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● *Technical Note*

INTERVENTIONAL ULTRASOUND ASSISTED EARLY LOCAL HEMOSTATIC DRUG THERAPY IN TRAUMATIC INTRACEREBRAL HEMORRHAGE

Cong Feng,*[,1] Sai Huang,[†,1] Xuan Zhou,*[,1] Lili Wang,* Xiang Cui,[‡] Li Chen,* Faqin Lv,[§] and Tanshi Li*

* Department of Emergency, First Medical Center, General Hospital of the PLA, Beijing, China; [†] Department of Hematology, First Medical Center, General Hospital of the PLA, Beijing, China; [‡] Department of Orthopedics, First Medical Center, General Hospital of the PLA, Beijing, China; and [§] Department of Ultrasound, Hainan Hospital of the PLA General Hospital, Sanya, China

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Abstract—This article aims to test a minimally invasive interventional approach by real-time transcranial contrast-enhanced ultrasound (CEUS) through a small bur hole to achieve an early local hemostatic drug therapy in a novel traumatic intracerebral hematoma (ICH) model of pigs with hemostatic abnormalities. The effects of hemostasis in the hemocoagulase atrox (HA) injection group and saline injection group groups were observed by transcranial CEUS at three time points: 0 s, 10 s, 2nd. We successfully established a novel traumatic ICH model of pigs with hemostatic abnormalities by the methods of interventional ultrasound techniques and observed the effect of hemostasis by using HA in a local injection method with the assistance of minimally invasive interventional ultrasound technique. At 0 s, four pigs (100%) were observed that active bleeding was significantly weakened, and the range of hematoma became smaller in the HA group. At 10 s, four pigs (100%) were observed that active bleeding became much weaker, and the range of hematoma became further smaller in the HA group. At 2nd, zero pigs (0/4, 0%) were observed that active bleeding could be clearly identified and four pigs (100%) with ICH could also be observed in the HA group. We believe this useful technique could minimize the invasiveness and be operated at the bedside, which would bring much more benefits for traumatic ICH patients. (E-mail: lvjin8912@163.com) **© 2019 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Minimally invasive intervention, Contrast-enhanced ultrasonography, Local hemostatic drug therapy, Intracerebral hemorrhage.**

INTRODUCTION

The growth of intracerebral hematoma (ICH) with a resulting volume during the early hours of onset is one of the most vital factors associated with the highly traumatic ICH mortality and poor outcomes, especially in the patients receiving antithrombotic medication due to the increased tendency of bleeding (Brott et al. 1997; Hemphill et al. 2001; Davis et al. 2006; Chang 2007; Baharoglu et al. 2017; Beynon and Unterberg 2017). Effective hemostatic therapy of traumatic ICH in the early or ultra-early stage is critical to cease bleeding and prevent the hematoma expansion, which could be biologically modified (Mayer et al. 2008; Santagostino et al. 2015; Broderick 2018).

In the early or ultra-early stage of ICH which are underlying hemostatic abnormalities and without large ICH, the major managements of promoting hemostasis are currently including blood pressure control and antagonization of the effect of antiplatelet and anticoagulation (Wartenberg and Mayer 2015; Gulati et al. 2017). However, the effects of these hemostatic therapy methods in traumatic ICH patients are still with limitations and need further clinical investigation (Baharoglu et al. 2017). With the development of imaging techniques, the minimally invasive intervention has played a much more important role in managing traumatic ICH which with polytrauma or clinical deterioration (Barnes et al. 2014; Dey et al. 2014; Morotti and Goldstein 2016). However, local hemostatic drug therapy based on the minimally invasive interventional techniques in the early or ultra-early stage of traumatic ICH has less been reported.

Meanwhile, many procedures of minimally invasive intervention could not be operated at the bedside because they usually require surgical neuronavigation or other

Address correspondence to: Faqin Lv, Department of Ultrasound, Hainan Hospital of the PLA General Hospital, Sanya 572000, China. E-mail: lvjin8912@163.com

[1] Cong Feng, Sai Huang and Xuan Zhou contributed equally to this work.

large imaging equipment assistance, which is at particular risk for the increased tendency of bleeding in traumatic ICH patients (Teernstra et al. 2003; Thiex et al. 2004; Marquardt et al. 2005; Wu et al. 2013). Therefore, this study tested a new minimally invasive approach of local hemostatic drug therapy by the real-time guidance of transcranial contrast-enhanced ultrasound (CEUS) in a novel traumatic ICH model of pigs which are underlying hemostatic abnormalities. Furthermore, the use of transcranial CEUS to early identify the active bleeding and ICH was also observed and discussed.

