Usefulness of contrast-enhanced ultrasonography in daily clinical practice: A multicenter study in Spain

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Abstract

Objectives: We aimed to determine whether the use of ultrasonographic contrast agents improves the diagnostic accuracy of ultrasonography (US).

Material and methods: We carried out a prospective multicenter study in 42 hospitals. We included 1786 patients with inconclusive US; 84.9% of the inconclusive studies were abdominal US (including studies of the liver, kidneys, spleen, and other sites), 6.2% were studies of the...
peripheral vessels, 4.3% were breast studies, and 4.6% were other studies. We evaluated the type of contrast-enhanced US (color Doppler or contrast-specific method), type of contrast agent, dose and number of doses, and type of administration (bolus or infusion). We evaluated whether the findings at contrast-enhanced US improved the diagnostic accuracy of unenhanced US and whether they enabled a conclusive diagnosis to be reached.

**Results:** The contrast agent SonoVue was used in 99.9% of the studies; a single dose of contrast agent was used in 84.8%, and the contrast agent was administered in bolus in 98.5%. Contrast-enhanced US improved the diagnostic accuracy in 91.6% of cases and enabled a conclusive diagnosis in 69.2%. The best diagnostic accuracy was obtained in the supraaortic vessels, where a definitive diagnosis was reached in 95.4% of cases, followed by the abdominal area, with a conclusive diagnosis in 72.6% of cases.

**Conclusions:** The use of contrast-enhanced US significantly improved the diagnostic accuracy of US and enabled a conclusive diagnosis in most cases.

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**PALABRAS CLAVE**

Ecografía; Medios de contraste; Ecografía con contraste

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**Utilidad de la ecografía con contraste en la práctica clínica diaria. Estudio multicéntrico español CEUS**

**Resumen**

**Objetivos:** El objetivo de este estudio multicéntrico ha sido evaluar si la ecografía con contraste permite aumentar el rendimiento diagnóstico de la ecografía basal.

**Material y métodos:** En este estudio prospectivo multicéntrico realizado en 42 hospitales se incluyeron 1.786 pacientes con estudios ecográficos considerados como no concluyentes. El 84,9% fueron ecografías abdominales (incluyendo estudios hepáticos, renales, esplénticos y de otras localizaciones), el 6,2% fueron estudios vasculares periféricos, el 4,3% fueron estudios mamarios y el 4,6% fueron estudios de otras localizaciones. Se evaluó el tipo de ecografía con contraste (Doppler color o método específico de contraste), el tipo de contraste, la dosis y el número de dosis y el tipo de administración (en forma de bolo o infusión). Sobre los hallazgos obtenidos en la ecografía con contraste se valoró si conseguía aumentar el rendimiento diagnóstico de la ecografía basal y si permitía un diagnóstico concluyente.

**Resultados:** El 99,9% de los estudios se realizó con SonoVue, con una dosis de contraste (84,8%) y en forma de bolo (98,5%). En el 91,6% de los casos la ecografía con contraste aumentó el rendimiento diagnóstico de la ecografía basal, y en el 69,2% permitió un diagnóstico de certeza. El mayor rendimiento diagnóstico se obtuvo en los estudios de troncos supraaórticos con un diagnóstico definitivo en el 95,4% de los casos, seguido por el área abdominal con resultado concluyente en el 72,6% de los casos.

**Conclusiones:** El uso de la ecografía con contraste aumentó significativamente el rendimiento diagnóstico de la ecografía basal, y se obtuvo un resultado concluyente en la mayoría de los casos.

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**Introduction**

Ultrasound is an imaging technique that is most frequently used to evaluate abdominal, musculoskeletal and vascular diseases. However, in a radiology department daily practice, ultrasound findings are not specific enough to make a definitive diagnosis. Duplex Doppler ultrasound provides valuable information on vascularization, since it permits confirmation of vascular patency, the direction and velocity of flow, and may, occasionally, contribute to the characterization of focal lesions. However, its usefulness in detection of slow flow or flow in deep vascular structures is limited, and it cannot be used to adequately detect tumor or parenchymal microvasculature. When ultrasound does not permit a conclusive diagnosis, it is usually necessary to use other imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), or to perform a biopsy or needle aspiration to reach a definitive diagnosis. For both CT and MRI, administration of intravenous contrast enables evaluation of the microvascular characteristics of the organs and potential tumors; an assessment of the type of uptake is required to make a final diagnosis.

