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Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement

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ABSTRACT

The use of contrast-enhanced ultrasound (CEUS) in adults is well established in many different areas, with a number of current applications deemed "off-label", but the use supported by clinical experience and evidence. Paediatric CEUS is also an "off-label" application until recently with approval specifically for assessment of focal liver lesions. Nevertheless there is mounting evidence of the usefulness of CEUS in children in many areas, primarily as an imaging technique that reduces exposure to radiation, iodinated contrast medium and the "patient-friendly" circumstances of ultrasonography. This position statement of the European Federation of Societies in Ultrasound and Medicine (EFSUMB) assesses the current status of CEUS applications in children and makes suggestions for further development of this technique.

Introduction

Ultrasound (US) has long been established as the ideal first imaging examination in children, with excellent diagnostic capabilities in the investigation of diverse body parts such as the abdomen, the neonatal brain or the pleural cavity. Nevertheless, inherent limitations and the frequently inconclusive nature of B-mode US may require further cross-sectional imaging including Computed Tomography (CT) or Magnetic Resonance (MR) imaging in order to increase diagnostic certainty. These investigations require contrast administration, inevitably in CT and frequently in MR imaging. Contrast agents in CT and MR imaging are associated with increased risks both in the adult and child, with gadolinium agents facing greater scrutiny as to long term adverse effects, pertinent to the child [1]. A further "hazard" with the child entailed in CT and more often in MR imaging is the need to render the child immobile throughout the examination either with conscious sedation or general anaesthesia. However the need to reduce radiation exposure in the child is the over-riding aim of every imaging work-up algorithm; cancer risk from medical exposure is not a trivial issue [2 – 4]. Any adjuvant to the baseline US investigation that can obviate the need for further CT or MR imaging in the child would be valuable.

Contrast-enhanced ultrasound (CEUS) with the currently commercially available second generation US contrast agents (UCA) has become a standard imaging option in adult clinical practice for a number of years with an exceptionally high safety profile [5]. Adult CEUS practice across many body organs is established with detailed guidelines on the application published [6, 7]. Many of the applications are "off-label" but the justification for this is often supported by clinical evidence of the usefulness of CEUS [8, 9]. The extension of CEUS into paediatric clinical practice has been slow to develop, mainly hampered by the lack of a "licence" and clinical experience; neither an unsurmountable issue. The use of "off-label" drugs in paediatric practice is well known [10 – 12] and the justification for "off-label" use is sanc-

tioned by the medical regulatory authorities [13]. Previously the only licence for the use of CEUS in paediatric practice was for vesico-ureteric reflux using an agent not currently marketed [14]. There is increasing evidence for the safe intravenous use of UCA in children [15 – 17]. Diagnostically efficient investigations using intravenous CEUS in children are increasingly reported [18 – 21].

Among the currently available second generation UCA, two have been already used in children; SonoVue™ (Bracco SpA, Milan) containing sulphur hexafluoride gas microbubbles and Optison™ (GE Healthcare Inc., Princeton, NJ) containing perflutren gas microbubbles. Recently the Food and Drug Administration (FDA) in the United States of America has authorized the use of SonoVue™ under the commercial name Lumason™ for liver applications in paediatric patients, which is likely to have a profound effect on paediatric US imaging worldwide [22, 23]. This position statement of the European Federation of Societies in Ultrasound and Medicine (EFSUMB) assesses the current status of CEUS applications in children and makes suggestions for further development of this technique.

General Considerations

The issue of consent for the CEUS examination is complex. In most cases the administration of the UCA is "off-label", and written consent for UCA administration may be a hospital requirement. The consent should be obtained from parents or legal guardians prior to examination. However, local policies may vary and informed verbal consent is all that may be required. Some hospital authorities require written consent for all contrast examinations, and administration of an UCA should also be included in this requirement.

The standard manufacturer's list of contraindications needs to be observed. Contraindications include a history of known hypersensitivity to the active substance or excipients, children with right-to-left shunts, severe pulmonary hypertension, uncontrolled systemic hypertension, and uncertain pregnancy status where applicable.

As with all contrast administration, ready access to resuscitation equipment is mandatory and should be in close proximity to the room where CEUS examinations are conducted. All personnel involved with UCA administration in children should have basic skills in identifying and treating a contrast reaction in a child.