METHODS

Ethics

The experimental protocol was approved by the Ethics Committee for Animal Research from the General Hospital of the People's Liberation Army (PLA) , and all experimental pigs received human care.

Experimental animals

A total of eight healthy male miniature pigs weighing 10 ± 1 kg were provided by the Experimental Animal Center of the PLA General Hospital (Beijing, China).

Drugs and reagents

Pentobarbital sodium (National Pharmaceutical Group Chemical Reagent Co., Ltd. Shijiazhuang, Hebei, China), Heparin sodium injection (Shanghai First Biochemical Pharmaceutical Co., Ltd., Shanghai, China), Ultrasound contrast agent (SonoVue, Bracco, Milan, Italy), Saline for injection (Beijing Shuanghe Pharmaceutical Co., Ltd., Beijing, China), Hemocoagulase Atrox for injection (Penglai Nuokang Pharmaceutical Co., Ltd., Penglai, Shandong, China).

Main equipment

Color Doppler Ultrasound Scanner (GE US General Electric LOGIQ E9 XD Clear, Milwaukee, WI, USA) with low-frequency interventional ultrasound probe (3CRF-D, 1∼6MHz); 16-gauge ultrasound biopsy kit (Bard Biopsy System, Covington, GA, USA). 21-gauge percutaneous transhepatic cholangiography (PTC) puncture needle (Bard Biopsy System, Covington, GA, USA); 7-mm perforator drill (Shanghai Medical Devices Co., Ltd. Surgical Instrument Factory, Shanghai, China), 18-gauge intravenous catheter (Shanghai Medical Devices Co., Ltd., Shanghai, China).

Experimental groups

Pigs were randomly divided into two groups. (1) SL injection group (n = 4) with 1 mL SL injection into the area of the active bleeding precisely in each pig and (2) HA injection group (n = 4) with 1 mL SL injection into the area of the active bleeding precisely in each pig.

Preparation of the animal model

We mimic clinical conditions of traumatic ICH by a novel animal model. Pigs were anesthetized by intramuscular injection of 3% pentobarbital sodium (30 mg/kg). After administration of anesthesia, the pigs were fixed on a board in a prone position and heparin (300 IU/kg) was given intravenously to resist the coagulation system. An 18 gauge intravenous catheter was placed in an internal jugular vein to provide a pathway of contrast agent injection. The fur on the head was also shaved.

We used the back of the ear as the study area due to the thinner skull window could be observed by ultrasound to achieve transcranial ultrasound examination and minimally invasive interventional therapy. First, one side of the brain underwent a conventional ultrasound (CU) examination to find an intracerebral artery (Fig. 1a, 1b). After identifying the target intracerebral artery, the ultrasound probe was adjusted and fixed so that the center of the puncture guideline could pass through the arterial blood vessel (Fig. 1b). Then, a bur hole (4.0 mm diameter) in the skull was produced by a perforator drill (7.0 mm diameter) along the direction of the ultrasound guideline. Subsequently, a 16 gauge biopsy needle was inserted across the bur hole into the brain along with the guideline slowly close to the arterial blood vessel by the real-time guidance and tracking by the transcranial ultrasound (Fig. 1c). After the needle at the right position within the maximum diameter to the targeted intracerebral artery, the biopsy was triggered for puncturing the blood vessel and removed out of the brain (Fig. 2).

The identification of active bleeding and ICH

After modeling, both SL and HA groups were detected by both CU and CEUS immediately and simultaneously in a real-time transcranial way for an attempt to identify the ICH and active bleeding. The skull thickness in the acoustic window used for imaging was 3.68 ± 0.86 mm. The operational process of the CEUS was according to Xuan Zhou's recommendations (Zhou et al. 2013). About 4−6 MHz for fundamental imaging and 5 MHz for CEUS were used. The low acoustic power of 0.15−0.17 (mechanical index) was used for contrast pulse sequencing which employed by CEUS and acoustic power of 0.39−0.42 was used for micro-vascular density. A dose of 0.01 mL/kg of contrast agent was rapidly administered through the internal jugular vein and followed by a 5 mL SL solution immediately. The images and evaluation of ICH and active bleeding were both recorded in all pigs and real time. The investigator who identified the ICH and active bleeding was blinded to the model development.

