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A cost-effective measure to prevent hemorrhage in ultrasound-guided percutaneous liver biopsy

Qingyuan Cai[1*] and Xiaomin Wu[1]

Abstract

Background Liver biopsy is a procedure whereby a biopsy needle is used to extract tissue from the liver parenchyma or focal lesions of the liver for pathological or microbiological examination. Percutaneous liver biopsy(PC-LB) is the most commonly employed and least expensive modality. However, it is associated with a significant risk of bleeding complications, which may potentially result in patient mortality. The objective of this study was to investigate the efficacy of Absorbable Gelatin Sponge sheet filler agent (AGS-SFA) in preventing bleeding complications during liver tissue biopsy and to validate a cost-effective surgical technique.

Methods In this study, patients who underwent ultrasound-guided percutaneous liver tissue biopsy at our hospital were selected and randomly assigned to either an observation or control group. The observation group employed the use of AGS-SFA to fill the biopsy needle channel. Immediately following the biopsy procedure, the biopsy needle path was examined using Doppler ultrasound. The incidence of bleeding complications following biopsy and the associated factors influencing bleeding were analysed in the two groups.

Results The observation and control groups were successfully biopsied, with a 100% success rate for both. The incidence of bleeding complications was significantly lower in the observation group than in the control group. Four factors, including fatty liver, prothrombin time, albumin and INR, were found to have a significant effect on biopsy bleeding in the control group.

Conclusion The use of coaxial needles to inject AGS-SFA is an effective and economical procedure that significantly improves the safety of biopsy without increasing the burden of patient care.

Keywords Percutaneous liver biopsy, Adverse events, Ultrasound, Tissue acquisition, Absorbable gelatin sponge

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Background

In accordance with the principles of evidence-based medicine, an increasing number of patients are undergoing liver puncture biopsy for the purpose of obtaining a definitive diagnosis in clinical practice [1]. This study focuses on biopsies for diffuse liver diseases (e.g., hepatitis, fatty liver), excluding focal lesions. The most commonly used methods for liver biopsy are percutaneous liver biopsy(PC-LB), transjugular liver biopsy(T-LB) and endoscopic ultrasound-guided liver biopsy(EUS-LB). It is evident that the biopsy tissue obtained by EUS-LB is of a lesser quality than that obtained by PC-LB, due to the limitations imposed by the needle size(smaller needles) and the use of aspirators. To circumvent this limitation and procure a greater quantity of tissue, a greater number of punctures could be performed(i.e., more liver capsule and liver parenchyma punctures). However, this is contrary to the objective of reducing the incidence of adverse events associated with liver biopsy. T-LB and EUS-LB require sedation, yield less tissue volume, are more invasive and more costly than PC-LB [2–8]. The risk of bleeding after liver biopsy was 10.9%, which could lead to patient death [9]. In addition, moderate to severe pain was reported in 0.34% of patients [10]. Absorbent gelatin sponges are commercially available as both a particle embolic agent and a sheet filler agent. For the purposes of this study, the sheet filler agent was selected for investigation.The objective of this study was to validate the efficacy and cost-effectiveness of Absorbable Gelatin Sponge sheet filler agent (AGS-SFA) for needle paths, provided that a sufficient tissue volume could be obtained.

Table 1 The characteristics and indications of all patients

	observation	control
Number of patients	231	231
Age, years	49.1 ± 4.0	53 ± 5.8
Men/women, n	149/82	160/71
Biopsy site(Left Liver/Right Liver)	228/3	225/6
Operative time	7.6 ± 0.4 min	4.1 ± 0.3 min
Hemostasis time	0.4 ± 0.2 min	5.3 ± 1.7 min
Adverse event rate	1.3%(3/231)	22.1%(51/231)
Platelets, 1000/mm3	256 ± 47	240 ± 38
Albumin	37.43 ± 5	38.63 ± 5
INR	1.15 ± 0.28	1.10 ± 0.21
PT	12.1 ± 1.7	11.5 ± 2.0
FLD(Y/N)	152/79	148/83
Admission diagnosis		
Chronic hepatitis B	188	198
Unexplained abnormal liver function	8	10
Autoimmune hepatitis(AIH)	6	3
Hereditary metabolic liver disease	2	0
Alcoholic liver disease	7	2
Non-alcoholic fatty liver disease (NAFLD)	20	18

