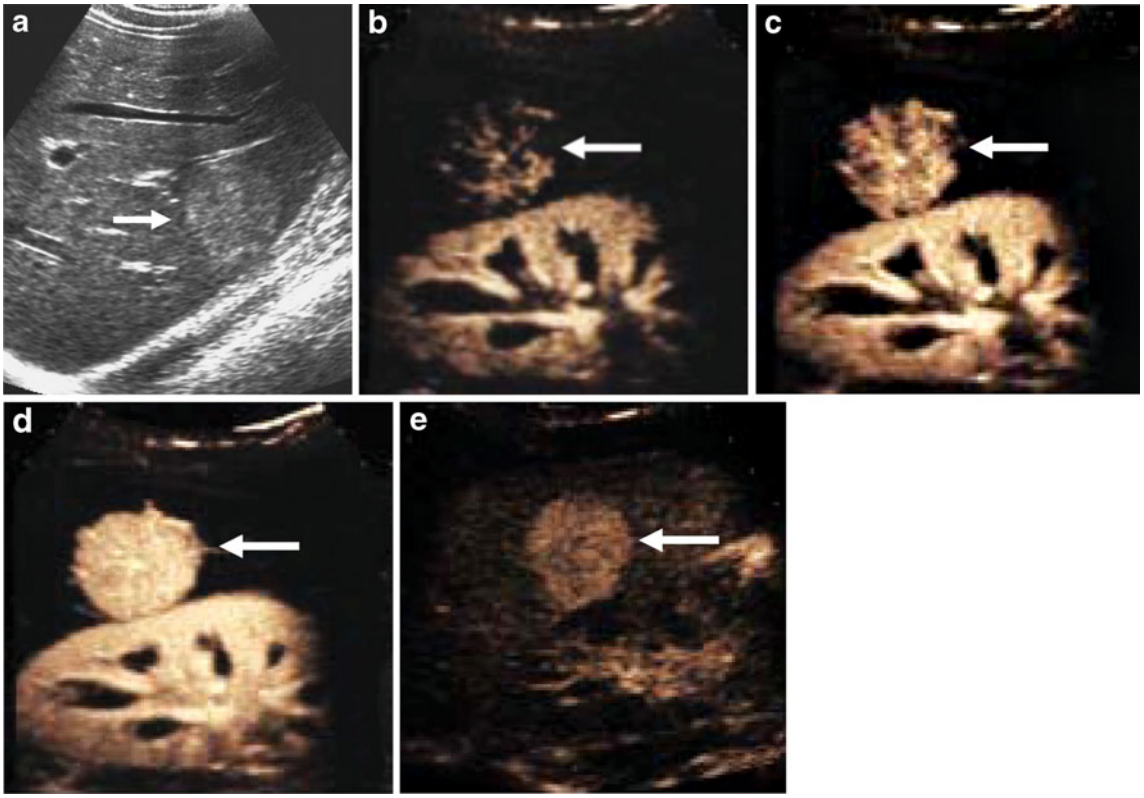

Fig. 2 Clinical example of contrast-enhanced US in a 14-year-old boy who presented with right flank pain. **a** Baseline scan shows a subtle mildly echogenic liver mass (*arrows*). **b-d** Contrast-enhanced US arterial phase sequential frames show stellate vessel morphology and uniform hypervascularity. **e** Portal venous phase image at 4 min shows sustained enhancement such that the mass is still brighter than the liver, indicative of a benign tumor. (Courtesy of S. Wilson, Calgary, Canada)

abdominal tumors (liver), abdominal trauma and inflammatory conditions in the abdomen and other parts of the body [33, 51]. These basically fall within the indications listed for adults in the EFSUMB "Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS)" [24, 52].