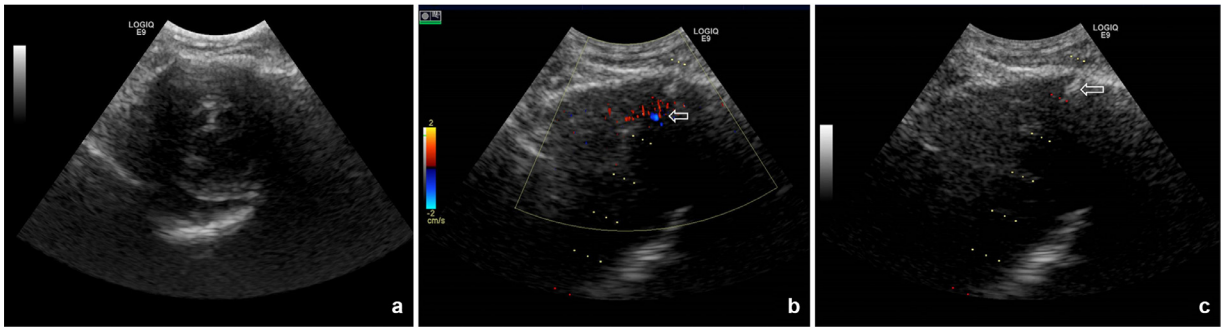

Fig. 1. The establishment process of an animal model to mimic ICH under the guidance of ultrasound. (a) Normal intracerebral imaging findings by transcranial CU. (b) Target intracerebral artery (as shown by the white arrow) was identified by transcranial ultrasound with CDFI, and the ultrasound probe was adjusted so that the center of the puncture guideline (dotted line) could pass through the arterial blood vessel. (c) Real-time tracking of the biopsy needle (as shown by the white arrow) guided by the transcranial ultrasound along with the guideline slowly close to the arterial blood vessel. The biopsy was triggered for puncturing the targeted intracerebral artery after the needle at the right position within the maximum diameter. ICH = intracerebral hematoma; CU = conventional ultrasound; CDFI = Color Doppler Flow Imaging.

Process of minimally invasive local hemostatic drug therapy

After identifying the ICH and active bleeding, both SL and HA groups received a minimally invasive local hemostatic drug therapy under the guidance of transcranial CEUS. The ultrasound probe was adjusted and fixed to make the center of the puncture guideline that could pass through the area of active bleeding. A 21 gauge PTC puncture needle was inserted across the bur hole into the brain along with the guideline slowly close to the area of active bleeding under the real-time guidance and tracking by the transcranial CEUS. After the needle arrived at the right position, the core was removed from the needle and connected by an injector. Then 1 mL drugs in different groups were injected under the real-time observation of CEUS. The effects of hemostasis in two groups were observed by transcranial CEUS at three time points: after injection immediately (0 s), at 10 s after the injection (10 s) and at the second time CEUS after the first contrast agents disappeared (2nd). The investigator who observed the effects of hemostasis in two groups was blinded to each time point. The timeline of the experiment is shown in Figure 3.

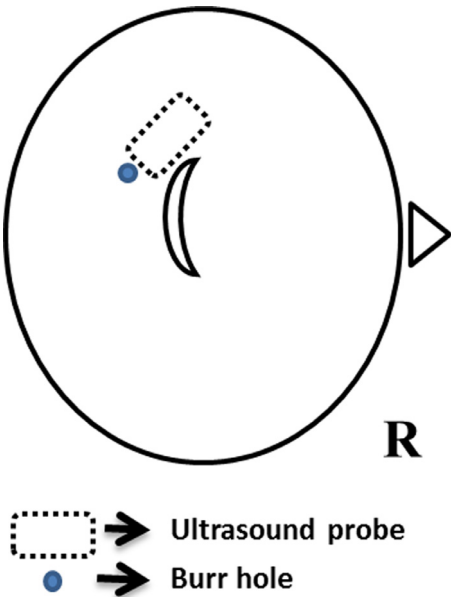

Fig. 2. One interventional bur hole is placed for the insertion of biopsy, whose position is followed by the ultrasound probe (R: right half of the face).

RESULTS

The establishment of ICH model

The models of ICH in eight pigs were all successfully established using an interventional method by the transcranial ultrasound. The ICH was also formed and confirmed by the transcranial ultrasound (Fig. 4a). The maximum diameters of the hematoma could also be measured (Fig. 4b). After the needle reached at the ICH, the blood was seen flowing out from the needle as soon as the core was removed out of the needle, which further confirmed the model of ICH was successfully established.

