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Contrast-enhanced ultrasonography for the evaluation of kidneys in children – a preliminary report

Wykorzystanie ultrasonografii wzmocnionej kontrastem w ocenie nerek u dzieci – doniesienie wstępne

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Abstract

Introduction and objective: Ultrasonography is the first-line imaging method for evaluating kidneys in children. Computed tomography (CT) or magnetic resonance imaging (MRI) are often needed to increase diagnostic certainty. However, these modalities involve patient's exposure to ionising radiation, adverse effects of contrast agents and sometimes general anaesthesia. Contrast-enhanced ultrasonography (CEUS) has become a recognised diagnostic tool in many countries. It is used for the imaging of various organs in adults. In Europe, intravenous administration of ultrasound contrast agents for abdominal organ assessment is generally not approved for patients under 18 years of age. However, an increasing amount of published data indicates the usefulness and safety of CEUS in children. The aim of the study was to assess the usefulness of CEUS in differentiating focal renal lesions and assessing perfusion of transplanted kidneys. **Materials and methods:** The study included 18 patients, with a total of 28 CEUS kidney examinations performed. CEUS results were categorised into three groups (benign focal lesions, malignant focal lesions, perfusion disorders of the transplanted kidney) and were compared with reference CT or MRI findings. **Results:** CEUS identified benign focal lesions in 9 out of 14 (64%) patients, potentially malignant lesions in 5 out of 14 (36%) patients, and ischaemic foci in 2 out of 4 (50%) kidney transplant recipients. Comparison of definitive CEUS findings with reference results showed full agreement. **Conclusions:** CEUS is a useful tool for differentiating focal lesions and monitoring ischaemic renal foci in paediatric patients. CEUS may reduce the number of reference CT and MRI scans in the future. However, the use of CEUS in paediatric diagnosis requires further research.

Keywords: children, contrast-enhanced ultrasonography (CEUS), ultrasound contrast agent (UCA), focal kidney lesions, transplanted kidney

Streszczenie

Wprowadzenie i cel: Badaniem obrazowym pierwszego rzutu w ocenie nerek u dzieci jest ultrasonografia. Często, w celu zwiększenia pewności diagnostycznej, konieczne jest wykonanie tomografii komputerowej (*computed tomography*, CT) lub rezonansu magnetycznego (*magnetic resonance imaging*, MRI) ze środkiem kontrastującym. Badania te wiążą się z narażeniem pacjenta na promieniowanie jonizujące, niepożądane działania środków kontrastujących, a czasami konieczność znieczulenia ogólnego. Ultrasonografia wzmocniona kontrastem (*contrast-enhanced ultrasonography*, CEUS) stała się w wielu krajach uznaną metodą diagnostyczną wykorzystywaną do obrazowania różnych narządów u osób dorosłych. W Europie dożylne podawanie ultrasonograficznych środków kontrastujących w ocenie narządów jamy brzusznej nadal nie jest dopuszczone u pacjentów poniżej 18. roku życia. Coraz więcej opublikowanych danych wskazuje jednak na użyteczność i bezpieczeństwo stosowania CEUS u dzieci. Celem pracy jest określenie przydatności CEUS w różnicowaniu zmian ogniskowych i w ocenie perfuzji w nerkach u dzieci. **Materiał i metody:** Do badania włączono 18 pacjentów, u których wykonano 28 badań CEUS