Paediatric CEUS Safety Considerations

Safety regarding the intra-venous use of UCA in the children is principally focused on the "off-label" usage. Despite the variability in the legislation between different countries, the "off-label" use of pharmaceutical products in children is a relatively common phenomenon; 11 – 37 % of outpatient treated children, 16 – 62 % of in-patient treated children and 51 – 80 % of neonatal patients may have received "off-label" medications [10 – 12]. The "off-label" use of a pharmaceutical product may be considered appropriate in cases where the benefits of its use outweigh the potential risks of non-treatment. In this context, paediatric CEUS has the potential to influence or even change the diagnostic and therapeutic decisions.

The safety profile of UCA during intravenous administration has been documented in a large cohort of 23 188 adults with the second generation UCA SonoVue/Lumason™ (Bracco SpA, Milan), with no fatal event encountered and only 29 (3 severe, 3 moderate and 23 mild) adverse reactions noted [5]. The overall rate of adverse events (0.0086 %) was comparable to the administration of contrast media used in MR imaging (0.0088 %) [24] and considerably lower than iodinated contrast media used in CT imaging (0.6 %) [25].

The safety profile of UCA in children is based on limited information; there are only three dedicated safety studies which have included vital signs monitoring, all using perflutren containing UCA [17, 20, 26]. In a study of 13 children who underwent intravenous CEUS with escalating doses of UCA based on the body surface, three children experienced mild adverse events; two had altered taste and one mild tinnitus and light-headedness [20]. In a further study by the same group, 134 CEUS examinations in 34 children (median age 8.7 years) were evaluated, reporting a similar frequency and nature of adverse reactions [17]. In a study of 20 children (median age 15 years) four experienced adverse reactions, three children developed transient headache and one reported brief alteration of taste sensation [26].

A sulphur hexafluoride gas containing UCA was also evaluated in a dedicated safety evaluation study of 161 intravenous CEUS investigations in 137 children (median 10.2 years) [21]. In a single case (0.6 %), severe anaphylactoid shock, potentially life threatening and directly related to the intravenous UCA administration was encountered. Observed symptoms were generalized pruritus, nausea, and hypotension with tachycardia initially then bradycardia. Management consisted of oxygen, intravenous epinephrine and fluids (0.9 % normal saline) with resolution in two hours. In 37 children who underwent intravenous CEUS, an 8-year-old girl reported nausea 15 minutes after UCA administration, which continued for 30 minutes [27]. In addition, a retrospective survey analysis of 948 examinations (29 European centres) all performed with SonoVue™/Lumason™, five minor adverse events were recorded; skin reaction, unusual taste and hyperventilation were observed [28].

More extensive safety data has been recorded with intra-vesical administration of UCA during contrast-enhanced voiding urosonography (ceVUS) in a total of 13 studies encompassing 2087 children [29 – 42]. In the majority of these studies safety data was acquired from the time of the examination and up to 48 hours following the examination. No serious adverse events were encountered, with only 3.7 % of children reporting minor adverse events in one safety-dedicated study, which included symptoms of dysuria, abdominal pain, blood and mucous discharge, perineal irritation and urinary tract infection [35]. Symptoms such as anxiety and crying over micturition were also encountered and were likely attributed to the procedural technique rather than the UCA administration, as similar events are reported with other imaging examinations entailing bladder catheterization. Furthermore, Included in the retrospective survey analysis among 29 European centres, 4131 children underwent ceVUS with only minor dysuria symptoms reported [28].

No study has evaluated the in-vivo interaction between UCA and bladder urothelium. A few experimental studies have shown

that in the presence of gas-filled microbubbles, the interaction of tissues and US waves may result in decrease of tissue cavitation threshold and possible disruption of cellular membranes resulting in haemolytic events. However, this phenomenon, which is frequency dependent, has been described in-vitro, with US frequencies that are above the diagnostic medical range [43].

Position Comment

The evidence to date suggests than the safety profile of UCA in adults is good, and comparable to contrast agents used in MR imaging, better than the contrast agents in CT imaging. The more limited safety data in children suggests that UCA are as safe in children as in the adult population.