The appearance of ultrasound contrast agents composed of gaseous micro-bubbles stabilized with other substances, has revolutionized ultrasound diagnosis for many diseases. In Europe, two contrast agents are approved for radiological use: Levovist (Schering, Germany), which is made up of air with galactose and palmitic acid as surfactant agents, and SonoVue (Bracco, Italy), which is composed of sulfur hexafluoride in a phospholipid capsule. The low solubility...
and greater stability of sulfur hexafluoride (SonoVue) allow studies to be performed in real time, when used gently to avoid destruction of the micro-bubbles. Its primary use is in characterizing focal liver lesions, follow-up of tumors after percutaneous treatment, and evaluating parenchymal perfusion of different organs, including trauma, infection, and ischemic conditions. Various multicenter studies with large patient cohorts have already demonstrated the excellent diagnostic accuracy of contrast ultrasound for characterization of focal hepatic lesions, but to our knowledge, no multicenter study has yet evaluated the usefulness and diagnostic accuracy of contrast ultrasound for general practice. The objective of this study is to describe how contrast ultrasound is routinely used in Spain and to evaluate whether contrast sonography increases the diagnostic accuracy of baseline ultrasound studies as well as their capacity to yield a definitive diagnosis.

Materials and methods

Patients. In this multicenter study performed in 42 Spanish hospitals, which we called the CEUS study, 1,786 patients were included; of those patients, 886 were men (53.6%) and 767 were women (46.4%), with an average age of 59.8 years (range, 14-93 years). Only patients with a non-diagnostic or inconclusive baseline ultrasound were included. Of these patients, a contrast ultrasound study was performed on 1,683 patients (94.2%). The rest (103 patients) did not undergo contrast ultrasound for the following reasons: performance of another diagnostic technique (83 patients, 80.6%), patient’s decision (16 patients, 15.5%), or contraindications (10 patients, 9.7%, due to severe heart or respiratory disease). The study did not require specific informed consent because only patients who had received a contrast ultrasound according to the normal diagnostic guidelines and protocols of each center were included.

Ultrasound. All patients who participated in the study underwent an ultrasound with intravenous contrast administration. The ultrasound studies were performed with Toshiba equipment in 46% of cases (Apio platform in 37.6%, Xario in 8.4%), Siemens equipment in 21% of cases (SonoVue was not used, Levovist was administered, while in 6.7% (109 patients), color Doppler ultrasound was used), and a color Doppler ultrasound was used in 5000 in 8.4%, and others in 2.8%), General Electric in 11.9% (SonoVue was not used, Levovist was administered, while in 6.7% (109 patients), color Doppler ultrasound was used), and Esaote in 2.9% (SonoVue was not used, Levovist was administered, while in 6.7% (109 patients), color Doppler ultrasound was used). The contrast used was SonoVue in 99.9% of cases. In the only case in which SonoVue was not used, Levovist was administered, and a color Doppler ultrasound was used to evaluate vascular patency. The most frequently used dosages were 2.4-2.5 ml (64.9%) and 4.8-5.0 ml (18.2%). For the majority of patients (84.8%), only one dose was administered. For 15%, two doses were administered, and for the remaining patients (0.2%), more than two doses were injected. The two most frequent reasons for using two or more doses were to study several lesions (59.4%) and an inconclusive study with one dose (33.1%). In 98.5% of patients, the method of administration was through a contrast bolus, vs. infusion for the remaining (1.5%). The average time used to complete the ultrasound study was seven minutes.

Variables analyzed. The following variables were analyzed on baseline ultrasound: characteristics of the structures explored and why the initial ultrasound was not conclusive (multiple-choice questionnaire). On contrast ultrasound, the following parameters were evaluated: type of contrast ultrasound (color Doppler or specific contrast method), type of contrast used, dosage and number of doses, type of administration (bolus or infusion), and time needed to perform the study. From the results obtained by contrast ultrasound, we evaluated whether it had higher diagnostic accuracy compared to the baseline ultrasound, yielded a definitive or conclusive diagnosis and detected more lesions. When evaluating whether the contrast exam was conclusive, we only included patients with histologically or cytologically confirmed diagnoses, with a diagnosis achieved with some other imaging modality (CT or MRI) considered “gold standard”, or with contrast ultrasound studies that met the criteria of enhancement previously accepted as conclusive in the medical literature. Finally, the operator’s and patient’s satisfaction with the scan were evaluated, on a scale of 0 to 3, where 0 = bad, 1 = fair, 2 = good, and 3 = very good.

Results

Initial baseline ultrasound. Concerning to the initial baseline ultrasound, table 1 lists the area or structures explored, with the abdominal area being the most frequent (84.9% of cases), especially the liver (71.2% of cases), followed by the kidney (10% of cases). Regarding the reasons that made ultrasound examination not conclusive, the most frequent cause was the presence of a lesion that could not be definitively identified by ultrasound (23.1% of cases), followed by non-evaluable or inconclusive vascularization (table 2).