PT, prothrombin time; FLD, fatty liver disease

Materials and methods

Study populations

A total of 462 patients underwent ultrasound-guided liver tissue aspiration biopsy at our hospital between September 2019 and March 2023. Of these, 309 were male and 153 were female. The median age of the patients was 47.8 ± 3.9 years (range, 16 to 73 years). The demographic characteristics of the participants are presented in Table 1. Participants were randomly assigned to either the observation or control group using a computer-generated randomisation sequence. Each group consisted of 231 cases. The observation group comprised 149 males and 82 females, while the control group consisted of 160 males and 71 females.All patients provided informed consent for the intervention. Inclusion criteria: The inclusion criteria were as follows:

1. Absence of serious coagulation dysfunction, prothrombin time(PT) < 15s, platelets > 50×10^9, and no application of double antibiotics;
2. Absence of obvious obstructive jaundice, no ascites;
3. Absence of serious heart, liver and kidney failure.

Exclusion criteria:

1. 1.Use of anticoagulants or antiplatelet agents within 7 days prior to biopsy;
2. 2.Presence of hepatic tumors or focal lesions;
3. 3.Severe cardiopulmonary comorbidities contraindicating biopsy.

Materials

A diagnostic Doppler ultrasound machine such as PHILIPS EPIQ5 ultrasound system(Netherlands), 18G biopsy needle and 17G coaxial biopsy needle(Canyon, China), puncture frame(LEAPMED, China), and Absorbable Gelatin Sponge(specification: 60 mm×20 mm×5 mm, China). All operations were performed by the same ultrasound interventionalist with more than 5 years of experience.

PC-LB

The biopsy modalities employed in the control group are as follows: The patient was positioned supine on the operating table, with the abdomen fully exposed. An ultrasonographic examination was then performed to assess the target area for biopsy. Subsequently, the area was disinfected and a towel was placed over it. Local anaesthetic (2% lidocaine) was then infiltrated layer by layer from the subcutis to the hepatic peritoneum. Subsequently, the 17G coaxial biopsy needle was punctured into the liver under ultrasound guidance to a depth of

2 cm or more. The assistant then withdrew the needle core, and the 18G biopsy needle was introduced via the coaxial needle. Subsequently, the coaxial biopsy needle was extracted following the acquisition of two liver tissues. Subsequently, Doppler ultrasound was employed in real time to monitor the puncture needle path (the blood flow scale was calibrated to 10.3 cm/s). It is important to note that the time of disappearance of the blood flow signal in the needle path should be observed and recorded.

The biopsy modalities employed in the observation group are as follows: The biopsies were conducted in accordance with the methodology employed in the control group. The AGS-SFA was then divided into smaller sections. Following the biopsy of two strips of tissue, the assistant fills the AGS-SFA into the sheath and advances it through the coaxial needle core into the puncture channel, while gradually retracting the coaxial biopsy needle. A Doppler ultrasound was employed to observe the puncture needle path in real time, with the blood flow scale adjusted to 10.3 cm/s. The cessation of the blood flow signal in the needle path was duly noted and recorded (Fig. 1).

Observation indicators

The preoperative clinical data of all patients were recorded, including gender, age, the presence or absence of FLD, PT, INR, platelet, and albumin. Criteria for successful puncture included the presence of two strips of tissue measuring approximately 2 cm in length and 1 mm in thickness, as well as the observation of more than six confluent areas under pathoscopic examination. Bleeding complications were defined as: (1) Persistent blood flow signal in the needle path on Doppler ultrasound > 5 min post-procedure; (2) Clinical signs of hemorrhage (e.g., hypotension, dropping hemoglobin > 2 g/dL). Severe bleeding required transfusion or intervention.Haemostasis time was defined as the interval between the withdrawal of the biopsy needle following biopsy and the disappearance of the blood flow signal within the needle path.