Intravesical applications

Diagnostic imaging for vesicoureteric reflux (VUR) is a common procedure in pediatrics. Three modalities are available for VUR diagnosis: voiding cystourethrography (VCUG), radionuclide cystography and contrast-enhanced voiding urosonography (ceVUS). Contrast-enhanced voiding urosonography is performed with US after intravesical administration of US contrast agent, thus eliminating exposure to ionizing radiation. The availability of US contrast agents containing stabilized microbubbles opened the door for rapid development of contrast-enhanced voiding urosonography and its acceptance as an option for routine diagnostic imaging of VUR. A comprehensive account of the use of contrast-enhanced voiding urosonography in children over two decades has been published [5, 17, 18, 53].

Contrast-enhanced voiding urosonography

Contrast-enhanced voiding urosonography is performed in four basic steps: (1) Pre-contrast scan of the urinary tract, (2) intravesical administration of US contrast agent and normal saline solution, (3) post-contrast scan of the urinary tract during and after voiding and (4) post-contrast transperineal scan of the urethra [5, 17, 54]. Grading of VUR is carried out in a similar manner to that of VCUG [55]. SonoVue®, a second-generation lipid/sulfur hexafluoride US contrast agent (Bracco, Milan, Italy), was approved in the European Union for IV use in adults in 2001 and now is also used off-label for pediatric contrast-enhanced voiding urosonography [5, 54, 56–61].

Clinical examples

The depiction of VUR in contrast-enhanced voiding urosonography has been made much easier by the implementation of hardware and software optimizations of US machines for contrast-enhanced US by the manufacturers. In a number of institutions in Europe contrast-enhanced voiding urosonography has completely replaced the conventional methods VCUG and radionuclide cystography and in many

it has taken over at least for the following indications: initial reflux diagnosis in girls, follow-up studies and screening for VUR in boys and girls. Thus in children coming for reflux diagnosis the exposure to radiation can be completely eliminated or significantly curtailed, as cases from Germany and Spain demonstrate (Figs. 3, 4 and 5).

Diagnostic comparison

Numerous studies have compared contrast-enhanced voiding urosonography with VCUG or radionuclide cystography [14]. The reflux detection rate using contrast-enhanced voiding urosonography was higher by 9% compared to VCUG [18]. It is important to note that 70% of refluxes missed at VCUG and detected solely in contrast-enhanced voiding urosonography were higher grades (II-V), whereas the opposite was true for VCUG; namely 68% were low-grade (I). In a recent meta-analysis encompassing 26 comparative studies of contrast-enhanced voiding urosonography with VCUG as a reference method, 2,341 children with 4,664 pelvi-ureteric units demonstrated a contrast-enhanced voiding urosonography sensitivity of 90% and specificity of 92% [62]. The comparative benefits of contrast-enhanced voiding urosonography were summarized in an editorial in the journal *Radiology:* "No radiation, no bladder catheterization, no sedation, low cost, high sensitivity, and excellent anatomic detail—now that would be the perfect screening cystographic examination. With all these factors considered, cystosonography is fairly close to the mark" [63].

Safety

Studies indicate that both IV contrast-enhanced US and intracavitary contrast-enhanced US are safe in children. Five studies have evaluated IV non-cardiac contrast-enhanced US in a total of 123 children ranging in age from 2.5 years to 20.8 years. An additional 948 children were studied in the European pediatric contrast-enhanced US survey. In both of these groups minor adverse events, potentially caused by the IV US contrast agent administration, were detected in approximately 0.1–0.5% of pediatric patients. No severe adverse events were reported. In addition, 15 studies have evaluated the safety of intravesical contrast-enhanced US in a total of 2,951 children ranging in age from 2 days to 20 years. In a European survey, 4,131 children in this group were evaluated. The adverse events were attributed to the catheterization rather than to the US contrast agent. These safety studies are described in greater detail below.