Current Applications

Focal Liver Lesions

Background

The evaluation of focal liver lesions (FLL) that are detected during baseline US in underlying normal or diseased livers is an important application for CEUS in children. Similarly to that established in adults, there is the potential in paediatric diagnostic practice for CEUS to have a higher diagnostic accuracy in the evaluation of a FLL compared to grey scale US supplemented by colour Doppler techniques and perhaps with comparable accuracy to contrast-enhanced CT and MR imaging. This could potentially include Focal Nodular Hyperplasia (FNH) with typical and diagnostic appearances on CEUS but non-specific B-mode US features, obviating the need for further cross-sectional imaging. Other commonly reported benign FLL that could be accurately characterized by CEUS in children are haemangiomas, hepatocellular adenomas, hepatic cysts, abscesses, regenerative nodules and focal areas of fatty sparring or infiltration. Furthermore, CEUS can provide information in identifying viable tissue within a FLL, allowing a targeted biopsy and facilitating accurate tissue sampling. Contrast-enhanced ultrasound can reveal the presence of additional lesions, not detected during preceding B-mode US.

Technical Aspects

Following intravenous administration of a single UCA dose, targeted evaluation of enhancement dynamics is performed under real-time US imaging in all vascular phases. The enhancement patterns of the FLL are similar to the well-described enhancement patterns noted in CT and MR imaging, with the hallmark of contrast "hypo-enhancement" during the portal venous phase being indicative of malignancy [6]. There are no standardized dosage schemes of the administrated UCA for paediatric CEUS. In published studies of paediatric liver CEUS with SonoVue™/Lumason™, the volume of a single SonoVue™/Lumason™ dose ranges between 0.1 mL to 4.8 mL. The volume of the administered UCA is extrapolated from the licensed adult dose for liver applications and has been described to be adjusted according to child's age, body surface or body weight in the case of obese children as well as the type of US scanner, transducer and processing software used e. g. (a) 0.1 mL of SonoVue™/Lumason™ for each year of age [27] and (b) standard single dose of 0.1 mL, 0.5 mL, 1 mL, 1.2 mL, 2.4 mL or 4.8 mL of SonoVue™/Lumason™ [44 – 47]. The recommendation of the FDA for the dose of SonoVue™/Lumason™ in children is based on body weight; 0.03 mL/kg as an intravenous injection, up to a maximum of 2.4 mL per injection [23]. Overall, it is accepted that the dose of the administrated UCA may be reduced in children. Moreover, the timing of the liver vascular phases is different in children compared to adults and significantly varies depending on the child's age [48]. It should be noted that arterial phase imaging of liver in infants might begin approximately 5 – 6 seconds following intravenous administration of microbubbles and the site (peripheral or central) of intravenous access has further influence [49].

Level of Evidence

There is accumulating evidence regarding the intravenous applications of UCA for the characterization of FLL in children. This experience stems from limited cohort studies and case reports encompassing exclusively paediatric patients as well as from larger studies entailing mixed adult and paediatric patients.

In total 4 original paediatric studies including 125 children (newborn to 18 years old) have been conducted for evaluation of FLL [21, 27, 45, 46]. The largest series of FLL evaluated with CEUS to date described 44 children (median age 11.5 years) evaluated for the characterization of FLL detected during B-mode US imaging [45]. In all cases CT imaging was used as a reference examination and in some cases MR/ PET CT/histology results were also available. This study included primarily benign FLL and demonstrated 98 % specificity of CEUS in accurately confirming the benign nature of FLL based on the enhancement patterns and the absence of contrast "wash-out" during portal venous phase. Importantly, many original studies, including mixed adult and paediatric patients, have been conducted for evaluation of FLL [50 – 59]. All studies demonstrated the feasibility, safety and high diagnostic accuracy of CEUS regarding the characterization of FLL, similar to CT and MR imaging. In the European survey of paediatric CEUS, of the 948 pediatric CEUS examinations performed with intravenous UCA [28], evaluation of FLL was the most common indication. A recent review of the literature on paediatric intravenous applications of CEUS in 2015 described 540 published paediatric CEUS examinations with liver examinations the most frequent indication, 41 % of these cases [16].

A further six review articles that emphasize the advantages of paediatric intravenous CEUS for the evaluation of FLL and promote the need for incorporation of CEUS into routine clinical practice have been published [15, 45, 60 – 64]

Position Comment

Characterization of FLL in children is among the most commonly reported application of paediatric intravenous CEUS. The enhancement patterns of FLL in CEUS are similar to other imaging modalities and contrast "hypo-enhancement" during portal venous phase is highly specific for malignancy.