Statistical analysis

SPSS 20 statistical analysis software was used, and measurements conforming to normal distribution were expressed as ($\bar{x} \pm s$), and the Fisher exact probability method or chi-square test was used for count data. Comparisons between the two methods were made using the independent samples t-test. Differences were expressed as statistically significant at $P < 0.05$.

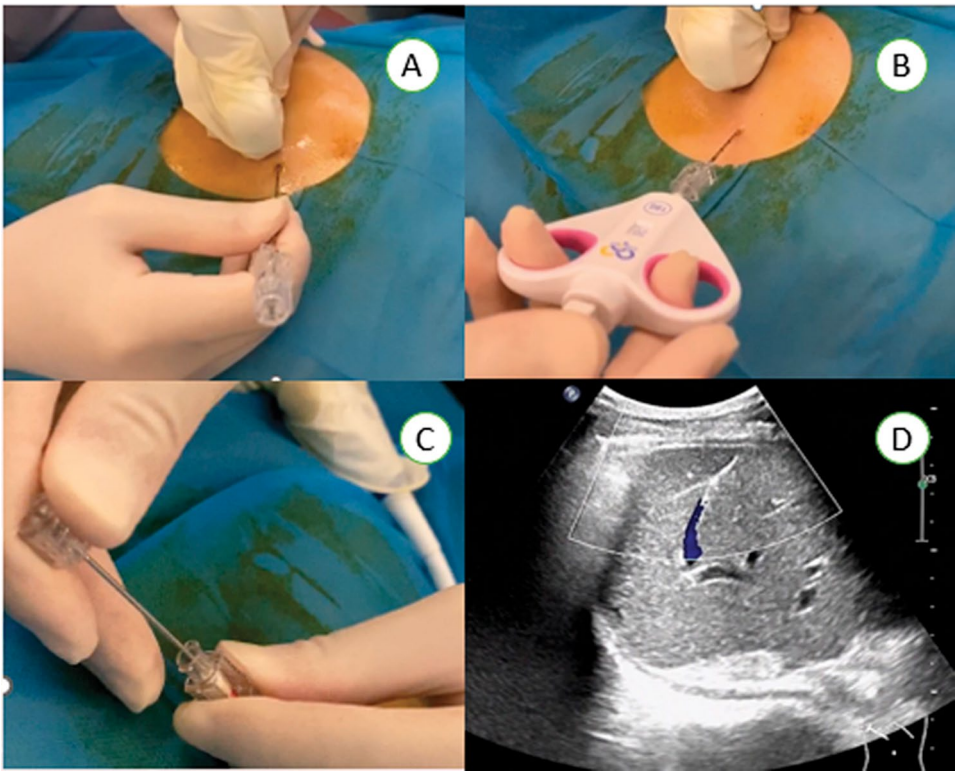

Fig. 1 Demonstrates how to use the AGS-SFA to fill a needle path over a coaxial needle. **a**. ultrasound-guided placement of sheath, **b**. a biopsy needle is being inserted in the sheath, **c**. the AGS-SFA to fill a needle path over a coaxial needle, **d**. Doppler ultrasound display of no blood flow signal in the needle path

Table 2 Multifactorial logistic regression analysis of biopsy bleeding in the control group

variant	β	Wald	*P*	OR(95%CI)
FLD	1.676	6.392	0.011	0.187(0.051∼0.686)
Albumin	1.357	7.233	0.007	0.257(0.096∼0.692)
PT	5.021	21.233	0.000	0.007(0.001∼0.056)
INR	5.445	24.902	0.000	0.004(0.001∼0.037)

PT, prothrombin time; FLD, fatty liver disease

Results

Patient characteristics

The observation and control groups were successfully biopsied, with a 100% success rate for both. No fatal bleeding events occurred in either group. The incidence of bleeding complications in the observation and control groups was 1.3% (3/231) and 22.1% (51/231), respectively. The mean time required for haemostasis was 0.4 ± 0.2 min in the observation group and 5.3 ± 1.7 min in the control group. The operation lengths were 7.6 ± 0.4 min and 4.1 ± 0.3 min, respectively, with statistically significant differences($P < 0.05$). No statistically significant differences were observed in age, biopsy site, INR, PT, albumin, platelets, biopsy site and FLD between the two groups($P > 0.05$).

