

Comparison of Two EUS-Guided Liver Biopsy Techniques (“Wet Heparin” and “Wet Saline”) For Benign Parenchymal Liver Disease

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Abstract

Background: Endoscopic ultrasound-guided liver biopsy (EUS-LB) has emerged as a viable mean to obtain core tissue. Different wet suction techniques using saline or heparin have been described. We aimed to compare tissue adequacy with the “wet saline” (WS) technique compared to the “wet heparin” (WH) technique.

Methods: We conducted a retrospective review of patients who underwent EUS-LB and Percutaneous liver biopsy (PLB-LB) for benign parenchymal liver disease between May 2017 to October 2019. All procedures were performed at a single tertiary Veterans Affairs Medical Center (VAMC).

Results: A total of 257 biopsies from 217 patients were included. Among the 102 EUS-LB specimens, 53 were obtained using WS technique and 49 were obtained using WH technique. Specimen adequacy was similar in the both groups. Median ASL and length of longest piece did not differ significantly between both groups. Clots were present more frequently in the WS group. Among patients who underwent EUS-LB of both right and left liver lobes, an adequate biopsy was obtained in 85% of patients in the WS group and 96% of patients in the WH group. EUS-LB showed lower risk of post procedural pain and complication rates when compared with percutaneous liver biopsy (PLB). To our knowledge, this is the first study to compare diagnostic accuracy between WH and WS EUS-LB techniques, and to compare post-procedure pain between EUS-LB and moderate sedation PLB. WH-EUS-LB may be preferable to WS because of fewer clots in the specimen. Prospective studies are needed to further verify these findings.

Introduction

Despite the development of non-invasive tests like elastography (e.g. – transient elastography, magnetic resonance elastography) and serum tests, liver biopsy remains the reference standard for evaluating the etiology and severity of parenchymal liver disease^{1,2}. Because diagnosis, grading, and staging of non-neoplastic diffuse parenchymal liver disease is dependent on an adequate sized biopsy, guidelines recommend that the specimens submitted should contain at least 2–3 cm of tissue with at least 11 complete portal tracts (CPTs)¹. Liver biopsy is traditionally performed using a percutaneous or a transjugular approach. Approximately 85% of patients experience pain following percutaneous liver biopsy (PLB), of which 30–50% require analgesic medications, and 1–5% experience pain that is moderate to severe³. An additional disadvantage of PLB is that tissue is obtained from only the right lobe of the liver, so sampling error is a concern. The incidence of abdominal pain is lower with transjugular liver biopsy, but specimen adequacy may be inferior to PLB⁴. With both techniques, if the patient requires an upper endoscopic procedure for a related or unrelated reason, the liver biopsy is performed as a separate procedure.

Endoscopic ultrasound-guided liver biopsy (EUS-LB) has emerged as a viable mean to obtain core tissue⁵.⁶ The technique is an attractive alternative to PLB and TLB for several reasons: in patients undergoing upper endoscopy for a related or unrelated reason, EUS-LB can allow for tissue acquisition during the

same procedure. Unlike PLB or TLB, tissue is obtained under continuous ultrasound guidance, which may in theory reduce risk of bleeding and bile duct injury. Avoiding skin puncture, and avoiding vascular structures and bile ductules in the needle trajectory could potentially reduce post-procedure pain. Given that EUS-LB is a relatively new procedure, the optimal tools and techniques for EUS-LB remain an area of active investigation. With EUS-LB, the goal is not merely to maximize cellularity, but also to preserve tissue architecture. In a randomized trial, EUS-LB using wet suction improved specimen adequacy compared to dry suction techniques⁵. The standard approach to performing wet suction tissue acquisition during EUS-FNA is to “prime” the needle with saline⁷. An alternative approach that potentially reduces blood clot formation within the needle during actuations is to prime the needle with heparin. However, data comparing the two approaches are lacking. Also, there are scant data to assess whether EUS-LB reduces pain compared to PLB.

The primary aim of our study was to compare tissue adequacy with the “wet saline” technique (WS-EUSLB) compared to the “wet heparin” (WH-EUSLB) technique. Additionally, we sought to compare post-procedure complication rates, pain, and analgesia use between wet suction vs. wet heparin EUS-LB, and between EUS-LB vs. PLB.