Renal

Background

The clinical impact of CEUS in renal disease is less well-documented than in the liver, and its ultimate role is still subject to debate, with a recent review documenting current adult practice [65]. The most frequent paediatric CEUS application of the urinary tract is ceVUS, with the intra-vesical UCA administration for the assessment of vesical-ureteric reflux (VUR). The EFSUMB guidelines have established adult indications of renal intravenous CEUS [7] with little published data available regarding paediatric indications [66, 67]. Potential uses of intravenous CEUS in children include diagnosis and follow-up of complicated infection (abscess), cystic masses and complicated cysts, renal trauma, infarction, cortical necrosis [68], transplants, tumour vascularity, renal artery stenosis and where there is a contraindication to CT or MR imaging contrast agents.

Technique

With a single vascular supply to the kidney, compared to the dual supply of the liver, a smaller dose of the UCA is needed for renal opacification. After a very short period of cortical enhancement (5 – 10 seconds after IV bolus injection), UCA can be seen the medulla which lasts 45 – 120 seconds after injection. The contrast enhancement of the cortex occurs almost immediately after the arrival of the UCA in the main renal artery, with rapid subsequent renal vein enhancement [65, 69]. Limitations of renal CEUS are identical to all US abdominal studies in children; lack of respiratory cooperation can limit the observation during the short cortical phase and the simultaneous comparison with contralateral kidney is not possible. Furthermore, as the contrast agents are not excreted by the kidney, function and evaluation of the pelvicalyceal system is not possible.

Level of Evidence

Diagnosis of abscesses complicating pyelonephritis and response to antibiotic treatment can be documented by CEUS (a central defect with rim enhancement). Complicated renal cysts are infrequent in children but CEUS may be appropriate for renal cyst classification with the modified US Bosniak system [65], and the true nature of indeterminate masses in children may be helped using CEUS. A particular advantage of a CEUS examination is the better depiction of internal vascularity of a lesion compared to MR or CT imaging, potentially evaluating solid renal tumor vascularity prior to and during chemotherapy [67]. CEUS can be used to determine the extent of renal parenchymal injury in blunt abdominal trauma, and useful in the followup of parenchymal injuries or for the assessment of complications after the admission CT imaging [70, 71]. Acute renal transplant rejection may potentially be diagnosed by CEUS, as well as stenosis and occlusion of the transplant renal artery in the early stages [72].

Position Comment

Renal assessment in blunt abdominal trauma is promising with evidence to indicate usefulness in follow-up. There is no data available on the assessment of focal lesions, cysts and in the assessment of renal transplants in the child; indications are likely to be similar to those in the adult with more emphasis on childhood renal lesions with attention to tumour vascularity.

Abdominal Trauma

Background

The use of paediatric CEUS in the clinical setting of blunt abdominal trauma is attractive. Other techniques that assess blunt abdominal trauma in children such as Focused Assessment with Sonography for Trauma (FAST) and CT imaging both have inherent constraints. A FAST examination is sensitive in detecting free peritoneal fluid as an indirect sign of injury but has poor sensitivity in directly revealing solid organ injury. Contrast-enhanced CT is over utilized in trauma patients, imaging unnecessarily a wide spectrum of severity, ranging from minor, single-system injuries to devastating, multi-trauma; a balance needs to be achieved in the child. As in adults, paediatric CEUS is an effective alternative or supplementary imaging option to CT imaging in the following situations: (a) in haemodynamically stable patients who sustained isolated, low or moderate energy blunt abdominal trauma; (b) in patients with indeterminate or normal CT findings and suspicious laboratory tests; (c) in the follow-up of traumatic injuries that are managed conservatively in order to ensure resolution of the lesions or detect any associated complications, including pseudoaneurysm formation [19, 71, 73 – 75]. CEUS can identify traumatic injuries and evaluate their extension with higher diagnostic accuracy compared to baseline US and comparable to CT imaging, and can detect associated complications [76].

Technique

CEUS in trauma is performed following bolus intravenous administration of two separate UCA doses. The first dose is administered to investigate organs in the right upper quadrant (kidney, adrenal gland, pancreas and liver), whereas the second is administered to evaluate organs in the left (kidney, adrenal gland and spleen). The CEUS examination should commence from the side of clinical concern. The kidney should be examined first as this will rapidly enhance, with a detailed examination throughout arterial phase, whereas the spleen, and liver are evaluated during the portal venous phases. Any traumatic lesion, laceration or contusion, will appear as a clearly demarcated hypoechoic area compared to the adjacent parenchyma. Follow-up CEUS imaging targets only the organ identified on baseline imaging, and a single dose of UCA will suffice.

