

Adverse reactions after the use of SonoVue contrast agent

Characteristics and nursing care experience

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Abstract

The aim of this study was to analyze the clinical manifestations of adverse reactions after the use of SonoVue contrast agent from a large retrospective database, and to evaluate the nursing care strategies and the efficacy of standardized procedure for adverse reactions of SonoVue (SPARS).

From January 1, 2012 to December 30, 2018, 34,478 cases of contrast-enhanced ultrasonography were performed in our center. The clinical manifestations of adverse reactions after the use of SonoVue contrast agent were identified and analyzed. The nursing care strategies were evaluated and the outcomes of patients with moderate and severe adverse reactions before and after the application of SPARS were compared.

Of the 34,478 cases, 40 cases (0.12%) of adverse reactions after the use of SonoVue were identified. Adverse reactions included anaphylactic shock, skin allergies, nausea or vomiting, dizziness or headache, numbness, chest distress, back pain, and local reactions of the injection site. Most of the adverse reactions were mild and self-limited. Only 3 cases of anaphylactic shock and 2 cases of severe rash underwent further treatments. The 3 patients who were managed by SPARS recovered quicker and spent less comparing with the other 2 patients who were not.

SonoVue was a safe contrast agent, with few and mostly mild adverse reactions. SPARS may be an efficient way in tackling moderate to severe adverse reactions, although of which the incidence was rare.

Abbreviations: CEUS = contrast-enhanced ultrasonography, IQR = interquartile range, SPARS = standardized procedure for adverse reactions of SonoVue.

Keywords: adverse reaction, contrast-enhanced ultrasonography, nursing care, SonoVue, standardized procedure

1. Introduction

SonoVue (Bracco SpA, Milan, Italy) is the most commonly used contrast agent in contrast-enhanced ultrasonography (CEUS).^[1] It is one kind of intravascular microbubbles with a shell of phospholipids

that are filled with sulfur hexafluoride gas, allowing the visualization of the tiny vessels in the capillary bed, thus permitting the dynamic detection of capillary microvascularization. Through using SonoVue, CEUS can achieve a real-time imaging permitting the characterization of target lesions due to its ability to demonstrate the vascularity of the lesion.^[2] Sulfur hexafluoride is the active ingredient of SonoVue, which can be rapidly excreted through the pulmonary circulation. It is currently recognized that SonoVue has a good safety profile, and the incidence of severe adverse reactions is between 0.0086% and 0.9%.^[3-6] Most adverse reactions reported were mild, including skin erythema, tachycardia, and palpitations. However, severe adverse reactions such like anaphylactic shock^[7] were scatteredly reported and even fatal cases were documented in the literature,^[8] highlighting the importance of precaution and predisposed management measures during SonoVue usage. Until now, there is no published consensus or protocol regarding the management of adverse reactions of SonoVue.

The aim of this study was to retrospectively analyze the adverse reactions of SonoVue during CEUS performed in our institution from January 2012 to December 2018. The manifestation and outcome of adverse reactions and management experience including nursing care experience were reported, and the utility of so-called standardized procedure for adverse reactions of SonoVue (SPARS) established by our institution was also evaluated.

2. Methods

2.1. Study populations

This is a retrospective cohort study. This work was approved by the Medical Ethics Review Committee of the Second Affiliated

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Hospital of Zhejiang University School of Medicine. Clinical data of patients underwent CEUS in our institution from January 2012 to December 2018 were retrospectively accrued. The sites of CEUS included the thyroid, breast, lymph nodes, liver, gallbladder, pancreas, spleen, kidney, prostate, and women's reproductive organs. Patients were excluded if there were contraindications for SonoVue usage, such as a history of allergies to sulphur hexafluoride or other components, left-to-right shunt congenital heart disease, severe pulmonary hypertension (pulmonary arterial pressure >90 mm Hg), uncontrolled hypertension, adult respiratory distress syndrome, and women during pregnancy or breastfeeding. All patients signed an informed consent before the procedure.