nerek. Wyniki CEUS podzielono na 3 grupy (zmiana ogniskowa łagodna, zmiana ogniskowa złośliwa, zaburzenia ukrwienia nerki przeszczepionej) i porównano je z wynikami badań referencyjnych CT i/lub MRI. **Wyniki:** W badaniu CEUS u 9/14 (64%) pacjentów rozpoznano w nerkach zmianę ogniskową łagodną, u 5/14 (36%) – zmianę potencjalnie złośliwą, a u 2/4 (50%) pacjentów po przeszczepieniu nerki – ogniska niedokrwienia w grafcie. Porównanie wyników CEUS z wynikami badań referencyjnych wykazało pełną zgodność. **Wnioski:** CEUS może być wykorzystana u dzieci do różnicowania zmian ogniskowych w nerkach i do kontroli ognisk niedokrwiennych w nerce przeszczepionej. CEUS może w przyszłości ograniczyć liczbę wykonywanych badań referencyjnych CT i/lub MRI, zwłaszcza u pacjentów z upośledzoną funkcją nerek i po przeszczepie nerki. Wykorzystanie CEUS w diagnostyce pediatrycznej wymaga dalszych badań.

Słowa kluczowe: dzieci, ultrasonografia wzmocniona kontrastem (CEUS), ultrasonograficzne środki kontrastujące (UCA), zmiany ogniskowe w nerkach, nerka przeszczepiona

INTRODUCTION

Conventional grey-scale ultrasound (US) with colour and spectral Doppler is the primary and widely recognised first-line tool for the imaging of focal lesions in abdominal parenchymal organs in children and adolescents[1]. However, this method has some limitations, and the frequently ambiguous nature of detected pathologies often necessitates further imaging, such as contrast-enhanced computed tomography (CECT), or contrast-enhanced magnetic resonance imaging (CE-MRI), to enhance diagnostic certainty[1]. Nevertheless, these imaging modalities are not optimal for children due to exposure to ionising radiation, the potential adverse effects of iodine- or gadolinium-based contrast agents, and the frequent need for sedation or general anaesthesia[1]. Recent years have seen significant technological progress in ultrasonographic techniques, including sonoelastography, contrast-enhanced ultrasonography (CEUS), and novel microvascular Doppler techniques[2,3].

CEUS has been widely used for imaging various organs in adults for many years and is known for its high safety profile[4].

In 2016, the U.S. Food and Drug Administration (FDA) approved Lumason (SonoVue), a second-generation ultrasound contrast agent (UCA), for three paediatric indications: the evaluation of focal liver lesions, echocardiography via intravenous (IV) administration and the assessment of voiding urosonography via intravesical administration[5,6].

Intravenous UCAs are not approved for patients under 18 years of age in Europe. Currently, all CEUS applications in children remain off-label in Poland. Nevertheless, a growing body of published evidence supports the usefulness and safety of CEUS in the paediatric population[1,5,7].

In adults, the use of CEUS for assessing parenchymal focal lesions improves diagnostic sensitivity and specificity compared to conventional US, reaching levels comparable to those of CECT and CE-MRI[9–11].

In 2017, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued a statement on the role of CEUS in paediatric practice, evaluating its current applications and offering suggestions for its further development. Potential applications of CEUS in paediatric renal diseases include the diagnosis and monitoring of complicated infections (such as abscesses), cystic masses and complicated cysts, tumour vascularity, renal trauma, infarction, transplants, and cases where there is a contraindication to computed tomography (CT) or MRI contrast agents[12–15].

This paper presents our experience with CEUS in evaluating the nature of focal lesions in native and transplanted kidneys, as well as assessing graft perfusion in the early postoperative period in pediatric patients.

AIM OF THE PAPER

The aim of this study was to evaluate the clinical value of CEUS in differentiating benign from malignant renal lesions and diagnosing ischaemia in transplanted kidneys in paediatric patients, as well as to compare CEUS findings with those of reference imaging modalities used for assessing parenchymal organs (CECT and CE-MRI).

MATERIALS AND METHODS

Between 2020 and 2023, a prospective single-centre study on the use of CEUS for assessing focal lesions in parenchymal organs in children was conducted at the Children's Memorial Health Institute in Warsaw (CMHI) as part of the internal research grant no. S185/2019. The study received approval from the CMHI Bioethics Committee. Prior to CEUS, informed written consent was obtained from both legal guardians and patients over 16 years of age for study participation and intravenous (IV) second-generation UCA administration.