Level of Evidence

There are a number of studies relating specifically to the assessment of blunt abdominal trauma in children [19, 68, 71, 73, 75, 77]. The largest series of children (n = 74) underwent comparative B-mode US, CEUS and CT [19]. The diagnostic performance of CEUS was better than B-mode US and similar to CT imaging. Moreover, CEUS identified prognostic factors for the clinical course of trauma patients, such as parenchymal active bleeding (n = 8) and partial splenic devascularization (n = 1). A previous study with a smaller number of children (n = 27), demonstrated a sensitivity and specificity for CEUS compared to CT for the detection of solid organ injuries at 92.2 % and 100 % respectively [73]. A

study that evaluated the incidence of post-traumatic complications in a cohort of 17 children, demonstrating 83 % sensitivity and 92 % specificity of CEUS for the accurate detection of liver and splenic pseudoaneurysms [71]. A number of case reports present CEUS imaging findings in isolated pancreatic and splenic injuries, as well as a case of renal cortical necrosis [68, 71, 75]. A number of studies including a mixture of adult and paediatric patients are described in the literature, all large cohorts, demonstrating the feasibility and the high diagnostic accuracy of CEUS in the diagnostic algorithm of solid organ injuries [19, 73, 74, 76 – 84].

Position Comment

CEUS has shown to be a reliable tool in the diagnosis and follow-up of solid organs injuries in paediatric patients who sustained low to moderate energy traumatic events, with the important advantage of being a highly sensitive, radiation free and child friendly imaging technique, allowing for repeated imaging. This should form the basis of follow-up of solid organ injury to reduce radiation and the use of iodinated contrast agents.

Pediatric Transplantation

Background

Possible indications for the application of CEUS in children with transplantations (renal, liver, pancreas and renal combined), are likely similar to adult indications, and the application of CEUS to the imaging assessment is likely to be of substantial clinical relevance. Most adult investigations have focused on the liver [51, 85 – 88] pancreas [89]and kidney [90 – 95]. Assessment of a number of potential areas in the transplanted child include differentiation of incidental focal liver lesions [96], suspected post-transplant-lymphoproliferative disease (PTLD), paediatric tumour characterization before and after transplantation, depiction of vascularity, vascular patency before and after solid organ transplantation (liver [97], kidney, pancreas, bowel) or skin flaps [98], ischemic alterations such as infarction, active bleeding, graft vs. host disease (GVHD) [99] of the bowel and infectious complications after transplantation.

Level of Evidence

Nearly all studies of the use of CEUS in transplantation combine adult and paediatric patients. The identification of complications following solid organ or stem cell transplantation using CEUS can confirm the preliminary clinical diagnosis, provide additional information relevant to the therapeutic management and obviate any additional diagnostic procedure.

Position Comment

The application of CEUS in the child following transplantation is likely to be similar to the adult, with vascular patency, areas of necrosis, assessment of new focal lesions and the assessment of post-operative complications (e. g. fluid collections) most likely the areas of use.

Lung and Pleural Space

Background

Although US has been applied for the evaluation of consolidated lung and the adjacent pleural spaces in adults, the use of CEUS in children has not been comprehensively described. However, there are reports that suggest that CEUS may improve the diagnostic confidence of grey scale US supplemented by colour and power Doppler imaging in differentiating consolidated lung from cavitating pneumonia in children, and better delineating the extend and contents of associated para-pneumonic fluid collections [100 – 107]. In addition, there is limited evidence that CEUS can evaluate the enhancement dynamics in cases of pleural-based lesions, allowing for their improved characterization [101, 106].

Technique

Following UCA administration, targeted evaluation of the lung and pleural spaces is performed in coronal plane using lateral and posterior acoustic windows, in a comparable manner to grey scale lung US. There are no standardized dosage schemes for this application in the pediatric population; however a single dose of 2.4 mL has been described [100].

Level of Evidence

There is one study presenting the CEUS patterns in cases of pneumonia in a population group consisted of 50 adults and children older than 17 years. In this study, evaluation of the affected lung in terms of blood supply and enhancement could be used as prognostic indicator for development of associated complications [100]. Investigation by CEUS of lung and pleural lesions in children are also described [101, 104].