The identification of active bleeding and ICH by transcranial CU and CEUS

Eight pigs were examined totally in two groups, and all of them (8/8, 100%) with active bleeding were identified by transcranial CEUS and zero pigs (0/8, 0%) by transcranial CU. In the observation of ICH, eight pigs (8/8, 100%) were observed by transcranial CEUS and seven pigs (7/8, 75%) by transcranial CU (Fig. 5 and Table 1).

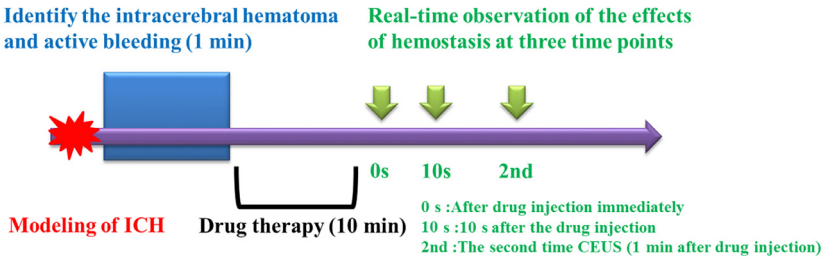

Fig. 3. The timeline of the experiment.

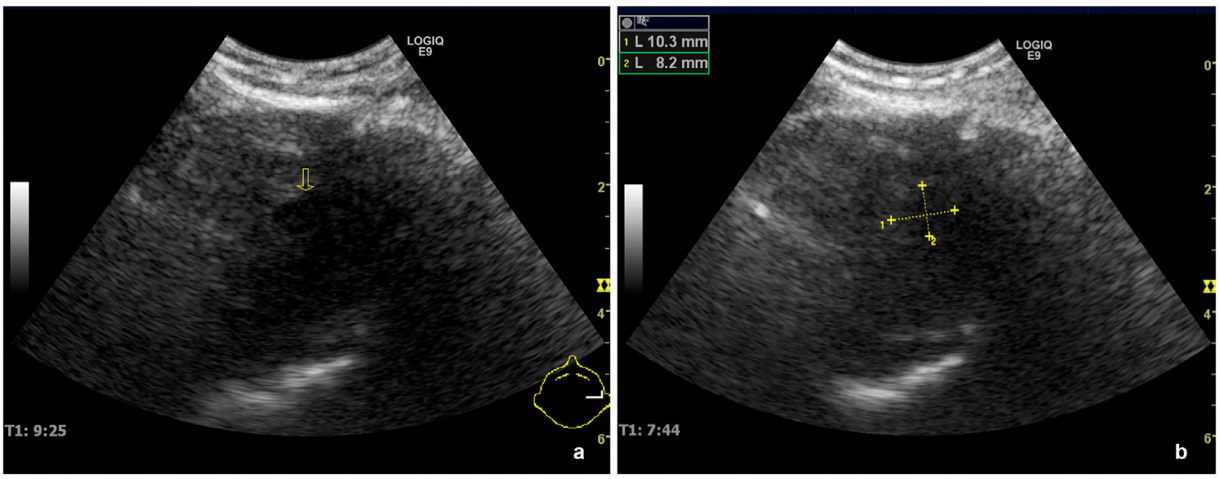

Fig. 4. The transcranial ultrasound findings of the animal model for ICH. (a) The ICH was successfully established, and the ICH was formed (as shown by the yellow arrow) and confirmed by the transcranial ultrasound. (b) The maximum diameters of the hematoma could also be measured. ICH = intracerebral hematoma.

The effect of hemostasis in two groups at different time points

At 0s after injection (0s): 4 pigs (4/4, 100%) in the HA group and 0 pig (0/4, 0%) in the SL group were observed that active bleeding was significantly weakened; 4 pigs (4/4, 100%) in the HA group and 0 pig (0/4, 0%) in the SL group were observed that the range of hematoma became smaller as contrast agents were less assembled at the hematoma area. (Figs. 6 and 7) (Table 2).

At 10s after injection (10s): 4 pigs (4/4, 100%) in the HA group and 0 pig (0/4, 0%) in the SL group were observed that active bleeding became much weaker; 4 pigs (4/4, 100%) in the HA group and 0 pig (0/4, 0%) in the SL group were observed that the range of hematoma became further smaller. (Figs. 8a and 9a) (Table 2).