A total of 100 CEUS examinations of parenchymal organs were performed in paediatric patients hospitalised at CMHI, including 28 kidney examinations.

The indications for performing renal CEUS included:

- focal lesion in the kidney detected by grayscale US;
- suspected impaired blood supply to a kidney transplant in Colour Doppler US.

Patient inclusion criteria for the study:

- the assessed renal focal lesion is visible on grayscale US;
- consent of parents/legal guardians and patients over 16 years of age to participate in the study using SonoVue,

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Fig. 1. Patient A with suspected traumatic renal haematoma in US – performed 32 seconds after intravenous UCA administration demonstrated intense contrast enhancement of the majority of the suspicious area, indicating the presence of a well-vascularised solid lesion; a non-contrast-enhanced (black) area of haematoma is visible on the periphery of the focal lesion

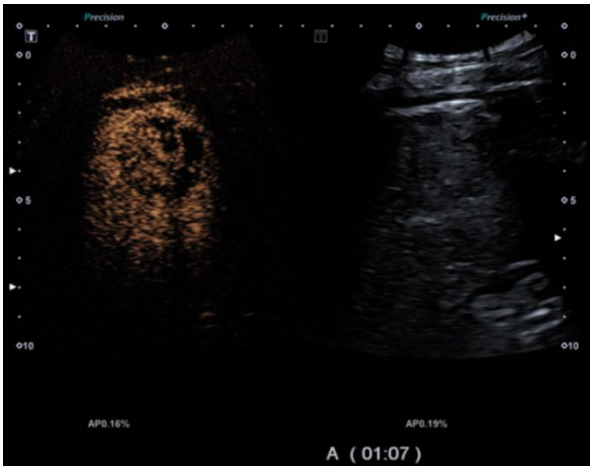

Fig. 2. Patient A (continued) (suspected traumatic haematoma in the kidney) – CEUS performed at 1 minute of observation showed faster washout of the contrast agent from the focal lesion than from the surrounding healthy renal parenchyma, which indicates its malignant nature

an intravenous second-generation UCA (off-label administration);
- patient's age from 3 to 18 years;
- cooperative patient;
- no contraindications to UCA (severe pulmonary hypertension, large right-to-left shunt, treatment-resistant arterial hypertension).

CEUS

All US and CEUS examinations were performed at the Department of Diagnostic Imaging (CMHI) using Canon Aplio i700 (Toshiba) device and a convex transducer.

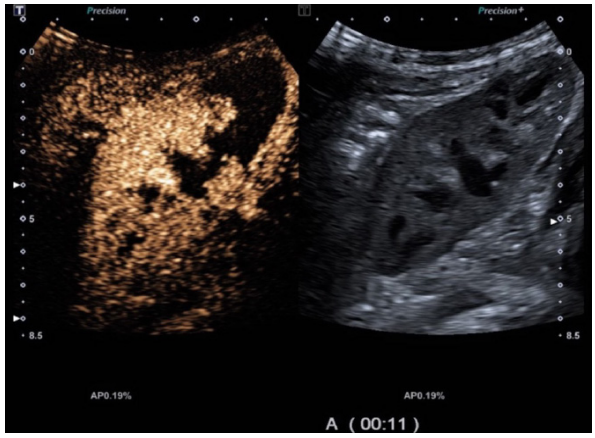

Fig. 3. Patient B with suspected perfusion impairment in the transplanted kidney in Doppler ultrasound – CEUS performed at 11 seconds after intravenous UCA administration revealed an absence of contrast enhancement in the entire lower pole of the graft (visible as a black area), indicating ischemia in this region. The grayscale US image of the graft (right) did not show any visible focal lesions