Contrast ultrasound. Technique. Regarding the type of contrast ultrasound, the results were as follows: in 93.3% of cases (1,514 patients) a “specific contrast mode” was used, while in 6.7% (109 patients), color Doppler ultrasound was used (the type used for 60 patients is unknown). The contrast used was SonoVue in 99.9% of cases. In the only case in which SonoVue was not used, Levovist was administered, and a color Doppler ultrasound was used to evaluate vascular patency. The most frequently used dosages were 2.4-2.5 ml (64.9%) and 4.8-5.0 ml (18.2%). For the majority of patients (84.8%), only one dose was administered. For 15%, two doses were administered, and for the remaining patients (0.2%), more than two doses were injected. The two most frequent reasons for using two or more doses were to study several lesions (59.4%) and an inconclusive study with one dose (33.1%). In 98.5% of patients, the method of administration was through a contrast bolus, vs. infusion for the remaining (1.5%). The average time used to complete the ultrasound study was seven minutes.

Contrast ultrasound. Findings. In table 3, we show the definitive diagnoses obtained in the study; the most frequent lesions were hepatocarcinomas (20%), metastasis (17.1%), and hepatic hemangiomas (13.3%). In studies of focal lesions, contrast ultrasound allowed for better characterization of the lesion in 87.9% of cases, better delineation of the lesion in 83.9% of cases and generation of a differential diagnosis in 84.9% of cases. Contrast ultrasound was also able to detect more lesions as well as smaller lesions (fig. 1). Regarding its
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In 91.6% of cases, contrast ultrasound increased the accuracy of the baseline ultrasound. This increase in accuracy was greater for neurological studies (98.2%), followed by the abdomen (92.8%), lymph nodes (84.8%), and to a lesser extent, the breast (66.7%) (table 4). In addition, in 69.2% of cases, contrast ultrasound enabled to make a definitive diagnosis with certainty; without it, a conclusive diagnosis could be reached in only 30.8% of cases. When the results were analyzed with respect to the anatomical areas most frequently explored (table 5), we found that 95.4% of neurological studies obtained a conclusive diagnosis, as well as 73.6% of abdominal scans (73.6% hepatic, 71.6% kidney (fig. 2), 61.5% spleen, and 59.3% pancreas). However, a conclusive diagnosis was obtained in only 20.4% of lymph node studies and in 13.2% of breast studies.

Finally, when degree of satisfaction was examined, in 85.5% of studies, the operator’s degree of satisfaction was good or very good, while in 98.2% of cases, the patient’s satisfaction with the exam was also good or very good.

Discussion

Our study shows that contrast ultrasound resolves the majority of inconclusive ultrasound studies, not merely increasing diagnostic accuracy, but also yielding a conclusive diagnosis, as occurred with 69.2% of the patients included in our study. Reaching a definitive diagnosis using contrast ultrasound has advantages over using other...
imaging techniques; these advantages include availability, few contraindications (only patients with severe cardiac disease), absence of ionizing radiation, no contraindication for patients with nephropathy, and reduction of time to diagnosis.  

The most frequent indications for contrast ultrasound in our study were characterization of focal hepatic lesions and evaluation of the response to percutaneous treatment of focal hepatic lesions. Because of its high sensitivity for detecting microvasculature, contrast ultrasound identifies the enhancement patterns of the most frequently focal hepatic lesions, as has been described in other studies. In two recent multicenter studies in which 1,328 and 1,034 hepatic nodules were studied using contrast ultrasound, a sensitivity of 95.8% and specificity of 83.1% were reached by Strobel et al., and a sensitivity of 79.4% and specificity of 88.1% were reported by Tranquart et al. Furthermore, contrast ultrasound was more accurate to establish whether a percutaneously treated lesion showed residual tumor (persistent enhancement) or a complete response (absence of enhancement) (fig. 3). However, we have obtained better diagnostic accuracy in ultrasonographic studies of the supra-aortic vessels, and we have replicated the excellent results obtained by other studies (fig. 4). as well as for the suspicion of occlusion of the internal carotid artery. With duplex Doppler ultrasound, it is very difficult to evaluate the arteries of...