IV administration

Extensive data have demonstrated the safety of IV contrast-enhanced US in adults [64] and additional publications specifically address the safety of IV contrast-enhanced US in children [65–67]. The most comprehensive pediatric IV contrast-enhanced US safety study was conducted by McCarville et al. [68] during prospective evaluation of abdominal and pelvic tumors. Optison® (GE Healthcare, Princeton, NJ), a commercial US contrast agent composed of human serum albumin microspheres encapsulating octafluoropropane gas, was used in a total of 28 IV contrast-enhanced US procedures in 13 children (8 boys and 5 girls with a mean age 10.8 years). Adverse events were assessed by continuous electrocardiogram (ECG) monitoring, cardiologist evaluation of an ECG rhythm strip, review of a 12-lead ECG within 4 h after the contrast-enhanced US, pulse oximetry, blood pressure, heart rate and respiratory rate. In addition, children and parents or guardians were interviewed after each injection and 24–48 h later. Focused neurological examinations, cardiac and pulmonary auscultations and fundoscopies were done. Four children had transient adverse events that included one of the following: mild tinnitus/lightheadedness, taste alteration, irritability/hyperactivity and possible decreased deep tendon reflex; however, these children were also undergoing chemotherapy, which might have caused some of these transient adverse events. After reviewing the results the authors concluded that the US contrast agent was "safe and generally well tolerated in subjects as young as 2 years of age" [68].

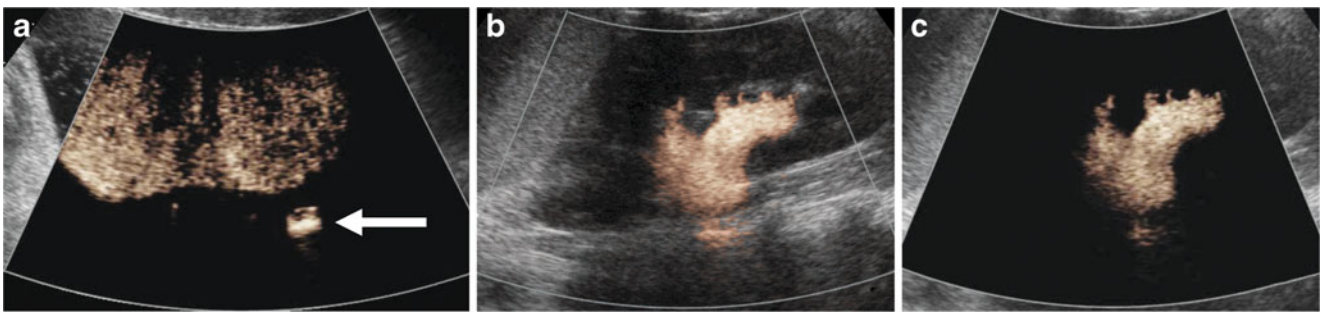

Fig. 3 Contrast-enhanced voiding urosonography in a 3-year-old girl with history of urinary tract infection demonstrates reflux in the left ureter (*arrow*) (**a**) and grade 2 VUR in the ipsilateral kidney (**b, c**)

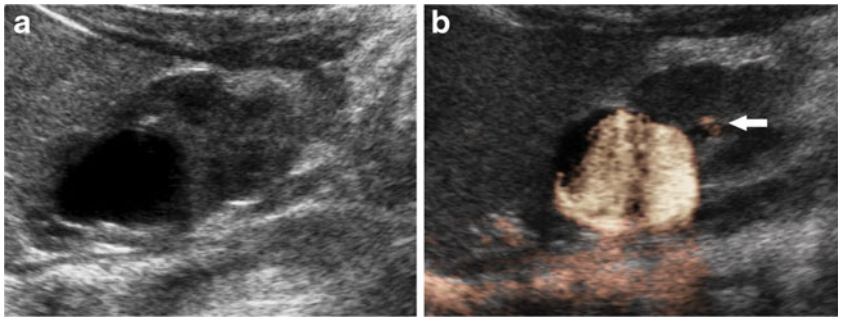

Fig. 4 In this 2.5-year-old girl contrast-enhanced voiding urosonography was carried out because of marked dilatation of the upper moiety pelvicalyceal system of the left duplex kidney. **a** Pre-contrast image. **b** VUR was detected in both the upper and lower moieties (*arrow*)