At the second CEUS after the first contrast agents totally disappeared (2nd), zero pigs (0/4, 0%) were observed that active bleeding could be clearly identified in the HA group and four pigs (4/4, 100%) in the SL group; four pigs (4/4, 100%) with ICH could also be clearly observed in the HA group and four pigs (4/4, 100%) in the SL group (Figs. 8b and 9b) (Table 2).

DISCUSSION

Currently, the management of hemostasis in early or ultra-early stage of traumatic ICH, especially with hemostatic abnormalities, has become a studying hot point, which mainly focuses on the antagonization of the effect of antiplatelet and anticoagulation (Barnes et al. 2014; Dey et al. 2014; Wartenberg and Mayer 2015; Morotti and Goldstein 2016; Baharoglu et al. 2017; Gulati et al. 2017). The transcranial ultrasound assistant minimally invasive local hemostatic drug therapy in traumatic ICH has less been reported.

We successfully established a novel traumatic ICH model of pigs with hemostatic abnormalities by the methods of interventional ultrasound techniques. This animal model was simple, useful and reproducible. Moreover, we could use the back of the ear to mimic the thinner skull window to achieve transcranial ultrasound examination and minimally invasive interventional therapy, which were in accordance with clinical conditions.

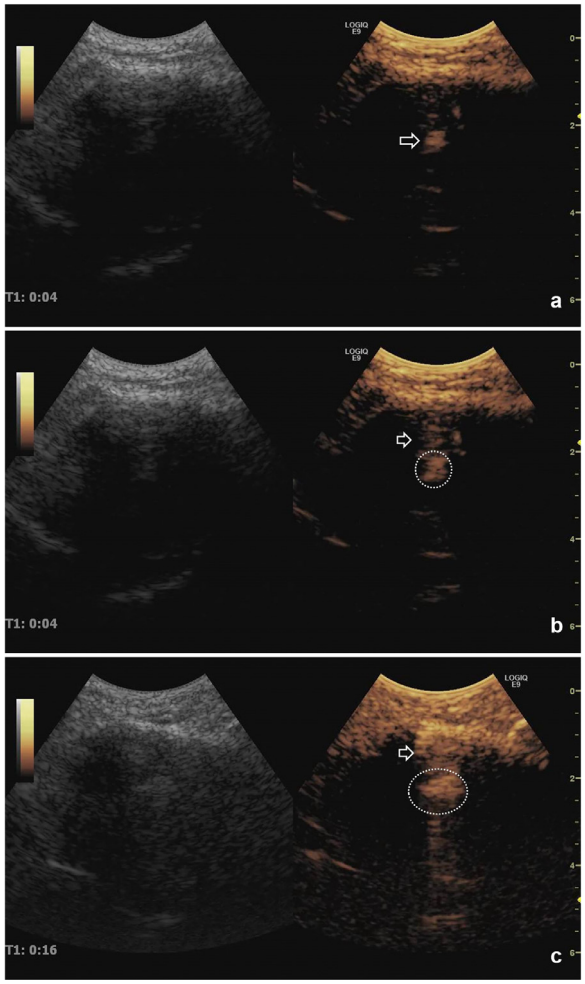

Fig. 5. Findings of ICH by the transcranial CEUS and B-mode ultrasound. (a) ICH was detected by transcranial CEUS as soon as the successful establishment of the animal model. At the beginning of the transcranial CEUS examination, the image of ICH was observed, where the contrast agents were assembled at the hematoma area (as shown by the white arrow). (b) After a few seconds, active bleeding was observed, where the contrast agents with the blood had overflowed to the extravascular space and pooled. (c) At the peak of imaging, both hematoma and active bleeding were observed much more clearly. The hematoma area became larger (as shown by the white dotted circle) and active bleeding became more assembled (as shown by the white arrow). At the whole process of examination, B-mode transcranial ultrasound could not find active bleeding clearly. ICH = intracerebral hematoma; CEUS = contrast-enhanced ultrasound.

Table 1. The identification of active bleeding and ICH by transcranial CU and CEUS

Features	Active bleeding (8)	ICH (8)
CU	0	7
CEUS	8	8

ICH = intracerebral hematoma; CU = conventional ultrasound; CEUS = contrast-enhanced ultrasound.