Methods

We conducted a retrospective review of prospectively maintained databases of patients who underwent EUS-LB and PLB for benign parenchymal liver disease between May 2017 to October 2019. All procedures were performed at a single tertiary veterans affairs medical center (VAMC), which is one of only 6 transplant VAMCs in the United States. The study was approved by the Institutional Review Board (IRB) at the Central Virginia VA Healthcare system.

Patient selection

Patients were included if they underwent EUS-LB or PLB for assessment of benign parenchymal liver disease. We excluded patients who underwent targeted liver biopsy of a mass lesion. We also excluded patients with documented ascites or coagulopathy (platelet count < 50,000 or International Normalized Ratio (INR) > 1.5) within 30 days of the procedure, as these are relative contraindications to EUS-LB and PLB. In order to allow for a meaningful comparison of post-procedure pain between EUS-LB and PLB, we excluded PLB patients if moderate sedation was not utilized.

EUS-LB procedures

EUS-LB procedures were performed using moderate sedation or monitored anesthesia care. An appropriate site for biopsy that was free of intervening intrahepatic bile ducts and vasculature was selected. A 19-gauge Expect fine needle aspiration needle (Boston Scientific, Boston MA) was utilized for all procedures. The stylet was withdrawn and the needle was primed with either heparin (WH) or saline (WS). The needle was inserted approximately 1 cm into the hepatic parenchyma. The ultrasound processor was used to measure distance that the needle could be further advanced for biopsy. Using 20

cc of suction, the needle was rapidly thrust into the hepatic parenchyma up to the previously measured distance, then slowly withdrawn. Fanning technique was used. Three such actuations were performed. The specimen was placed in formalin and sent for histopathology. Among patients who underwent EUS-LB of right and left lobes, tissue from each lobe was placed in separate jars. Following the procedure, patients were monitored in the recovery area for 30 minutes, then discharged if they met the unit's standard criteria. Our general practice was to contact patients approximately a week after the procedure to assess for any post-procedure complications.

PLB procedures

PLB procedures were performed under moderate sedation using fentanyl and midazolam. The skin was prepared with Betadine. The area was isolated with sterile drapes. The skin and subcutaneous tissue was anesthetized with 1ml of 1% of Lidocaine. After medication was administered, and the patient satisfactorily demonstrated breath holding, the biopsy was performed with a 16-gauge Microvasive biopsy device. The specimen was placed in formalin and sent for histopathology. Patients were then rolled onto the right lateral decubitus position. Following the procedure, patients were monitored for 60 minutes, then discharged if they met the unit's standard criteria. Our general practice was to contact patients approximately a week after the procedure to assess for any post-procedure complications.

Pathology interpretation

All specimens were fixed in formalin, embedded in paraffin, and stained with Hematoxylin & Eosin (H&E) and Trichrome. A pathologist who was a study co-investigator was blinded to the liver biopsy technique and to the lobe of the liver biopsied assessed each specimen for each of the following variables: ability to interpret specimen, number of complete portal tracts (CPTs), aggregate specimen length, length of the longest piece, number of small (< 4 mm), medium (5–8 mm), and large (\geq 9 mm) fragments, and amount of clot in specimen. Among the subset of patients with suspected fatty liver disease, the pathologist also assessed disease severity using the validated non-alcoholic steatohepatitis Clinical Research Network (NASH-CRN) semi-quantitative scoring system^{8,9}. The NASH CRN score is a composite of steatosis, lobular inflammation, cytological ballooning, and fibrosis^{8,9}.

Statistical analyses

Baseline variables were summarized using descriptive statistics, i.e. - mean or median for continuous variables, and frequencies or percentages for categorical variables. Mann Whitney test was used to compare number of CPTs, aggregate specimen length, and length of longest piece in the 2 EUS-LB groups. The primary outcome was tissue adequacy between wet-saline and wet-heparin techniques. A biopsy from a single lobe was defined as adequate if aggregate specimen length (ASL) \geq 15 mm, and > 5 CPTs present in sample⁵. We assessed the primary outcome using Fisher's exact test. Based on our review of the literature, we hypothesized that the EUS-LB with WH would yield adequate tissue in 97.5% of passes⁵, and EUS-LB with WS would yield adequate tissue in only 75% of passes. Using a significance level of 0.05 and power of 80%, we calculated that 33 biopsy passes would be required in each group, i.e.