Position Comment

Lung CEUS is a relatively new diagnostic method that could potentially increase the diagnostic confidence to differentiate consolidated lung from cavitating pneumonia in children. This technique may also improve the visualization of pleural fluid.

Spleen

Background

Trauma is an indication for use of CEUS of the commonly injured spleen in children, with CEUS of significantly higher sensitivity for the diagnosis of splenic laceration, rupture, fracture or active bleeding than B-mode or Doppler US [19, 71, 74, 75, 108]. This has the potential to reduce the radiation exposure [109] with follow-up imaging performed with targeted CEUS of the spleen once baseline imaging (either CT or US as the situation decrees) confirms the site and extent of injury [7, 71]. Splenic diffuse or focal pathology is difficult to characterize and differentiate on any imaging modality. Suitable indications in children are the differential diagnoses of splenic focal lesions (e. g. lymphoma, haemangioma [110], complex cyst and abscess) and vascular alterations such as splenic infarction, aneurysms and quantification of viable parenchyma in hyposplenia in sickle-cell disease [67]. In children, the percentage of inborn focal splenic lesions such as hamartoma

or lymphangioma and the range of differential diagnoses due to metabolic diseases might be higher compared to adults.

Technique

The intravenous administration of US contrast will mirror the doses in adults; usually a smaller dose (typically 1.2mLs SonoVue™/Lumason™ in adults) will suffice in the child. Careful consideration of the unique vascularization pattern of the spleen to avoid misinterpretation of abnormalities must be observed [7]. Typically, evaluation of the splenic parenchyma is performed during venous and delayed phases.

Level of Evidence

Evidence for splenic pathology, apart from trauma, is sparse. There is strong evidence for the application of CEUS in splenic trauma.

Position Comment

Diagnosis and follow-up of splenic trauma in children is an ideal application of CEUS.

Adrenals

The value of conventional US in the detection of adrenal gland tumours is well known; lesions > 10 mm are detectable, but characterisation is more difficult. The differentiation of benign and malignant adrenal gland tumours is not possible using CEUS [111 – 113]. No data regarding the use of CEUS in children for further characterization of adrenal gland tumours is available. Isolated case reports documenting adrenal lesions in children are available [114, 115]. Evaluation of trauma to the adrenal gland and differentiation of haematoma from underling adrenal gland tumour may be helpful [77]. Future perspectives of CEUS include evaluation of haemorrhage in neonates.

Position Comment

Adrenal CEUS could be used in trauma or haematoma of the adrenal, evaluating resolution in place of CT.

Inflammatory bowel disease

Background

The diagnosis of inflammatory bowel disease (IBD) in children and the classification of Crohn's disease (CD) or ulcerative colitis (UC) is achieved with the combination of endoscopy, biopsy, laboratory markers and imaging work-up. Though CT Enterography (CTE) and MR Enterography (MRE) are the diagnostic examinations of choice for IBD in children, the role of CEUS is increasing. Similarly to adults, paediatric CEUS has proved to determine accurately the extent of the disease, differentiate between actively inflamed bowel and chronic fibrotic strictures, evaluate the response to treatment, and identify the presence of associated mural and extramural pathology. In addition, post-processing quantitative evaluation of the visualized bowel wall enhancement through assessment of time-intensity curves allows for objective and reproducible evaluation of the degree of bowel wall enhancement.

Technique

A fasting period of 6 hours is required. Initially, an unenhanced US examination is performed supplemented by colour and power Doppler US to identify the pathologically thickened loop of small bowel. Following intravenous UCA administration, the involved intestinal segment is targeted for CEUS evaluation of the degree of bowel wall enhancement. There is no standardized dosage scheme for CEUS performance in IBD. The most commonly used schemes are associated with the frequency of the used transducer and are the following: (a) 1.2 mL SonoVue™/Lumason™ in the case of low-frequency transducers [116, 117], and (b) 2.4 – 4.8 mL in the case of high-frequency transducers [116]. The first-pass of the small bowel enhancement is generally monitored 5 sec after UCA injection and the maximum enhancement of the bowel wall is visualized after approximately 12 – 20 sec. Serial static images and multi-frame cine-clips during breath-holding are acquired and are available for post processing quantitative analysis, which includes evaluation of the following parameters in an operator-defined Region of Interest (ROI): percentage of maximal enhancement, time to peak, and area under the curve. These parameters were shown to have good correlation with endoscopy and histology grading.