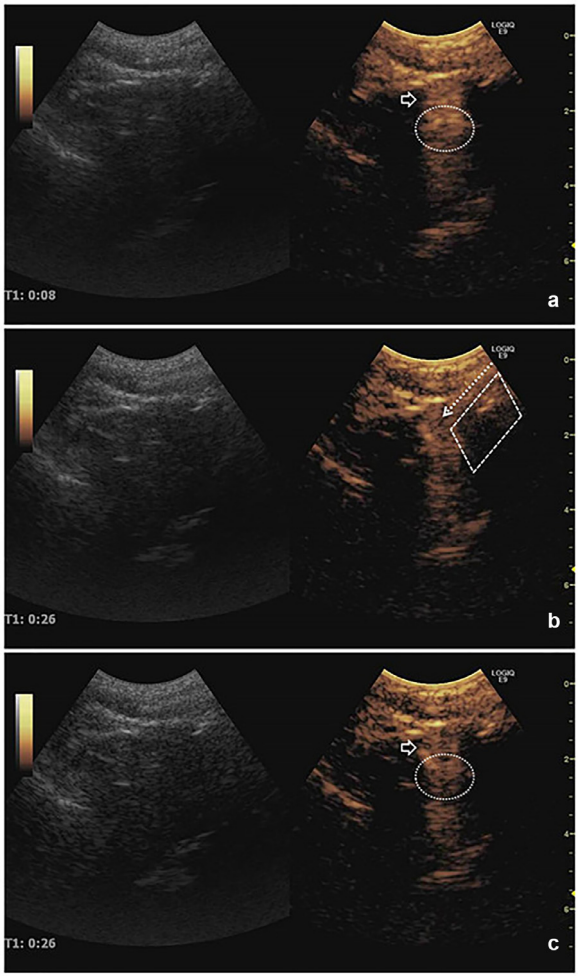

Fig. 6. The process and observation of minimally invasive local drug hemostasis therapy for ICH under the guidance of transcranial CEUS in the SL group. (a) At the beginning of the transcranial CEUS examination in the SL group, the image of ICH (as shown by the white dotted circle) and active bleeding (as shown by the white arrow) were clearly observed. (b) The SL (1 mL) was injected into the area of the active bleeding precisely under the guidance of transcranial CEUS. The white dotted arrow indicates the puncture needle, and the enclosed area of the white dotted frame indicates they formed artifact moment of injection. (c) After injection, contrast agents were also assembled at the hematoma area (as shown by the white dotted circle) and active bleeding was also observed (as shown by the white arrow), which indicated that the effect of hemostasis was not obviously at the early stage. ICH = intracerebral hematoma; CEUS = contrast-enhanced ultrasound; SL = saline.

In this study, we could obtain the clear and real imaging characteristics of active bleeding and hematoma formation from this novel model.

In the identification of active bleeding, CEUS got a better result than CU. Although computed tomography (CT) is currently the first and best choice for ICH, it also has some limitations such as could not be taken as a bedside, real-time and radiation-free way (Chang et al.