Four larger pediatric studies on IV contrast-enhanced US were each performed for a different indication: juvenile rheumatoid arthritis, Legg-Calvé-Perthes disease, liver transplant complications and blunt abdominal trauma [47–50]. The earlier two studies used Levovist®, a first-generation US contrast agent [47, 48]. The two more recent studies used SonoVue®, a second-generation US contrast agent [49, 50]. The studies involved a total of 110 children, boys and girls with an age range of 2.6-19.9 years. Although no specific safety evaluation was performed, there was no mention of any kind of adverse event. In addition, Piskunowicz et al. [6], in a review of pediatric IV contrast-enhanced US with second-generation US contrast agents, analyzed seven case reports, two original research studies and 23 original papers (with at least one child younger than 18 years). The authors concluded that no adverse events were reported. The European survey described pediatric IV contrast-enhanced US at 30 centers, reporting 948 examinations in children with a mean age of 5 years (0–18 years) [51]. The group included twice as many girls as boys. An overlap with the above reported cases seems less likely. A total of six minor adverse events were reported in five (0.5%) children from four centers: urticaria and rash (n=2), taste alteration (n=3) and hyperventilation (n=1).

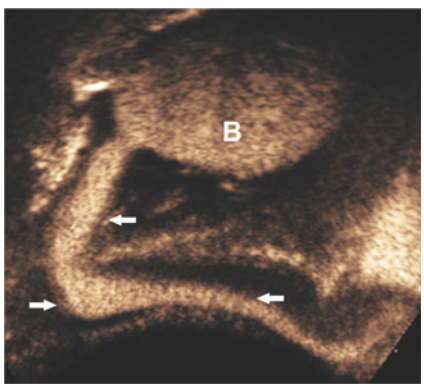

Fig. 5 Transperineal US in a 6-month-old boy during voiding, in the setting of contrast-enhanced voiding urosonography, demonstrates the bladder (B) and a normal urethra (*arrows*). For ease of presentation, the image has been inverted vertically. (Courtesy of C. Duran, Sabadell, Barcelona, Spain)

Taken together, the prospective study of IV contrast-enhanced US in children by McCarville et al. [68], the four additional studies [47–50], the review by Piskunowicz et al. [6] and the European survey [51] indicate that pediatric IV contrast-enhanced US has a low rate of adverse events and that, indeed, the types of adverse events encountered in children and adults appear to be similar [64]. In addition, no severe adverse events have been reported with IV contrast-enhanced US in children.

Intravesical administration

A large body of safety data on intravesical contrast-enhanced voiding urosonography in children has been published, mainly from comparative studies with VCUG or direct radionuclide cystography (DRC) (Table 1). The most comprehensive study primarily addressing safety of intravesical administration of US contrast agents in children was reported by Papadopoulou et al. [7]. This study stands out for the following reasons:

- The study was prospective.
- Because contrast-enhanced voiding urosonography was the only modality, the potential compounding effects of VCUG/DRC in a comparative study setting were eliminated.
- The only objective of the study was assessment of adverse events caused by contrast-enhanced voiding urosonography and not diagnostic efficacy.
- This was the largest single pediatric study of contrast-enhanced voiding urosonography, evaluating a total of 1,010 children (563 girls and 447 boys) with a mean age of 2.9 years (15 days—17.6 years).
- All the bladder catheterizations and examinations were conducted by the same experienced pediatric radiologist.
- Thorough and systematic monitoring for adverse events with vital signs recording was performed with observation of the patients for 1 h after the examination and a follow-up phone call of all parents and guardians 1 week later. Urinalysis and urine cultures were done 3–5 days prior

Table 1 Safety evaluation of intravesical administration of US contrast agents in children