Level of Evidence

There are no dedicated CEUS studies for the evaluation of IBD in children. Among several published studies, five included mixed population comprised of children older than 16 years of age and adults [116 – 120]. All of these studies demonstrated the effectiveness of CEUS in evaluation of IBD inflammatory activity and a strong correlation with the histological indices. A single case study regarding CEUS in epiploic appendagitis in child differentiation of phlegmonous infiltration from abscess formation appears to be a useful indication [121].

Position Comment

CEUS can be used as an alternative imaging modality for the follow up of children with known IBD to differentiate between active and quiescent disease and to evaluate the outcome of therapeutic strategies.

Intra-cavity

Background

Intra-cavitary and extravascular administration of UCA is an expanding off-label application, with numerous reported cases, but no prospective studies documented [7]. Although no specific recommendations have been issued, its use has been advocated where conventional techniques have either failed to reach a diagnosis or, importantly, are deemed to carry a higher risk (e. g. ionising radiation on sensitive organs). This is of particular importance in children, where efforts to find alternative imaging solutions to techniques involving ionizing radiation are paramount.

Technique

No standard doses are recommended with the reported range from 0.1 mL to 1 mL of SonoVue™/Lumason™ diluted in 0.9 % nor-

mal saline, depending on the type of cavity (physiological or not) and the aim of the study. To demonstrate a possible communication or fistulous track between two cavities a higher dose of 1 mL or 2 mL will be needed, whereas to delineate a pathological cavity (e. g. abscess), only a few drops are recommended to avoid artefacts and obscuration of the far field [122].

Level of Evidence

There is currently no literature focusing on intra-cavitary use of CEUS in children. A few applications of intra-cavitary CEUS in adults that can be applied to paediatric patients have been described. Trans-catheter use to evaluate the anatomy of the biliary tract and to detect obstruction or biliary leakage following T-tube removal has diagnostic accuracy comparable to percutaneous trans-hepatic cholangiography [122 – 126]. Trans-catheter CEUS in non-physiological cavities can allow identification of complications related to insertion of drainage tubes (such as dislocation or obstruction), and also give a quantitative measure of the volume of fluid present in a collection [127]. This technique may be uniquely useful in the nephrostomy tube or pleural space empyema where the visualization of the inter-costal drainage tube may be difficult. In the latter, trans-catheter CEUS could rapidly resolve this issue, even in a non-cooperating child, and direct management with fibrinolysis. Likewise, the injection of dilute UCA may guide adequate positioning of the tip of the catheter when managing a multi-loculated intra-abdominal or pelvic abscess.

Position Comment

The potential use of trans-catheter injection of UCA has been demonstrated in adults with possible uses in the child needing exploration, with the most likely use in the assessment of the pleural space in the presence of an empyema.

Vascular applications: Neurosurgical and tumour response to antiangiogenic therapy

Background

Although the use of CEUS has been established in the vascular field for carotid, abdominal aorta and cerebral vessels in the adult population, there is a limited role in children. One area that vascular application may be useful is in an intraoperative setting in neurosurgical intervention for the evaluation of brain lesions [128 – 130]. There is increasing evidence that CEUS can allow for evaluation of the enhancement pattern of the tumour compared to the adjacent normal parenchyma, improved delineation of the tumor borders, visualization of the afferent, efferent or intra-lesional vessels, differentiation between viable tissue and areas of cystic degeneration or tumor necrosis and potentially identification of residual tumor. Quantification methods looking at the vascularity of a tumour, based on the time-intensity curves is useful to monitor response to antiangiogenic therapy in malignancy [131] and this has been applied to tumour response in children [132].

Technique

Initially, the lesion is visualized during B-mode US imaging, along with the healthy brain tissue. The US transducer is positioned over the lesion and after a bolus UCA injection, a digital cine clip of the lesion is recorded for up to 2 – 5 min to allow for offsite evaluations. The most commonly reported SonoVue™/Lumason™ dose is 2.4 mL [128 – 130]. Qualitative analysis is performed for comparison of the enhancement pattern of the tumour compared to the adjacent normal brain tissue. In the tumour response patients, a bolus technique with the transducer placed over a region of interest, with subsequent evaluation of various aspects of the wash-in and wash-out curves [132].