2.2. Ultrasound instruments and the CEUS procedure

The ultrasound instruments used in this study included Mylab90 Twice (Esaote SpA, Genoa, Italy), Resona 7 (Mindray, Shenzhen, China), LOGIQ E9 (GE Healthcare, Sunnyvale, CA), EpiQ 5 (Philips Healthcare, Andover, MA), and Acuson S3000 (Siemens, Mountain View, CA).

The contrast agent used was SonoVue (Bracco). It was a commercially packed kit including 1 vial of gas and powder and 1 pre-filled syringe containing 5 mL of solvent. Each vial of the contrast agent contained 25 mg of lyophilized powder and 59 mg of sulfur hexafluoride gas. The working solution was prepared immediately before the CEUS test. According to the manufacturer's instruction, 5 mL of saline was injected into the vial, and the vial was shaken vigorously until the lyophilized powder was completely dispersed in a homogeneous white milky suspension. The injected doses of SonoVue were 1 to 4.8 mL for a single procedure, and the total dosage was less than 5 mL for each patient per day. During the examination, SonoVue was injected

as a bolus through antecubital vein, following by a flush of 5 mL saline solution.

The test of CEUS consisted of 2 steps. First, conventional color Doppler sonography was performed to detect the target organ. Second, the machine was switched to contrast-enhanced mode, and a double-width display of the contrast and grayscale modes were used. Following the injection of SonoVue, the contrast-enhanced ultrasonic images were dynamically displayed on the screen for evaluation (Fig. 1).

2.3. Definition of adverse reactions to SonoVue

Because there is no specific grading system for the severity of adverse reactions caused by acoustic contrast agents, the definition and grading of adverse reactions to SonoVue were established according to the American College of Radiology guidelines^[9] with minor modifications. The severity of the adverse reactions to SonoVue was graded into mild, moderate, and severe as follows:

- (1) Mild: symptoms and signs are mild and usually resolve without any specific treatment, including mild nausea or vomiting, flushing, pruritus, mild urticaria, and headache;
- (2) Moderate: symptoms and signs are more prominent and demand medical attention with specific treatment, including marked urticaria, severe vomiting, bronchospasm, facial edema, laryngeal edema, vasovagal attacks, and mild hypotension.
- (3) Severe: reactions that usually represent a progression of the moderate symptoms and are life-threatening, including anaphylactic shock, severe laryngeal edema, respiratory arrest, cardiac arrest, pulmonary edema, confusion, convulsions, coma, and even death.

