



● *Original Contribution*

A NOVEL APPROACH TO DETECTING POSTPARTUM HEMORRHAGE USING CONTRAST-ENHANCED ULTRASOUND

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Abstract—The aim of this study was to estimate the efficacy of contrast-enhanced ultrasound (CEUS) in detecting postpartum hemorrhage (PPH) after cesarean section. This is the first study of CEUS in obstetric hemorrhage. A total of 37 patients, operated at Nagoya University Hospital, underwent CEUS. We evaluated the findings of CEUS, which were qualitatively defined as positive when pooling or leakage of contrast agent was observed in the uterine cavity, by measuring the amount of bleeding during the first 4 h after cesarean section. The time–intensity curve patterns of leaked contrast agents were also analyzed for quantitative prediction of the amount of blood loss. Significant differences between the excessive hemorrhage ($N = 7$) and non-excessive hemorrhage groups ($N = 30$) were noted in the occurrence of positive CEUS ($p = 0.011$). Additionally, mean postpartum blood loss markedly increased in patients with a positive CEUS ($p = 0.002$). From a quantitative perspective, the time until leakage of contrast agents was detected correlated with the amount of bleeding, but the other characteristics of the time–intensity curve pattern did not provide valuable information. In conclusion, CEUS, which enables bedside assessment and rapid diagnosis, is a promising strategy for the detection of PPH. (E-mail: kenchan2@med.nagoya-u.ac.jp) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: Postpartum hemorrhage, Contrast-enhanced ultrasound, Perflubutane, Cesarean section, Obstetrics.

INTRODUCTION

Obstetric hemorrhage, especially postpartum hemorrhage (PPH), remains the leading cause of maternal mortality worldwide (Say et al. 2014). Studies have suggested that many deaths associated with PPH could be prevented with prompt recognition and more timely and adequate treatment (Berg et al. 2005; Della Torre et al. 2011; Kilpatrick et al. 2012). The risk factors for PPH are described in several guidelines, such as those from the American College of Obstetrician Gynecologists or Royal College of Obstetricians and Gynaecologists. However, these guidelines also note that most women who experience PPH do not have any known risk factors (Dahlke et al. 2015). Recent studies have reported that the shock index (heart rate/systolic blood pressure)

can help clinicians improve the outcomes in PPH (Le Bas et al. 2014; Sohn et al. 2013). A useful non-invasive approach for detecting PPH before vital signs become unstable is necessary for further improvement and to save the lives of mothers.

Although conventional ultrasound (US) is able to detect free blood, clots and hematomas, it cannot determine if bleeding is ongoing at the time of examination. A previous report found that visualization with color Doppler ultrasound (CDUS) could detect precise bleeding sites and help control PPH (Kondoh et al. 2015). CDUS is a sensitive modality for detecting hemorrhage in various organs. Because the ability of CDUS to detect the blood flow is dependent on flow velocity, detecting bleeding with a low flow velocity is difficult. Contrast-enhanced ultrasound (CEUS), which allows real-time scanning (Bauer et al. 2002), is a widely used diagnostic tool. Advances in CEUS have made it possible to visualize leakage of contrast agents. CEUS exhibits high sensitivity and high specificity for active bleeding and is useful in detecting less dramatic or non-arterial bleeding (Catalano et al. 2005; Tokunaga et al. 2013).

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However, to our knowledge, no studies have examined the efficacy of CEUS in detecting obstetric hemorrhage.

The purpose of this study was to evaluate the usefulness of CEUS as a novel approach for detecting PPH.

METHODS

This study was approved by the institutional review board and ethics committee of our institute, and written consent was received from all patients.

Patients

Between September 2015 and July 2016, 37 patients who underwent CEUS after cesarean section (CS) performed at our hospital were enrolled in the present study. To be included, women had to have been delivered by CS at a gestational age greater than 34 wk, with CEUS examination performed within 0.5 h of CS. All CSs were carried out under regional anesthesia. Primary management for intra-operative bleeding involved the use of uterotonic agents and manual uterine massage. If these procedures were ineffective, uterine compression sutures or postpartum balloon tamponade was added immediately. Working protocols for all participants in this study were consistent.

CEUS examination

Immediately after CS, each patient received a single injection of 0.015 mL/kg of a perflubutane-based contrast agent (Sonazoid, Daiichi Sankyo, Tokyo, Japan), which is identical to decafluorobutane. The US system (AplioXG, Toshiba, Tokyo, Japan) was equipped with a 3.5-MHz convex probe (PVT-375 BT, Toshiba) adapted for harmonic imaging. The imaging parameters were a mechanical index (MI) of 0.2 and frame rate of 15. CEUS images were recorded for 2 min after the injection and obtained in real time by slowly changing the scanning plane to find the leak, and, in positive CEUS cases, fixing the probe in position to acquire the time–intensity curve for quantification analyses. CEUS was performed by two obstetricians. These obstetricians had specific skills in CEUS and more than 10 y of experience with US examinations.

Imaging analysis

Contrast-enhanced ultrasound was classified as positive when pooling of leaked contrast agent was observed in the uterine cavity and as negative when no pooling or extravasation of the contrast agent was observed. The same obstetricians who performed CEUS classified the results as positive or negative. One operator examined a case, and the other doctor discussed and evaluated the image with the operator. There were no differences in judgments between the obstetricians. In positive CEUS cases,

a blinded reviewer obtained the time–intensity curve parameters (number of leaks, duration of leakage, peak intensity of leaked contrast agent and total area under the curve) by capturing the recorded images every 3 s and, instead of setting regions of interest, manually tracing the area of leaked contrast agent using ImageJ. The duration of leakage was determined as the time from injection of contrast agents to detection of contrast agent leakage.

Statistical analysis

All statistical analyses were performed using the SAS software package (Version 9.3, SAS Institute, Cary, NC, USA) or the Prism 5 software program (GraphPad Software, San Diego, CA, USA). A p value < 0.05 was considered to indicate significance. We applied a logistic regression analysis to determine the CEUS variables that independently predict the possibility of excessive hemorrhage. Pre-specified potential confounding factors included age at delivery, primipara status, body mass index (BMI), tocolysis with intravenous magnesium sulfate or ritodrine hydrochloride, massive intra-operative bleeding, uterine compression sutures and postpartum balloon tamponade. Student's t -test was also performed to compare the distributions of continuous data. The relationship between duration of leakage and amount of bleeding was estimated by simple linear regression.

Definitions

After CS, a dedicated napkin was placed under the patients' buttocks for blood loss measurement. This napkin essentially remained under the women's buttocks for at least 4 h, during which time blood loss was estimated cumulatively every 15 to 60 min. Excessive hemorrhage after CS was defined as blood loss > 121 g during the first 4 h after surgery, which was above the 90th percentile of the amount of post-operative bleeding calculated for all cases performed at our hospital between April 2014 and March 2015. Massive intra-operative bleeding was determined by the guidelines for obstetric practice in Japan as blood loss > 1500 g at singleton pregnancy and > 2300 g at twin pregnancy (Minakami et al. 2014).

RESULTS

Clinical features of all patients enrolled in the present study are listed in Table 1. In all cases, the CEUS images were adequate for assessment, and CEUS was performed without any complications. The obstetricians who participated agreed on the presence of leakage in all cases examined. Representative images of positive and negative CEUS examinations are provided in Figure 1.

Table 2 summarizes the results of univariate logistic regression analysis. The incidence of excessive

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