At the beginning of the examination, the parenchymal organ was assessed using B-mode ultrasound and Colour Doppler imaging. After identification of a focal lesion, the optimal locations for its CEUS imaging were selected. Then, second-generation UCA, SonoVue (Bracco, Milan, Italy), was administered intravenously at a dose of 0.03 mL/kg, up to 2.4 mL per injection, according to the manufacturer's recommendations. The contrast enhancement pattern (CEP) of the renal focal lesion was observed continuously for 5 minutes with intervals. Then, based on the obtained CEUS video recording, the following parameters were assessed:
- contrast agent wash-in and wash-out pattern within the focal lesion over time compared to the surrounding healthy renal parenchyma;
- vascularity and contrast homogeneity of the graft parenchyma.

Renal CEUS findings were then categorised into 3 groups:
1. enhancement pattern of a benign focal lesion with subsequent or simultaneous UCA wash-out as in healthy renal parenchyma;
2. enhancement pattern of the focal lesion suspected of malignancy, with more rapid UCA wash-out compared to healthy renal parenchyma (Figs. 1 and 2);
3. abnormal blood supply to the graft, with parenchymal contrast defects (Fig. 3).

Finally, the CEUS findings were compared with CECT and CE-MRI data, which served as reference standards for imaging solid organs in children.
Clinical data and information on diagnostic tests were obtained from patients' electronic medical records.

Study group

The study group of patients with renal lesions detected on US consisted of 18 children, including 6 girls and 12

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Diagnosis	CEUS + US	Reference tool
Benign lesion	CEUS – dilated calyx US – cyst	CTU – dilated calyx
	CEUS – hypertrophied column of Bertin US – inflammatory lesions	CECT – hypertrophied column of Bertin
	CEUS – post-inflammatory lesion US – no focal lesions	CE-MRI – post-inflammatory lesion
	CEUS – 2 patients with AML US – ambiguous lesion	CE-MRI – 2 patients with AML
	CEUS – IIF cyst US – a septate cyst	CE-MRI – Bosniak IIF cyst
	CEUS – calcification in the graft US – focal lesion with calcification in the graft	CT – calcification in the graft
	CEUS – simple cyst in the graft US – simple cyst in the graft	No additional investigations
	CEUS – AML US – AML	No additional investigations
Malignancy	CEUS – category III cyst US – a septate cyst	CE-MRI – Bosniak III cyst
	CEUS – tumour in a traumatic haematoma US – evolution of haematoma	CECT – tumour in a traumatic haematoma
	CEUS – lymphoma infiltration in the graft US – infiltration in PTLD	CE-MRI – PTLD
Unclear	CEUS – atypical AML or RCC US – lesion suspected of malignancy	CECT – inconclusive CE-MRI – inconclusive
	CEUS – atypical AML or RCC US – lesion suspected of malignancy	CECT – inconclusive CE-MRI – proliferative lesion PET – proliferative lesion
Graft perfusion	CEUS – normal in 2 patients US – no focal lesions, abnormal flow in the graft accessory artery	No additional investigations
	CEUS – 2 patients with ischaemic foci US – no focal lesions, quantitatively smaller vascularisation of the graft segment	CTA – ischaemic foci

AML – angiomyolipoma; **CECT** – contrast-enhanced computed tomography; **CE-MRI** – contrast-enhanced magnetic resonance imaging; **CEUS** – contrast-enhanced ultrasonography; **CTA** – computed tomography angiography; **CTU** – CT urography; **PET** – positron emission tomography; **PTLD** – post-transplant lymphoproliferative disorder; **RCC** – renal cell carcinoma; **US** – ultrasonography.

Tab. 1. CEUS + US vs. reference tools

boys aged 4 to 17 years, who underwent a total of 28 CEUS examinations.

Eleven patients were evaluated for focal lesions in the native kidney. This group included 5 patients with tuberous sclerosis complex (TSC), in whom routine abdominal US revealed either a rapidly enlarging lesion or an atypical appearance of a renal focal lesion. In another 5 patients, a focal kidney lesion was incidentally detected during an ultrasound examination. One boy was hospitalised and monitored with US due to a renal haematoma following abdominal trauma.