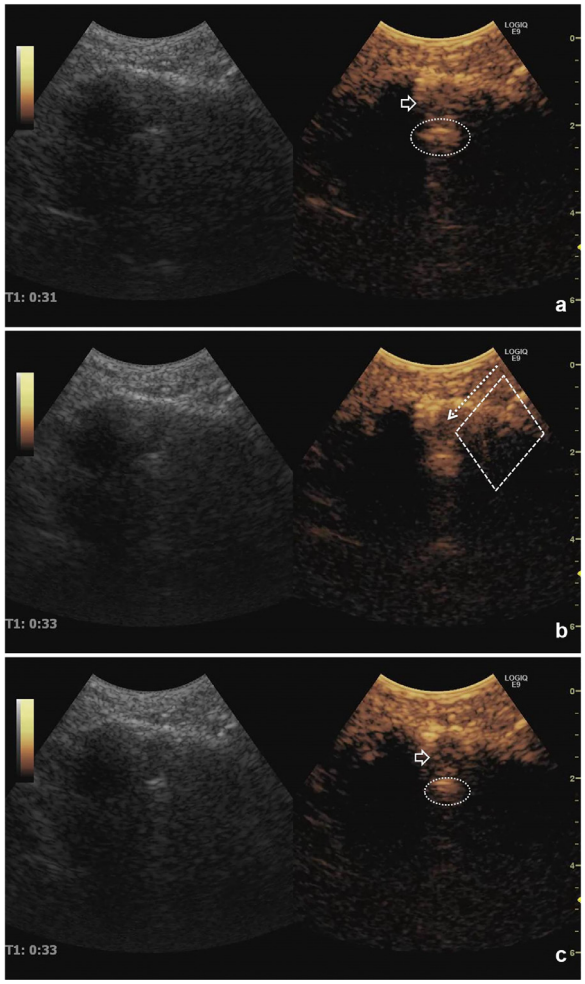

Fig. 7. The process and observation of minimally invasive local drug therapy for ICH under the guidance of transcranial CEUS in the HA group. (a) At the beginning of the transcranial CEUS examination in the HA group, the image of ICH (as shown by the white dotted circle) and active bleeding (as shown by the white arrow) were the same as that of in the SL group which were clearly observed. (b) The HA (1 mL) was injected into the area of the active bleeding precisely under the guidance of transcranial CEUS. The white dotted arrow indicated the puncture needle, and the enclosed area of the white dotted frame indicated they formed artifact moment of injection. (c) After injection, the active bleeding was significantly weakened (as shown by the white arrow) and the range of hematoma became smaller because contrast agents were less assembled at the hematoma area (as shown by the white dotted circle), which indicated that the effect of hemostasis was obviously at the early stage. ICH = intracerebral hematoma; CEUS = contrast-enhanced ultrasound; HA = hemocoagulase atrox.

Table 2. The effect of hemostasis in two groups at different time points

Features were clearly identified	Groups	0 s	10 s	2nd
Active bleeding	HA (4)	0	0	0
	SL (4)	4	4	4
ICH	HA (4)	0	0	4
	SL (4)	4	4	4

0 s: after injection immediately.
10 s: at 10 s after the injection.
2nd: at the second time of contrast-enhanced ultrasound after the first contrast agents were totally disappeared.
ICH = intracerebral hematoma; HA = hemocoagulase atrox; SL = saline.

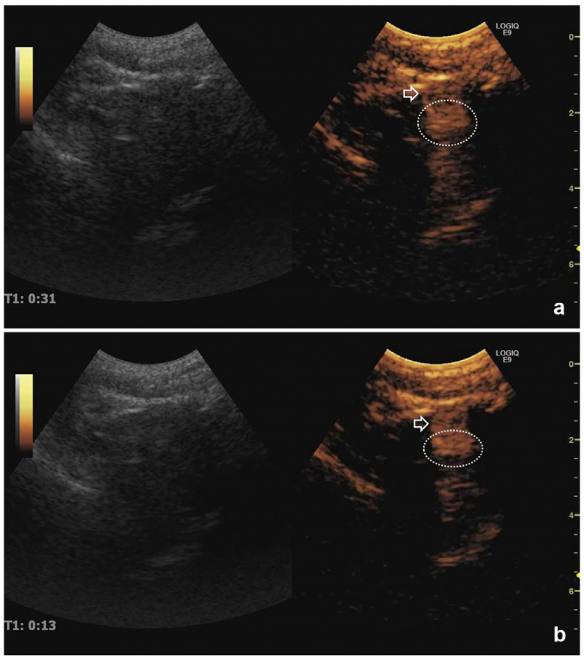

Fig. 8. The effect of hemostasis of SL group. (a) After the injection of the SL, we kept on observing by the transcranial CEUS for 10 s. At the 10 s after the local drug therapy, we could also clearly identify the image of ICH (as shown by the white dotted circle) and active bleeding (as shown by the white arrow). (b) We observed the ICH again by the transcranial CEUS after the first contrast agents totally disappeared and the image of ICH (as shown by the white dotted circle) and active bleeding (as shown by the white arrow) were still clearly identified, which strongly suggested that the hemostasis by SL injection was ineffective. SL = saline; CEUS = contrast-enhanced ultrasound; ICH = intracerebral hematoma.

2007; Alahmadi et al. 2010; Gregson et al. 2015; Hemphill et al. 2015; Chartrain et al. 2018). Another limitation is that the minimally invasive treatment based on CT requires to transport patients so that the patient's position change is likely to increase the risk of additional bleeding. Recently, the CEUS using contrast agents showed much more application valuable in evaluation of injuries, but there are less reports on traumatic ICH (Mooney 2002; Catalano et al. 2003; Catalano et al. 2004; Catalano et al. 2005; Catalano et al. 2006). Based on the result of this observation, transcranial CEUS could highly identify the intracerebral active bleeding