– a total of 72 biopsies would be necessary¹⁰. For the comparison between EUS-LB and PLB, we used Fisher’s exact test to compare: (a) the proportion of patients who reported increase in abdominal pain score post-procedure between EUS-LB vs. PLB, and (b) the proportion of patients who required post-procedure analgesics. We performed logistic regression to assess whether EUS-LB technique (WH vs. WS) was an independent predictor of specimen adequacy when adjusting for baseline variables that differed in the two groups. We also performed logistic regression to assess whether PLB was an independent predictor of pain and analgesia use when adjusting for baseline variables that differed in the EUS-LB and PLB groups

Results

We included 257 biopsies (102 EUS-LB, 152 PLB) from 217 patients (Table 1). Median American Society of Anesthesiologists (ASA) classification was 3 in the EUS-LB group and 2 in the PLB group, $p < 0.001$. Indication for the procedure was suspected fatty liver disease/NASH in 77% of PLB patients and 51% of EUS-LB patients, $p < 0.001$. Other baseline variables were similar between EUS-LB and PLB (Table 1). As expected, since all procedures were performed in a tertiary VAMC, most patients in both the EUS-LB and PLB were male (Table 1).

Table 1
Baseline variables in EUS-LB and PLB patients

| Variable | PLB (n = 152 patients) | EUS-LB (n = 65 patients) | P-value |
|--------------------------|---------------------------|-----------------------------|---------|
| Median Age (years) | 62 | 64 | 0.17 |
| Gender (Males) | 130 (86%) | 56 (86%) | 1.00 |
| Median Body mass index | 33 | 31 | 0.44 |
| Median ASA | 2 | 3 | < 0.001 |
| Indication for procedure | 117 | 33 | < 0.001 |
| Fatty liver/NASH | 35 | 32 | |
| Other | | | |

Among the 102 EUS-LB specimens, 53 were obtained using WS technique and 49 were obtained using WH technique; 60% of patients underwent EUS-LB of both left and right liver lobes. Between the WH and WS groups, there was a statistically significant difference in the proportion of males (98% WS vs. 68% WH, $p < 0.001$) and median body mass index (31 WS group vs. 33 WH, $p 0.03$) (Table 2). Other baseline variables were similar between WH and WS patients.

Table 2
Baseline demographics between between wet saline (WS) vs. wet heparin (WH)
Endoscopic ultrasound guided-liver biopsy (EUS-LB)

| Variable | Wet saline EUS-LB (n = 40 patients) | Wet heparin EUS-LB (n = 25 patients) | P-value |
|---|--|---|---------|
| Median Age (years) | 64 | 62 | 0.12 |
| Gender (Males) | 39 (98%) | 17 (68%) | 0.001 |
| Median Body mass index | 31 | 33 | 0.03 |
| ASA classification | 3 | 3 | 0.96 |
| Indication for procedure | 21 (53%) | 14 (56%) | 0.80 |
| Fatty liver/NASH | 19 (47%) | 11 (44%) | |
| Other | | | |
| ASA American Society of Anesthesiologists | | | |

For the primary outcome, specimen adequacy was similar in the two EUS-LB groups (81% WS vs. 84% WH, P-value = 0.8). Median ASL and length of longest piece did not differ significantly between WS and WH groups (Table 3). EUS-LB technique was not an independent predictor of specimen adequacy even when adjusting for body mass index (OR 0.3, 95% confidence interval 0.03, 3.33). Clots were present more frequently in the WS group; large clots were present in 53% of WS specimens but only 18% of WH specimens, $p < 0.0001$ (Table 3). Only 1 patient in the WS group and none in the WH group reported increase in abdominal pain compared to baseline after the procedure. The patient was admitted for observation and discharged the following day. There were no other adverse events.