The study group included 7 patients who had undergone kidney transplantation. In 4 of these children, CEUS was done in the early postoperative period due to suspected graft perfusion abnormalities. In 2 of these patients, more than one CEUS examination was performed, whereas reference CT angiography was done only once, at the beginning of the follow-up period. In another 3 patients, CEUS was performed in the late postoperative period due to a focal lesion detected in the graft.

A total of 18 CEUS examinations were included in the descriptive analysis, including 11 of the native kidney and 7 of the transplanted kidney (10 follow-up examinations of the same pathology were excluded).

Fourteen patients were included in the comparative analysis of CEUS vs. CECT and CE-MRI findings:

- CEUS vs. CECT – 10 exams;
- CEUS vs. CE-MR – 7 exams.

In 2 patients with TSC and an inconclusive focal lesion in the native kidney, CEUS, CECT, and CE-MRI were all performed as part of the diagnostic process. Additionally, positron emission tomography (PET) was performed in one of these patients.

The dose of intravenously administered second-generation UCA (SonoVue) ranged from 0.6 mL to 2.0 mL (0.03 mL/kg body weight).

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Category	Description	Management
I	Benign, simple fluid, thin wall, no calcifications or septa, no contrast enhancement, water attenuation	No need for further oncological evaluation
II	Benign thin-walled cyst: may have (1–2) thin septa (up to 1 mm thick) and minor calcifications in the wall or septa. Homogeneous, well-defined, denser cysts <3 cm in diameter, non-enhancing after contrast administration	No need for further oncological evaluation
IIF (follow-up)	Well-defined cysts, may contain multiple, thin septa that enhance slightly after contrast administration. The walls or septa may contain thick or nodular calcifications. Homogeneous, well-defined, denser cysts >3 cm in diameter. Cysts do not enhance after contrast administration	Require follow-up imaging (every 3–6 months, then yearly if the cyst is stable)
III	Unspecified cystic lesions with irregular, thick or smooth walls or with contrast-enhancing septa	Require surgical intervention of varying extent, although some of them may turn out to be benign
IV	Cystic masses with imaging findings similar to those of category III + soft tissue components adjacent to the wall or septa, enhancing after contrast administration	Require surgical intervention

Tab. 2. CT-based Bosniak classification of cystic renal masses

No adverse events (AEs) were observed in the study group following administration.

RESULTS

Based on the CEPs of focal renal lesions or graft perfusion assessment in the group of 18 patients, diagnoses were established and categorised into 3 groups:

1. benign lesion in 9 cases, including 2 cases of transplanted kidney;
2. suspected malignancy in 5 cases, including 1 case of transplanted kidney;
3. abnormal graft perfusion in 2 patients.

Diagnoses based on CEUS in 18 patients and comparison with other imaging tools are presented in Tab. 1.

In 10 patients, CEUS clearly differentiated between benign and malignant focal kidney lesions. Comparison with reference CECT or CE-MRI findings showed full diagnostic agreement. Conventional US diagnosis corresponded with CEUS findings in only 3 of the 10 cases: simple cyst, angiomyolipoma (AML), and lymphoma infiltration related to post-transplant lymphoproliferative disorder (PTLD).

CEUS results were inconclusive in 2 patients with TSC. Similarly, the US showed that the lesions that were neither typical of AML (hypoechoic and well vascularised), nor suggestive of malignancy. In one of these patients, CECT and CE-MRI findings were also inconclusive. In the other patient, CECT findings were inconclusive, whereas CE-MRI and PET suggested a malignant hyperplastic lesion. However, due to the lack of parental consent for surgical intervention and early follow-up imaging with US and CE-MRI, which showed no enlargement of the focal lesion and a reduction in its vascularisation, a benign atypical fat-poor AML was ultimately diagnosed.