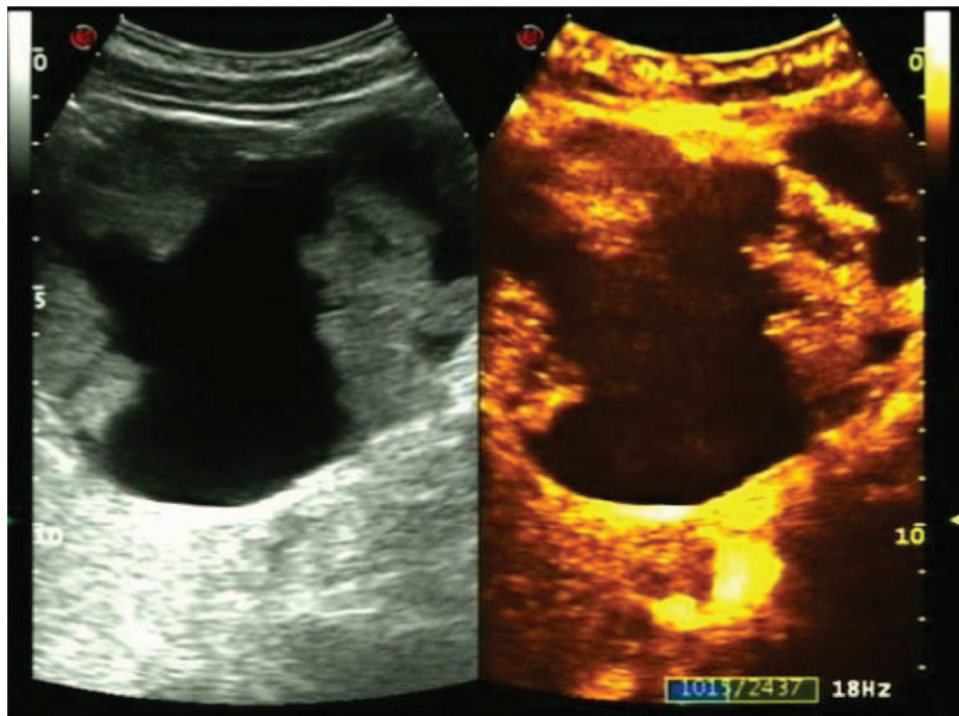


Figure 1. A CEUS image from a case of pancreatic mucinous cystadenocarcinoma (left: grayscale mode; right: contrast mode). CEUS=contrast-enhanced ultrasonography.

Detailed information of the above adverse reactions occurred was retrospectively collected and analyzed.

2.4. Nursing care measures and SPARS for moderate and severe adverse reactions to SonoVue

A smooth procedure of CEUS requires a close coordination of doctors and nursing staff. The nurse’s tasks mainly include establishment of peripheral venous access, preparing and injection of contrast agents, observation and monitoring the patient’s response, and fully prepared to cope with possible adverse reactions.

The test room is required to be equipped with a resuscitation cart for emergency use. The resuscitation cart should carry emergency medications (adrenaline, atropine, calcium gluconate, amiodarone, vasopressin, etc), medications used in the treatment of allergic reactions, basic airway equipment (including bag valve masks, oral and nasal airways, oxygen masks and nasal cannulas, and Magill forceps), and monitor equipment with a defibrillator or an Automated external defibrillator. Once a serious adverse reaction occurs, the rescue procedure will be started following the SPARS flow chart (Fig. 2).

After the completion of CEUS, the venous access is temporary preserved for additional 30 minutes, during which the patient is closely watched and monitored. Then the venous access gets removed if there is no sign of adverse reactions or patient

discomfort. Before the patient leaves, blood pressure, pulse, oxygen saturation, and the skin and injection site are rechecked.

3. Results

From January 2012 to December 2018, a total of 34,478 CEUS were performed in our institution. Among them, 15,446 cases were performed before the implementation of SPARS, which was initiated in January 2016. The remaining 19,032 cases were performed after the implementation of SPARS. There were 20,348 males and 14,130 females, with an average age of 46.2±15.5 years. A total of 40 (0.12%) adverse reactions were identified. These included anaphylactic shock in 3 cases (7.5%), skin allergic reaction in 12 cases (30%), injection site reactions in 8 cases (20%), dizziness or headache in 6 cases (15%), nausea or vomiting in 5 cases (12.5%), chest distress in 3 cases (7.5%), numbness in 2 cases (5%), and back pain in 1 case (2.5%). According to the grading of adverse reactions to SonoVue, there were 35 cases (87.5%) of mild adverse reactions, 2 cases (5%) of moderate adverse reactions, and 3 cases (7.5%) of severe adverse reactions (Table 1).

Of the 40 patients with adverse reactions, 85% (34/40) had a history of food or drug allergies, including 5 patients with alcohol allergy, 12 with penicillin allergy, 4 with sea food allergy, 3 with pollen allergy, and 10 with unknown allergies. Most adverse reactions occurred early after SonoVue injection, except for 1 patient with delayed-onset urticaria and angioedema that