Factors affecting bleeding on liver biopsy

The univariate analysis demonstrated that gender, age, and platelet levels had no statistically significant impact on biopsy bleeding in the control group ($P > 0.05$). Four factors, including FLD, PT, albumin, and INR, were found to have a significant effect on biopsy bleeding in the control group($P < 0.05$). The R value indicated that the magnitude of correlation between the four indexes and bleeding was in the order of INR, PT, FLD, and albumin(Table 2).

Discussion

The diagnosis and treatment of liver disease and focal liver lesions are complex and variable [11, 12]. A clear diagnosis is the basis for diagnosis and treatment and for assessing prognosis. Liver biopsy is a surgical procedure in which the liver parenchyma or focal liver lesions are biopsied with a biopsy needle to obtain tissue for pathological or microbiological examination. Despite advances in diagnostic and therapeutic techniques, complications associated with liver biopsy do occur. The incidence of bleeding after liver biopsy has been reported to be as high as 10.9%. The use of colour Doppler ultrasound has been shown to be an effective method of visualising the needle path after biopsy. The implementation of techniques to prevent needle path bleeding in this setting would be of significant benefit to both clinicians and patients.

In the past, scholars engaged in research on liver biopsy have predominantly employed the direct biopsy technique utilising biopsy needles [11]. Compared to the direct biopsy technique, the coaxial method used in this study prolonged operative time by 3.5 min (7.6 ± 0.4 min vs. 4.1 ± 0.3 min) but significantly reduced bleeding risk (1.3% vs. 22.1%). Prior studies have shown that coaxial techniques improve safety without compromising sample quality [17, 18], making them particularly suitable for patients with coagulation abnormalities or diffuse liver diseases. In this study, the coaxial needle technique (17G coaxial needle, 18G biopsy needle) was employed to puncture the target area and obtain two strips of tissue. Immediately following the biopsy, Doppler ultrasound was employed to demonstrate the blood flow within the puncture needle path and the time required for haemostasis in real time. The incidence of bleeding complications in the control group was 22.1%, with a hemostasis time of 5.3 min. This higher rate compared to the previously reported 10.9% may be attributed to differences in patient selection and detection methods. Our cohort predominantly included patients with chronic hepatitis B virus infection (82.7% in the control group), who frequently exhibit mild coagulation abnormalities and hypoalbuminemia [12]. Additionally, the use of real-time Doppler ultrasound likely increased the detection of subclinical bleeding events that might otherwise go unnoticed in studies relying solely on clinical symptoms. Univariate analysis revealed that four factors, namely fatty liver, PT, albumin, and INR level, had a significant impact on biopsy-related bleeding in the control group. The reduced likelihood of bleeding from liver puncture in patients with fatty liver may be attributed to the greater density of liver cellular tissue, which can compress the needle path following biopsy. The present study was a study of liver tissue biopsy, predominantly in patients with abnormal liver function, such as chronic hepatitis B virus infection, frequently concomitant with mild coagulation abnormalities and lower protein. The observers, who injected a AGS-SFA into the coaxial needle following biopsy, experienced a bleeding complication rate of 1.3%(3/231) and a haemostasis time of 0.4 ± 0.2 min, which were significantly lower than those observed in the control group. These findings suggest that the AGS-SFA was effective in providing haemostasis. The mean operative time for the observation group was only 3.5 min longer than that for the control group.