In 3 patients, CEUS revealed cystic lesions classified as simple cysts according to the Bosniak classification (Tab. 2) and the updated 2019 MRI-based classification[16]. These lesions were categorised as Bosniak IIF and III cysts, consistent with CE-MRI findings. Based on US, only a simple cyst was diagnosed, while the other two lesions were described as septate cysts, with their categories undetermined.

In 2 children, CEUS and US of a focal kidney lesion were considered sufficient for guiding further treatment, and no additional reference imaging was performed: one child presented with a simple cyst in the graft, and the other was a TSC patient with typical stable AML.

Four patients after kidney transplantation underwent CEUS due to suspected ischaemia in the graft identified during routine US. Doppler revealed reduced blood flow in a segment of the transplanted kidney, without any obvious focal lesions in 2 patients. In both cases, CEUS showed a lack of contrast in this graft fragment, which was confirmed in CT angiography (Fig. 3). In both patients, once fibrinolytic treatment was initiated, monitoring was conducted exclusively with CEUS: 8 and 4 exams, respectively.

In another two patients with suspected impairment of blood supply in the transplanted kidney, Doppler US detected abnormal flow in the accessory graft artery. CEUS, however, demonstrated normal perfusion throughout the transplanted kidney, and no further imaging was performed.

DISCUSSION

CEUS is considered a safe imaging modality for both adults and children[17,18]. Although IV CEUS is used off-label in the paediatric population in Europe, it is increasingly being investigated in clinical trials[7].

This paper discusses the observations of 28 CEUS examinations of both native and transplanted kidneys in children.

Based on the contrast enhancement patterns of focal kidney lesions in 14 patients included in the study, 9 were suspected to be benign and 5 malignant. The benign lesions diagnosed included AML, a simple cyst, a Bosniak IIF cyst (based on CT and MRI), a dilated calyx, hypertrophic Bertin column, post-inflammatory changes, and calcifications. Lesions suspected of malignancy included a Bosniak III cyst, a mass in a traumatic haematoma and a lymphoma infiltration of a kidney transplant in the course of PTLD. Although the results were inconclusive in 2 patients, the lesions were ultimately diagnosed as benign atypical AML in TSC children. The US and CEUS diagnoses (simple cyst, typical AML, and lymphoma infiltration) coincided in only

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3 patients. The agreement between the definitive CEUS diagnosis and reference CECT and CE-MRI in differentiating benign from malignant focal kidney lesions was 100% (10 out of 10 cases). Similar findings were reported in a meta-analysis by Rosado and Riccabona, who assessed CEUS diagnostic efficacy across various clinical indications, and found agreement between CEUS and reference modalities ranging from 83% to 100%[7].

Although based on a small sample, our findings suggest that CEUS is a promising, minimally invasive diagnostic tool for distinguishing potentially malignant from benign focal renal lesions through analysis of contrast enhancement and UCA washout. This is further supported by studies in adult patients[19]. Assessment of complex cysts, as set out in the EFSUMB recommendations for adults[20] and supported by numerous studies[21,22], is another promising application of CEUS.

It appears that once the initial diagnosis is established through CECT and CE-MRI, long-term monitoring of focal kidney lesions can be conducted using US and/or CEUS, thereby reducing the need for repeated CECT and CE-MRI in children[20].

An additional advantage of CEUS in assessing focal kidney lesions is that it can be performed during the initial US scan, enabling a shorter wait time for CECT and CE-MRI, earlier accurate diagnosis, and timely initiation of appropriate treatment.

CEUS may be particularly beneficial for patients with contraindications to standard imaging modalities for solid organs, including those with thyroid disorders (CECT), metallic foreign bodies (CE-MRI), impaired kidney function, or those who have undergone kidney transplantation[23]. Laboratory assessment of kidney function is not required before CEUS[4,20].