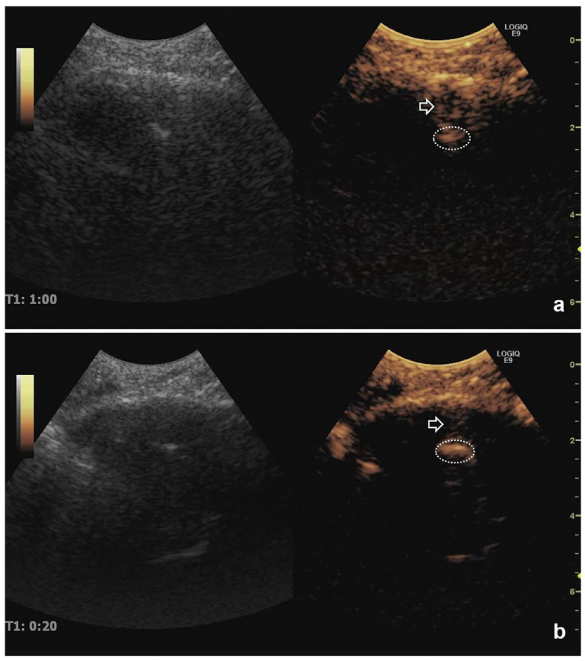

Fig. 9. The effect of hemostasis of HA group. (a) After the injection of the HA, we also kept on observing by the transcranial CEUS for 10 s. At the 10 s after the local drug therapy, we found that the active bleeding became much weaker (as shown by the white arrow) and the range of hematoma became further smaller (as shown by the white dotted circle). (b) We observed the ICH again by the transcranial CEUS after the first contrast agents totally disappeared; the image of ICH (as shown by the white dotted circle) could also be clearly observed but the active bleeding (as shown by the white arrow) could not be clearly identified, which strongly suggested that the effect of hemostasis by HA injection was satisfactory. HA = hemocoagulase atrox; CEUS = contrast-enhanced ultrasound; ICH = intracerebral hematoma.

than CU through the thin area of the skull or a narrow window that could be accessed by ultrasound, which would achieve real-time detection of deterioration and risk. Meanwhile, the location of active bleeding by CEUS also could be an important prerequisite for minimally invasive interventional therapy.

Minimally invasive local hemostatic drug therapy based on the interventional ultrasound technique has been confirmed effective in abdominal solid organ injuries (Valentino et al. 2006; Thorelius 2007; Valentino et al. 2007; Huang et al. 2018). According to the study of ICH, minimally invasive surgical techniques could offer more benefit compared with the open surgical evacuation, but there is still a lack of minimally invasive local hemostatic drug therapy for ICH at the bedside (Sun et al. 2010; Newell et al. 2011; Phillips et al. 2012; Mould et al. 2013; Barnes et al. 2014; Hemphill et al. 2015; Law et al. 2017; Manfield and Yu 2017). We first observed the effect of hemostasis by using the HA in a local injection method with the assistance of minimally invasive interventional ultrasound technique and achieved a satisfactory result. After HA injection, the active bleeding was significantly weakened and the range of hematoma became smaller, which indicated that the effect of hemostasis was obviously at the early stage. Moreover, in the 20 s after the local drug therapy, we further found that active bleeding became much weaker and the range of hematoma became further smaller. At the second time of transcranial CEUS, the image of ICH could also be clearly observed, but the active bleeding could not be clearly identified, which strongly suggested that the local hemostatic drug therapy for ICH was effective.

However, these new attempts also have many limitations. First, transcranial CEUS and CU could not scan all parts of the brain due to the limited physiologic window of the skull and the window is commonly narrow. Second, intracerebral drug injection could cause elevated intracranial pressure and other secondary complications would need further observation. Third, because the brain volume was small and the injection of coagulation drugs interfered with the initial bleeding site, the brain tissue was not successfully obtained for further analysis of the bleeding site. Fourth, it was hard to compare measured hematoma size evaluated with CEUS with CT images in this experiment. Fifth, the hematoma size was not to be used as an observation feature, which required further larger sample size studies. Sixth, it is still not completely ruled out that ultrasound + microbubbles may increase the risk of bleeding, and more research is needed to confirm it. Last but not the least, the feasibility and effectiveness of this new method require further animal and clinical studies.

CONCLUSION

We first tested a minimally invasive interventional approach by real-time transcranial CEUS through a small bur hole to achieve an early local hemostatic drug therapy in a novel traumatic ICH model of pigs with hemostatic abnormalities. We believe this useful technique could minimize the invasiveness and be operated at the bedside, which would bring much more benefits for traumatic ICH patients.

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Conflict of interest disclosure—The authors declare no competing interests.

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