Level of Evidence

Mixed case series of adult patients have described a few paediatric cases using intraoperative CEUS in diagnostics of brain lesions. This includes an 11-year-old patient in whom intraoperative CEUS was effective to precisely localize the brain tumour and search for tumour tissue residual after the initial resection [129], and the usefulness of intraoperative CEUS examination was evaluated in a 13-year-old patient with arteriovenous malformations to discriminate between the afferent and efferent vessels of the lesion [130]. A cohort of 17 patients assessed for tumour vascularity, targeting lesions in various locations, including liver and pleura, successfully predicted time to progression in a cohort of children and adolescents with recurrent solid tumours treated with antiangiogenic therapy [132].

Position Comment

CEUS is a promising imaging tool that may yield significant improvement in the macro- and micro-vascular assessment in transcranial ultrasound imaging. Tumour response following chemotherapy using the vascular enhancement may be better suited to follow-up in children.

Vesico-ureteral reflux (VUR)

Background

Contrast-enhanced voiding urosonography is a well-established application of paediatric CEUS. The examination entails bladder catheterization and intravesical UCA administration under real time US imaging. The main indications are the detection and grading of VUR and urethral imaging in children. There are numerous studies comparing ceVUS with the ionizing radiation counterparts of VCUG and DMSA [31, 32, 34, 36 – 42]. Contrast-enhanced voiding urosonography is a highly sensitive, alternative imaging modality for the evaluation of VUR in children and in many centers it has replaced the traditionally performed VCUG [35, 133]. New US techniques aimed at further improvement of the diagnostic capabilities of ceVUS include real time three- and four-dimensional ceVUS, which enables the volumetric visualization of contrast within a refluxing pelvicalyceal system, potentially improving grading [29], whereas intraoperative ceVUS can be used during endoscopic treatment of vesicoureteral reflux in children for direct evaluation of the operative outcome [33].

Technique

Following bladder catheterization, UCA is administered intravesically and real time US imaging of the kidneys and retrovesical space is performed during subsequent cycles of bladder filling and voiding with the child in supine and/or prone positions.

Regarding UCA administration into the bladder during ceVUS performance, two techniques have been developed, the one most commonly used entails direct UCA injection into a partially filled bladder [134]. The other method entails the administration of UCA into a saline bag and subsequent drip infusion of the solution via the catheter into the bladder [42]. The presence of echogenic microbubbles within the ureter, renal pelvis and calyces is indicative of VUR, graded in a similar manner to VCUG. At the end of the examination morphological and functional study of the urethra is performed during a dedicated voiding cycle, using transperineal or transabdominal scanning approach [39].

Level of Evidence

Numerous studies have demonstrated the high sensitivity of ceVUS for the detection and grading of VUR. From the time when second generations UCA became commercially available, 14 original studies have been conducted with the intravesical use of SonoVue™/Lumason™ for the diagnosis of VUR including 2087 children [29, 31 – 42, 133]. The majority of these studies are comparative studies entailing the consecutive performance of ceVUS and VCUG; in only two studies was ceVUS the only examination performed. The studies that compared csVUS and VCUG have demonstrated the superiority of ceVUS over VCUG in detecting higher grade VUR, hence of greater clinical significance. The largest study recruited 1010 children and was primarily devoted to the safety evaluation of the intravesical administration of SonoVue™/Lumason™ [35]. In addition, it is possible to image the urethra and accurately depict urethral abnormalities with a good diagnostic correlation as with VCUG [133]. A European survey has shown that ceVUS is being widely performed and up to 2012, a total of 4131 ceVUS examinations have been safely performed in 29 European centers [28].

Position Comment

Contrast-enhanced voiding urosonography has proven to be a safe and reliable imaging technique for detecting VUR and urethral abnormalities in children of both genders.

Future Perspectives

Contrast-enhanced ultrasound has a number of distinct and well known advantages over CT and MR imaging, particularly in children, highly important for the future perspectives of CEUS [45, 135]. The uncertainty surrounding the long-term effects of gadolinium deposition in children is a concern will drive the use of CEUS in children [136]. In addition to licensed indications with a focus on the liver and Doppler enhancement, CEUS is safe and effective for examination of almost all organs in adults, as indicated by the EFSUMB guidelines [6, 7]. “Off-label” use (and its funding) is the challenge in paediatric practice because many drugs are not tested by randomized trials in children, which also means that they are not specifically licensed for use in children. The recent licensing of SonoVue™/Lumason™ for use in paediatric liver US in the United States is a welcome first step towards the acceptance of this technique in the imaging of children.

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