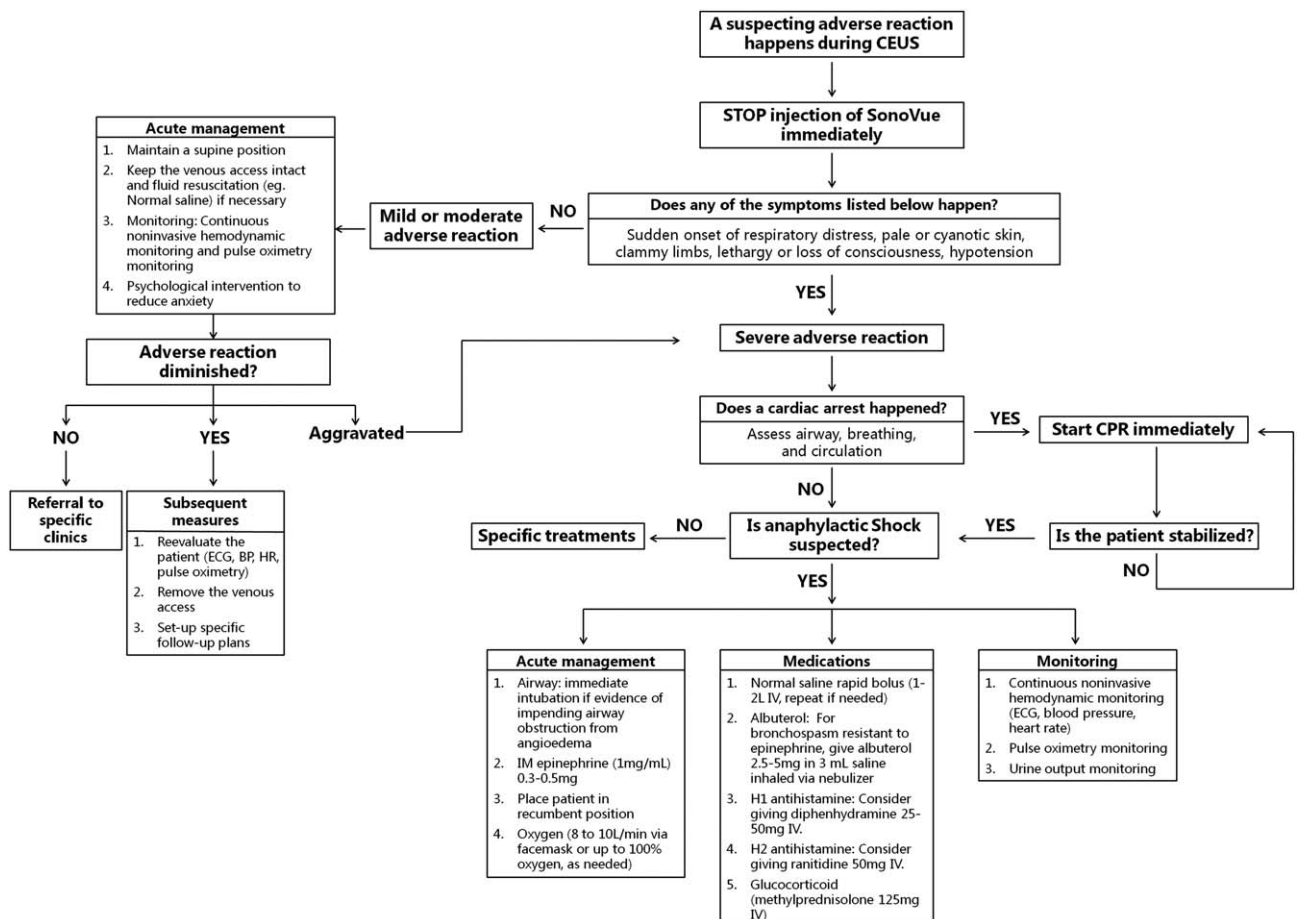


Figure 2. The standardized procedure for adverse reactions of SonoVue (SPARS).

Table 1
Cases of adverse reactions to SonoVue (n=40).

Types of adverse reactions	Number (%)	Severity (n)
Skin allergic reactions	12 (30%)	mild (10), moderate (2)
Injection site reactions	8 (20%)	mild (8)
Dizziness or headache	6 (15%)	mild (6)
Nausea or vomiting	5 (12.5%)	mild (5)
Chest distress	3 (7.5%)	mild (3)
Anaphylactic shock	3 (7.5%)	severe (3)
Numbness	2 (5%)	mild (2)
Back pain	1 (2.5%)	mild (1)

occurred 24 hours after SonoVue usage. The median time of the occurrence of adverse reactions after SonoVue injection was 13 minutes (interquartile range [IQR], 0.18–25.5 minutes). The average dose of SonoVue used in CEUS was 2 mL (IQR, 1.4–2.4 mL) (Table 2).