Year	Reference	Dose	US modality	Comparison	Patients			Age		Adverse events monitoring				Adverse events	
					Total	Boys	Girls	Mean	Range	Vital signs	Duration observation	Follow-up by phone			
												Type	Timing	Presence	n/%
2nd-generation US contrast agent: SonoVue®															
2004	Ascenti [57]	n/a	CS+low MI	VCUG	80	36	44	20 mo	3 mo–5 yr	no	12 h	passive	24 h	no	0
2004	Darge [58]	1% vol	CS+high MI	VCUG	27	8	19	n/a	2 mo–15 yr	no	n/a	passive	24 h	no	0
2009	Papadopoulou [59]	1 ml	CS+low MI	VCUG	228	123	105	17.6 mo	6 d–13 yr	no	6 h	active	24 h	no	0
2010	Kis [60]	1 ml	CS+low MI	VCUG	183	94	89	7.6 mo	2 d–44 mo	no	6 h	passive	24 h	no	0
2012	Kljucevsek [61]	1 ml	CS+low MI	VCUG	66	35	31	5.1 mo	5 d–1 yr	no	n/a	passive	48 h	no	0
2012	Duran [54]	1 ml infusion	CS+low MI	none	295	154*	153*	27.1 mo	13 d–8 yr	no	n/a	passive	48 h	no	0
2012	Papadopoulou [62]	1 ml	CS+low MI	none	1,010	447	563	2.9 yr	15 d–17.6 yr	yes	1 h	active	7 days	Yes	37/3.7%
TOTAL					1,889				2 d–18 yr						37/2.0%
1st-generation US contrast agent: Levovist®						296									
1999	Darge [69]	10% vol	Fundamental	VCUG	188	66	122	5 yr#	2 d–20 yr	yes	n/a	act./pas.**	24 h	Yes	2/1.7%
2001	Berrocal [70]	10 ml	Fundamental	VCUG	216	100	116	3.8 yr	3 d–18 y	yes	n/a	passive	24 h	Yes	15/6.9%
2001	Valentini [71]	8% vol	FI+CD	VCUG	74	n/a	n/a	5 yr	3 wk–16 yr	no	n/a	active	24 h	no	0
2002	Mentzel [72]	10%	Fundamental	VCUG	118	28	90	4.5 yr#	3 wk–16 yr	no	no	passive	3 d–2 wks	no	0
2004	Galia [73]	10%	FI+CD	VCUG	122	53	69		1 mo–7 yr	no	12 h	active	24 h	no	0
2006	Papadopoulou [74]	3.5/7.5/12.5 ml	HI high	no	112	48	64	2.9 yr	24 d–14 yr	yes	n/a	n/a	24 h	no	0
2008	Piscitelli [75]	10% vol	n/a	VCUG/DRC	157	105	52	9 mos	6 wk–4.7 yr	no	n/a	no	n/a	no	0
2009	Kljucevsek [76]	5% vol	Fundamental	US ureteric jet	75	18	57	4.8 yr	3–12 yr	no	n/a	no	n/a	no	0
TOTAL					1,062				2 d–20 yr						17/1.6%
European survey															
2012	Riccabona [51]	n/a	n/a	n/a	4,131	boy:girl=1:3		2.5	0–19 yr	n/a	n/a	n/a	n/a	no	0
GRAND TOTAL					7,082				0–20 yr						54/0.8%

CS contrast-specific modality; *FI* fundamental imaging; *CD* color Doppler; *VCUG* voiding cystourethrography; *DRC* direct radionuclide cystography; *mo* month, *yr* year; *n/a* not applicable/available
Dose [%] = % contrast volume in relation to bladder filling volume; # median age not mean; *from 307 exams; ** active part 1, passive part 2; n/% = number of adverse events/% of adverse events

and in case of an adverse event within 1 week after the contrast-enhanced voiding urosonography procedure.
- State-of-the-art imaging was employed with low mechanical index and contrast-specific modality using the second-generation US contrast agent SonoVue®.

The authors found no adverse events during the contrast-enhanced voiding urosonography or within 1 h after the study. Follow-up phone interviews revealed that 973 of the 1,010 children (96.3%) did not experience any adverse event. The remaining 37 children (3.7%) experienced one or more of the following adverse events: dysuria (n=26); urinary retention (n=2); increased frequency of micturition (n=1), urinary tract infection (n=1); blood and mucous discharge (n=1); perineal irritation (n=1); abdominal discomfort (n=2); anxiety/crying (n=2) and vomiting (n=1) [7]. There was no significant difference between the groups with and without adverse events with regard to age, gender, presence or absence of reflux, grade of reflux and frequency of cyclic bladder filling. All of these adverse events were attributed to the bladder catheterization rather than the US contrast agent itself.