Early and late complications following kidney transplantation remain a significant clinical concern due to the risk of graft loss[15]; therefore, prompt diagnosis and treatment are essential. CEUS enables precise graft evaluation, including vascular and parenchymal complications as well as focal lesions[15], as confirmed in the present study. In 4 post-transplant patients in the early postoperative period, no focal lesions were detected on US; however, Doppler raised a suspicion of perfusion abnormalities. CEUS revealed ischaemic areas, seen as contrast defects, in two children, while normal perfusion of the entire transplanted kidney was observed in the other two. Reference CT angiography was performed in patients with abnormal CEUS findings, which confirmed exactly the same ischaemic areas in the graft. Until normal graft perfusion was restored, treatment was monitored exclusively with CEUS, with 8 and 4 examinations performed in these two patients, respectively.

Follow-up US revealed focal parenchymal lesions in the graft, identified as a simple cyst, PTLD infiltration, and an indeterminate lesion with calcifications in 3 post-transplant patients. CEUS also revealed a simple cyst (therefore no reference examination was performed) and PTLD infiltration, which was confirmed by CE-MRI. In the third patient, CEUS and CT revealed only calcification without a focal lesion in the graft.

In light of the above, it is worth noting that CEUS may allow for the assessment of complications in the transplanted kidney, such as ischaemic changes, differentiation of focal lesions (as in native kidneys), or monitoring of PTLD treatment, with greater sensitivity than conventional US and comparable accuracy to reference imaging modalities.

None of the patients in this study experienced AEs following intravenous administration of UCA, confirming the favourable safety profile of CEUS. These findings align with those of a 2018 U.S. study, in which no AEs were reported across 287 CEUS examinations performed in children[24].

In 2021, a review of 57 original scientific studies on the safety of CEUS in children reported that 0.22% (10 out of 4,518) of children experienced serious AEs, and 1.20% (54 out of 4,518) experienced mild AEs[6].

In 2024, a study reported that the intravenous administration of UCAs in critically ill paediatric patients did not result in any serious adverse clinical events[25].

The absence of ionising radiation and nephrotoxic contrast agents, along with the ability to rapidly assess the enhancement pattern of renal focal lesions and perfusion in real time, are clear advantages of CEUS over reference imaging modalities such as CECT and CE-MRI.

LIMITATIONS

The small sample size and the low number of renal CEUS examinations performed prevents statistical analysis.

SUMMARY

Although the limited sample size of our study does not allow for clear conclusions, our findings support the potential utility of CEUS in characterising focal renal lesions (as cystic or solid, true or pseudo-lesions), differentiating benign from malignant lesions, as well as evaluating complications in transplanted kidneys in paediatric patients. As evidenced by numerous publications, CEUS shows high sensitivity and specificity.

CEUS is a safe and well-tolerated imaging modality posing no risk of ionising radiation or adverse effects associated with iodinated or gadolinium-based contrast agents. It can be performed at the point-of-care and requires no sedation.

The official approval of intravenous UCAs for use in children in Poland could contribute to a broader application of CEUS, thereby reducing the reliance on CECT and CE-MRI required for renal assessment in the paediatric population.

CONCLUSIONS

1. CEUS is a valuable imaging modality that can aid in differentiating benign from malignant renal lesions in paediatric patients.

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2. CEUS can be utilised for the long-term follow-up of renal focal lesions that do not require surgical intervention, as well as for the assessment and monitoring of complications following kidney transplantation.
3. CEUS has the potential to reduce the number of CECT and CE-MRI examinations performed in pediatric patients in the future.
4. Further research is needed on the use of CEUS in paediatric diagnosis, as intravenous administration of UCAs in children remains off-label in Europe.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication. Research under internal grant funding.

Author contribution

Original concept of study, Analysis and interpretation of data: DM. Collection, recording and/or compilation of data; writing of manuscript: DM, KP, KJB, KC. Critical review of manuscript: JR. Final approval of manuscript: DM, JR.

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