Most of these adverse reactions were mild, and no medication or further treatment was required. Only 5 patients with moderate or severe adverse reactions received further treatments, including 3 patients with anaphylactic shock and 2 patients with severe rash. All of the 5 patients got a full recovery after treatment. Among them, 1 case of anaphylactic shock and 1 case of severe

rash occurred before the adoption of SPARS and the other 2 cases of anaphylactic shock and the other case of severe rash occurred after the adoption of SPARS. The medical costs of the 2 patients whose adverse reaction occurred before the adoption of SPARS were 920 USD and 817 USD, respectively. And the treatment durations were 2 days and 3 days, respectively. In contrast, the medical costs of the other 3 patients whose adverse reaction occurred after the adoption of SPARS were 645 USD, 213 USD, and 128 USD, respectively. And the treatment durations were 1 day, 1 day, and 0.3 day, respectively (Table 3).

4. Discussion

Ultrasound is considered to be a safe, convenient, widely accessible, and cheap diagnostic tool. The main advantage of ultrasound is that certain structures can be observed without using radiation, facilitating its usage in a variety of clinical settings.^[10–12] CEUS is a real-time dynamic imaging technique based on conventional ultrasonography and its ability to demonstrate the vascularity of tissue and organs.^[13,14] Compared with contrast agents used in contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), the incidence of adverse reactions to SonoVue is much lower and the severity much milder. It was reported the incidence of adverse

Table 2
Basic characteristics of the patients that got adverse reactions to SonoVue (n=40).

	Cases occurred before implementation of SPARS (n=17)	Cases occurred after implementation of SPARS (n=23)
Age, median (IQR), yr	54 (45–65)	56 (44–65.5)
Sex, male	11	14
Allergic history		
Alcohol	3	2
Penicillin	5	7
Sea food	2	2
Pollen	1	2
Unknown	4	6
Grading of adverse reactions		
Mild	15	20
Moderate	1	1
Severe	1	2
Time of the occurrence of adverse reactions after SonoVue injection, median (IQR), min	12 (0.1–27)	14 (0.25–24)
Dose of SonoVue, median (IQR), mL	2 (1.5–2.5)	1.8 (1.35–2.1)

IQR=interquartile range, SPARS=standardized procedure for adverse reactions of SonoVue.

Table 3
Moderate and severe adverse reactions by SonoVue (n=5).

Cases	Age, yr	Sex	Manifestations of adverse reactions				Implementation of SPARS procedure	Medical costs, USD	Treatment duration, d	Outcome
			Main symptoms or signs	Accompanying symptoms and signs	Onset time (after SonoVue injection)	Grading				
1	78	Female	Anaphylactic shock	Tinnitus, dizziness	1 min	Severe	No	920	2	Full recovery
2	65	Male	Delayed-onset urticaria, and angioedema	Itching	24 h	Moderate	No	817	3	Full recovery
3	62	Male	Anaphylactic shock	Skin erythema	1.3 min	Severe	Yes	645	1	Full recovery
4	61	Female	Anaphylactic shock	Nausea, dizziness	1 min	Severe	Yes	213	1	Full recovery
5	48	Male	Extensive urticaria	Itching, sinus tachycardia	12 min	Moderate	Yes	128	0.3	Full recovery

SPARS=standardized procedure for adverse reactions of SonoVue.