In another study within the setting of a procedural optimization of contrast-enhanced voiding urosonography with SonoVue®, without combining with VCUG or direct radionuclide cystography, Duran et al. [54] looked for the presence of adverse events in 295 children (mean age 27.1 months). No adverse events potentially related to the intravesical administration of the US contrast agent were detected.

Five additional studies have evaluated intravesical administration of SonoVue® in a total of 584 children (296 boys and 288 girls) with an age range of 2 days to 15 years (Table 1) [57–61]. All compared the diagnostic efficacy of contrast-enhanced voiding urosonography with that of VCUG. In most cases contrast-enhanced voiding urosonography and VCUG were performed in the same examination session using the same catheter, one after the other. Adverse events were monitored with post-study observation at 6–12 h [57, 59, 60] and with a 24- to 48-h follow-up by phone [59]. No adverse events were reported in any of these studies.

Eight similar studies were carried out to assess adverse events during contrast-enhanced voiding urosonography with Levovist®, the first-generation US contrast agent (Table 1) [69–76]. A total of 1,062 patients (570 girls, 418 boys, 74 unspecified[1]) with an age range of 2 days to 20 years were studied. Most of these studies focused on a diagnostic comparison, with VCUG in five, VCUG or direct radionuclide cystography in one, and non-enhanced US ureteric jet assessment in another. Although the evaluation of safety was a secondary objective, the assessment of adverse events incorporated some or all of the following: search for signs and symptoms during and after the procedure, various levels of vital signs monitoring [69, 70, 74], observation for up to 12 h as an in-patient [73], a request to the child and parents to report any symptoms in the first 24 h post-procedure [70, 72] and a 24-h follow-up by phone [69, 71, 73]. A total of 17 children with adverse events were reported in two studies [69, 70]. Fifteen children had transient visible hematuria during or at completion of voiding at either voiding urosonography or VCUG [71] and one had transient mild abdominal pain, one transient urethral pain [69].

A recent Europe-wide survey at 29 centers reported on US contrast agent use in children for pediatric reflux diagnosis [51]. The centers used Levovist® or SonoVue® in a total of 4,131 children (approximately 75% girls and 25% boys) with a mean age of 2.5 years and a range from newborn to 18 years. The survey might have included some of the patients referenced in the earlier studies. Although adverse events were not a primary focus of the survey, none of the centers reported adverse events potentially related to the intravesical use of US contrast agents in children.

In sum, intravesical use of US contrast agents has been evaluated in a total of 7,082 children described in 15 studies and the European survey. Only 54 (0.8%) reported adverse events. All of these adverse events were transient and included dysuria, hematuria, urinary retention, urinary tract infection, blood and mucus discharge, perineal irritation, abdominal or urethral discomfort, anxiety/crying and vomiting. Considering the known adverse events attributed to bladder catheterization, as reported by Zerin and Shulkin [77], it is likely that the reported adverse events were related to the bladder catheterization rather than the US contrast agent [78, 79]. Thus evidence suggests that the intravesical administration of contrast agents for reflux diagnosis is not associated with any clinically apparent adverse event that can be attributed to the US contrast agent.

Conclusion

The increasing use of CT scans in pediatric medicine increases the exposure of children to ionizing radiation and creates a pressing need to explore effective radiation-free imaging alternatives. Pediatric contrast-enhanced US has high diagnostic efficacy and an extremely favorable safety profile, with few adverse events and no serious adverse events reported. Whether administered intravenously or intravesically, US contrast agents can be used to reliably assess a wide range of medical conditions, and their off-label clinical use in children is widely accepted throughout Europe and parts of the world other than the United States. The high level of clinical acceptance of pediatric contrast-enhanced US is reflected by its inclusion in imaging guidelines and recommendations established by several independent professional societies. Contrast-enhanced

[1] The study by Valentini et al. [71] includes 74 patients not identified by gender.

US, therefore, can be considered an important radiation-free option for diagnostic imaging of children [12].

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