Table 4  Increase in diagnostic accuracy with respect to the baseline ultrasound exam

<table>
<thead>
<tr>
<th>Area examined and Increase in accuracy of the ultrasound</th>
<th>Abdomen</th>
<th>Breast</th>
<th>Brain</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in accuracy</td>
<td>Yes</td>
<td>1,307 (92.8%)</td>
<td>107 (98.2%)</td>
<td>67 (84.8%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>101 (7.2%)</td>
<td>25 (33.3%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,408 (100%)</td>
<td>132 (100%)</td>
<td>69 (100%)</td>
</tr>
</tbody>
</table>

Table 5  Conclusive diagnosis depending on the area examined

<table>
<thead>
<tr>
<th>Area studied and diagnosis</th>
<th>Abdomen</th>
<th>Breast</th>
<th>Brain</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conclusive diagnosis</td>
<td>Yes</td>
<td>1,013 (72.6%)</td>
<td>10 (13.2%)</td>
<td>104 (95.4%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>383 (27.4%)</td>
<td>66 (86.8%)</td>
<td>5 (4.6%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,396 (100%)</td>
<td>76 (100%)</td>
<td>109 (100%)</td>
</tr>
</tbody>
</table>

Figure 1  A patient with hepatocellular carcinoma (HCC) for one year. a) On the baseline control ultrasound, two focal lesions were found in the right lobe that were suspicious for HCC, but this did not allow for a definitive diagnosis (arrows). b) Contrast ultrasonography showed enhancement in the arterial phase (arrows) in both lesions that was typical of HCC, and enabled detection of another tumor that was not shown in the baseline ultrasound (broken arrow). c) In the late phase, contrast had washed out of all three lesions, all of which appeared hypoechoic. The lesion in the anterior segment is shown (arrow). Findings were confirmed by CT and MRI (not shown).
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the circle of Willis or to detect very low flow or velocities in sub-occlusive carotid stenosis, especially in obese patients or those with short necks. Contrast administration enables the detection of vascular patency and can confirm occlusion via color Doppler and specific contrast methods. In addition, it avoids the necessity for more invasive diagnostic tests such as angiography.\textsuperscript{33,34}

Our study also supports the expansion of ultrasonography into other diagnostic areas. In our study the third indication has been suspicion of renal disease, fundamentally for complicated cysts and control of pyelonephritis, obtaining results similar to other studies.\textsuperscript{15,16,35,36}

Despite the significantly increased use of contrast ultrasonography in all of the areas we examined, its diagnostic accuracy does not permit a conclusive diagnosis in some areas, particularly in the breast and lymph nodes (fig. 5). Few published studies have described the different enhancement patterns of contrast in the breast and lymph nodes, in part due to the recent incorporation of high-frequency transducers compatible with the specific contrast programs.\textsuperscript{37,38} Our results are in agreement with findings from other studies that found that contrast ultrasonography can detect tumor microvasculature but cannot differentiate between different tumors. Thus, in the breast, some initial

Figure 2 A patient with multiple renal cysts and back pain. a) The baseline ultrasound scan showed a cystic lesion in the left kidney partially occupied by dense material that prevented to discard an intracystic neoformation. b) The contrast ultrasound confirmed the absence of intracystic uptake in all phases and was consistent with a complicated cyst without intracystic neoformation.

Figure 3 A patient with hepatocarcinoma (HCC) in the left hepatic lobe, treated with radiofrequency ablation. a) In a control ultrasound scan, the tumor was visualized with difficulty, and it was impossible to determine whether tumor was still present or if ablation had been completely successful. b) The contrast ultrasound study showed a lack of tumor enhancement in the arterial phase (arrow) and in all other phases, consistent with complete response.
studies investigated the usefulness of duplex Doppler contrast ultrasonography and reported that malignant lesions more frequently exhibited hypervascularization (95% of malignant compared to 21% of benign lesions, according to Moon et al.,39 or 78.1% of malignant lesions compared to 35.3% of benign lesions, according to Martinez et al. 40). The emergence of a second generation of contrast agents and improvements in ultrasound technology including the incorporation of specific methods of contrast has enabled not only the detection of vascularization, but also identification of the type of vascularization. Balleyguier et al.38 have reported that vascularization in malignant lesions is more prominent, that vessels are tortuous and irregular and, if uptake curves are obtained, that malignant lesions have earlier uptake and faster washout.

A theoretical limitation of our study is that no standardization for this technology exists, since different ultrasound equipment from different companies were used, with different dosages of contrast and different contrast protocols. Nevertheless, this theoretical limitation supports the contention that contrast ultrasonography can provide good results even with different techniques and dosages. In addition, our objective was to evaluate the diagnostic accuracy of contrast ultrasonography in the daily reality of the different hospitals that participated in the study. Another limitation was that not all of the focal lesions were confirmed through histology. However, diagnoses for the lesions that were included were confirmed using the established, accepted diagnostic criteria based on various imaging techniques.

In conclusion, we found that contrast ultrasonography significantly increased the diagnostic accuracy of ultrasound studies when the baseline study did not permit a definitive diagnosis, and a conclusive result was obtained in the majority of cases.

Conflict of interest
The CEUS study was sponsored by Laboratorios Farmacéuticos Rovi S. A. The authors of the study had total freedom...
to access data and total independence to develop the manuscript. None of them maintain any professional relationship with Laboratorios Farmacéuticos Rovi S. A.

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