reactions caused by CT and MRI contrast agents is about 2% to 3%, and a relatively small proportions of cases might lead to significant hypotension, loss of consciousness, laryngeal edema, and even death.^[15] In contrast, a study of 23,188 cases of CEUS reported that the incidence of severe adverse reactions was only 0.0086% (n=2) and the number of adverse reaction cases in total was 29.^[5] Similarly, in this study, the overall incidence of adverse reactions to SonoVue was 0.12% with an incidence of severe adverse reactions of 0.0098%. Until now, there are only 3 fatal cases that have been reported in temporal association with SonoVue, all of which occurred during cardiac imaging. In all of these 3 patients, there was no sign of hypersensitivity and they all had a high risk for major cardiac complications, which could explain the fatal outcome.^[16] Although severe adverse reactions are rare, it is still of great interest to be cautious when performing CEUS, especially in patients with a past history of food or drug allergies. As reflected in the study, 85% of patients who got severe adverse reactions had a past history of allergic reactions. A standard procedure to deal with severe adverse reactions to SonoVue is also warranted. However, most published studies focused on the prevalence and identification of adverse reactions, while fewer paid attention to the management strategies. This study reviewed the characteristics and management strategies of adverse reactions to SonoVue, especially the utility of nurse-physician collaboration during CEUS from nurses's perspectives.

In reviewing the nursing care experiences when performing CEUS and dealing with adverse reactions to SonoVue, specific nursing care strategies were summarized as follows:

- (1) Informing the patient the purpose, risks, and alternatives of CEUS with a writing consent;
- (2) Careful inquiring the history of allergies before CEUS;
- (3) Effective communication with patients to reduce their anxiety before CEUS;
- (4) Fully prepared for dealing with adverse reactions during the CEUS, closely watching for worsening symptoms, including signs of anaphylaxis;
- (5) Following the guidance of SPARS when adverse reactions occur;
- (6) The venous access should be reserved for at least 30 minutes after the complication of CEUS, during which time the patient will be closely watched with all rescue medications and equipments standby in case delayed adverse reactions would occur.

From nurses's perspectives, a good peripheral venous access and a proper injection method is another guarantee of a successful CEUS. Because SonoVue has special physical and chemical properties, if the injection pressure is too large during the injection process, it may damage the microbubbles and affect the imaging quality. Therefore, a proper intravenous injection site should be selected considering the diameter of veins and the convenience of injection procedure. The cephalic vein and median cubital vein are preferred. Furthermore, for patients who have undergone long-term chemotherapy, have diabetes, and other comorbidities that may lead to vascular sclerosis or fragility, rapid injection may cause drug extravasation. This may not only increase the risk of phlebitis, but can also result in failure of the CEUS. Therefore, after the establishment of the venous access, 5 mL of normal saline should be injected through the indwelling needle to check the patency of the access. If it is hard to find a proper injection site, the venous puncture can be performed under ultrasound guidance.

The establishment and implementation of the SPARS provided a standardized procedure for the medical staffs to respond more efficiently and timely to adverse reactions to SonoVue. There are many international guidelines on the use of CEUS in Liver and nonliver applications^[17,18]; however, currently, there is no specific guideline available for the management of adverse reactions of CEUS. Although the overall incidence of severe adverse reactions to SonoVue is extremely low, as in the study, the incidence of severe adverse reactions is only 0.0098%, but in large ultrasound centers, such like in our institution with an annual volume of CEUS over 6000 cases per year, the cumulative incidence of severe adverse reactions is not scarce. And once it occurs, if the identification and response are delayed, it may have serious consequences, even be life-threatening. In this study, although the number of moderate and severe adverse reactions is only 5, making an efficient statistical analysis impossible, the average medical costs and length of hospital stay of the 3 patients after the implication of SPARS (January 2016) were relatively lower than those of the 2 patients before the implementation of SPARS. A subsequent study with a larger sample may further validate the utility of the SPARS procedure.

There are several limitations in this study. First, it is a retrospective single-center study, and the sample size is low because of the rarity of adverse reactions caused by SonoVue, which makes statistical analysis impossible and conclusions less informative. Second, the dosage and protocol of injected SonoVue varied according to different purposes, all of which may affect the evaluation of adverse reactions. A larger, multi-institutional analysis may be valuable.

In summary, this retrospective study reviewed the characteristics and management strategies of adverse reactions caused by SonoVue, the most popular echogenic contrast agent used in CEUS. SonoVue was a safe contrast agent, with few and mostly mild adverse reactions. Severe adverse reactions were rare in this cohort. SPARS and nurse-physician collaboration during CEUS may be an efficient way in tackling severe adverse reactions.

Author contributions

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