Table 3

Comparison of study outcomes between wet saline (WS) vs. wet heparin (WH) Endoscopic ultrasound guided-liver biopsy (EUS-LB)

| Variable | Wet saline EUS-LB (n = 53) | Wet heparin EUS-LB (n = 49) | P-value |
|--|-------------------------------|--------------------------------|----------|
| Adequate ¹ | 43 (81%) | 41 (84%) | 0.80 |
| Number of CPTs | 13 (2–45) | 11 (1–48) | 0.19 |
| Large clots in specimen | 28(53%) | 9(18%) | < 0.0001 |
| Any clot (large or small) | 37(70%) | 23(47%) | 0.03 |
| ASL | 40 (10–95) | 43 (5-112) | 0.16 |
| Length of longest piece (mm) | 8 (2–24) | 10 (3–27) | 0.19 |
| Number of small fragments (< 5 mm) | 14 | 8 | |
| Number of medium fragments (5–8 mm) | 2 | 1.5 | |
| Number of large fragments (\geq 9 mm) | 0 | 1 | |
| NAS | 1 | 2 | |
| *Aggregate specimen length (ASL) of at least 15 mm, and at least 5 complete portal tracts (CPTs); NAS Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis score | | | |

Among patients who underwent EUS-LB of both right and left liver lobes, number of CPTs did not significantly between the two groups (24 WS, 26 WH) but ASL was significantly higher in the WH group (74 mm WS vs. 97 mm WH, p 0.02). It should be noted however, that in both groups, with dual lobe biopsy the ASL and number of CPTs far exceeded the thresholds recommended by the AASLD (ASL \geq 2 cm, \geq 11 CPTs). Among patients who underwent dual lobe EUS-LB, an adequate biopsy as defined by the AASLD was obtained in 85% of patients in the WS group and 96% of patients in the WH group, p 0.28. A discrepancy in non-alcoholic steatohepatitis (NAS) score between right and left lobes was noted in 5/33 (15%) patients undergoing EUS-LB for suspected NAFLD. Discrepancy was for lobular inflammation in 4 patients, and ballooning in 1 patient.

In the PLB group, 12/152 (8%) reported increase in immediate post-procedure pain. Eight patients (5%) required analgesics for post-procedure pain. One patient in the PLB developed a gallbladder hematoma that was managed conservatively. Although the percentage of patients experiencing immediate post-procedure pain and analgesics was higher in the PLB group compared to EUS-LB, these results were not statistically significant (Table 4). On logistic regression, neither LB technique (PLB vs. EUS), ASA classification, nor indication for procedure were independent predictors of post-procedure pain (Table 5).

Table 4
Comparison of pain, analgesic use, and complication rates between EUS-guided liver biopsy (EUS-LB) and percutaneous liver biopsy (PLB)

| | EUS-LB (n = 65) | PLB (n = 152) | p-value |
|------------------------------------|----------------------------------|--------------------------------|----------------|
| Increase in pain post proc | 1 (2%) | 12 (8%) | 0.12 |
| Analgesics for pain post-procedure | 1 (2%) | 8 (5%) | 0.29 |
| Complications requiring admission | 1 (1%) | 1(2%) | 0.51 |

Table 5
Logistic Regression assessing Predictors of post-procedure pain

| Predictor | Odds Ratio | 95% Confidence Interval |
|-------------------------------------|-------------------|--------------------------------|
| ASA \geq 3 | 0.5 | 0.1, 2.3 |
| Suspected NALFD indication | 1.7 | 0.2, 15 |
| Percutaneous liver biopsy technique | 5.8 | 0.7, 49 |

Discussion

EUS-LB is increasingly accepted as a viable means to obtain tissue suitable for histopathologic analysis. Yet, techniques that can optimize yield without increasing risk of complications are not yet fully understood. Consistent with previously published studies, our real-world experience demonstrates that EUS can provide an adequate sample in most patients. A single biopsy from one lobe provided a specimen that met AASLD criteria for tissue adequacy in > 50% of cases¹. When two biopsies were obtained (one right lobe, one left lobe) an adequate specimen was obtained in > 85% of patients. With dual lobe EUS-LB using WH technique, an adequate specimen was obtained in 96% of patients. With dual lobe EUS-LB using WH, median ASL (97 mm) and CPTs (26) far exceeded recommended thresholds for adequacy. As hypothesized, there were significantly fewer clots in the WH specimen. Substituting saline for heparin did not appear to increase risk of complications. Additionally, NAS between right and left lobes differed in 15% of patients. Our study therefore suggests that obtaining a single biopsy from the right lobe and a single biopsy from the left lobe using WH technique is the optimal EUS-LB approach.