Local injections of drugs commonly used in liver biopsy to prevent bleeding include thrombin, absorbent gelatin sponge particle embolic agent(AGS-PEA), and tissue glue. Thrombin is a coagulant that activates coagulation factors and platelet aggregation, thereby performing the functions of coagulation and reducing bleeding. However, it is a relatively expensive agent, and the time required for clot formation is dependent on the number of coagulation factors and platelets present [13, 14].

Tissue glue is composed primarily of butyl cyanoacrylate, a stabilising and blocking agent. It plays a role in the blood and tissue fluid as an anion, facilitating rapid curing and sealing of blood vessels, thereby achieving the purpose of embolism hemostasis. The time required for tissue gel injection to achieve hemostasis is faster than that for white-browed snake venom hemagglutinin, yet it is less stable in terms of hemostasis. Furthermore, it is a relatively expensive option [15]. AGS-PEA are liquid formulations that are injected through a syringe into a needle path to absorb water and blood from the wound site. The subsequent swelling of the agent within the path promotes hemostasis by filling the path and obstructing the blood flow [16]. Additionally, AGS-PEA can be combined with haemagglutinin to create a hybrid embolus [17, 18].

AGS-SFA was selected for this study primarily on the basis of economic considerations. The cost of commercially available bolus-structured gelatin sponge particles is considerable. AGS-SFA is priced at approximately two US dollars, while AGS-PEA costs approximately twenty US dollars, representing a tenfold difference in price. Furthermore, AGS-SFA can be prepared as PEA, but this process is arduous and necessitates the assistance of personnel, which ultimately diminishes the efficacy of liver biopsies. AGS-SFA promotes hemostasis by absorbing blood, swelling to mechanically compress vessels, and providing a scaffold for platelet aggregation. This dual action accelerates clot formation within the needle tract. Consequently, in the present study, AGS-SFA was cut into small pieces in order to block the needle channel through a coaxial needle, with a view to verifying its feasibility and safety.

In this study, all three cases of post-biopsy bleeding in the observation group occurred in patients with severe cirrhosis ($n = 3/231$), which may have contributed to tissue friability and compromised AGS-SFA efficacy, which may be due to the small amount of AGS-SFA filled or the deep filling position; an overly deep filling position may result in a subperiosteal bleeding site that cannot be treated promptly. A limitation of this study is that the amount of AGS-SFA filled could not be determined. An excess of AGS-SFA may obstruct the needle core and hinder its advancement. It is therefore recommended that the tip of the coaxial needle is withdrawn to a depth of 2 cm below the hepatic pericardium, filled with gelatin AGS-SFA and then withdrawn from the coaxial needle.

In conclusion, Ultrasound-guided PC-LB is a procedure with a high complication rate. Improvements in preoperative assessment, coagulation and preoperative discussion are necessary measures to reduce complications and doctor-patient disputes. However, this study has several limitations. First, the lack of operator blinding may introduce bias in the assessment of outcomes. Second, the single-center design and the fact that all procedures were performed by a single experienced operator may limit the generalizability of the findings to other healthcare settings with less experienced clinicians or different resources. Third, the absence of long-term follow-up data means we cannot assess delayed complications such as late bleeding or infection. The use of coaxial needles to inject AGS-SFA is an effective and economical procedure that significantly improves the safety of biopsy without increasing the burden of patient care.

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Author contributions
QC is responsible for the conception of the manuscript and the approval of article. XW is responsible for the interpretation and article drafting. QC is responsible for the review of the literature and the critical revision of article. All authors read and approved the final manuscript.

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Data availability
All data are included in the manuscript or supplementary files.

Declarations

Ethical approval and consent to participate
The protocol has been approved by the Ethics Review Committee of the Quanzhou First Hospital Afliated to Fujian Medical University for Health Statistics and written informed consent is obtained from participants. The methods used in this article were in accordance with the relevant guidelines and regulations.

Consent for publication
All authors had access to the study data and reviewed and approved the final manuscript.

Competing interests
The authors declare no competing interests.

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