In 2016, our group instituted a novel protocol for PLB, whereby patients receive moderate sedation with fentanyl and midazolam. With moderate sedation PLB, patients are currently discharged within an hour post-procedure. In our study, rate of post-procedure pain was relatively comparable between PLB with moderate sedation and EUS-LB. However, at most institutions in the United States, topical analgesia and a 2- to 4-hour recovery is typical for PLB. In these settings, EUS-LB could improve turnover and patient satisfaction¹¹.

In our study, EUS-LB was performed using a standard 19-gauge fine needle aspiration (FNA) needle. This needle size was chosen because available evidence to date suggested that diagnostic yield of a 19-gauge needle was superior to standard 22-gauge needles and 22-gauge core biopsy (FNB) needles. Recently, 19-gauge fork-tip and franseen FNB needles have become commercially available. In a large retrospective study using fork-tip and franseen FNB needles, Nieto and colleagues reported post-procedure abdominal pain occurred in 17% of patients¹². Hasan et al reported 100% specimen adequacy when three biopsies were obtained using a 22-gauge FNB needle, but post-procedure pain occurred in 15% of patients¹³. Thus, until head to head comparative trials are available, our results suggest that a single biopsy from the right lobe and one from the left lobe using a standard 19-gauge FNA needle primed with heparin may offer the optimal balance of cost (FNB > FNA), time (3 biopsies take longer than 2 biopsies), and possibly post-procedure pain.

To our knowledge, this is the first study to compare diagnostic accuracy between WH and WS EUS-LB techniques, and to compare post-procedure pain between EUS-LB and moderate sedation PLB. Our data documenting improved turnover and a relatively low incidence of post-procedure pain by using moderate sedation for PLB are also not previously described. Yet, our results must be interpreted in the context of certain limitations. Data were obtained retrospectively, and the decision to perform WH vs. WS EUS-LB was at the discretion of the endoscopist. More WS cases were performed earlier in our experience which could bias results in favor of WH EUS-LB. Because procedures were performed at a tertiary VA medical center, most patients were male, so our results may not generalize to centers with a higher proportion of females. Our sample size for dual lobe EUS-LB was relatively small, so we could not perform meaningful comparisons between dual lobe WH and WS. Finally, most EUS-LB cases were performed using monitored anesthesia care while PLB was performed with moderate sedation.

In conclusion, both WS and WH techniques can offer high rates of specimen adequacy with low rates of pain and other post-procedure complications. WH-EUS-LB may be preferable to WS because of fewer clots in the specimen. Use of moderate sedation during PLB not only reduces turnover time, but also reduces post-procedure pain to levels comparable with EUS-LB.

Declarations

Conflict of interest

All authors declare that they have no conflict of interest.

Ethical approval and informed consent

The study was approved by the Institutional Review Board (IRB) at the Central Virginia VA Healthcare system.

Data Availability:

The data is available upon request

Animal research (Ethics):

Not applicable.

Consent to participate (ethics)

The study was approved by the Institutional Review Board (IRB) at the Central Virginia VA Healthcare system.

Consent to publish (ethics)

The study was approved by the Institutional Review Board (IRB) at the Central Virginia VA Healthcare system

Plant Reproducibility:

Not applicable.

Clinical Trials registration:

Not applicable.

Authors contribution:

HS, MF and TS were involved in concept design. HS, TA, RH and SS were involved in data collection. RL was involved in interpretation of pathology data. PP and PM were involved in statistical analysis. HS and TL wrote the entire. All authors revised the manuscript, edited as needed and approved the final draft.

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