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Pain in percutaneous liver core-needle biopsy: a randomized trial comparing the intercostal and subcostal approaches

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Abstract

Purpose: Effective pain control during and after percutaneous core needle liver biopsy is important with regard to ethical considerations and patient comfort. In this randomized double-blind study, we compared post-biopsy pain in the patients undergoing liver core-needle biopsy using either subcostal or intercostal approaches.
Methods: All patients referred for ultrasound-guided CNLB between July 2017 and January 2018 to our interventional radiology department were randomized into two groups. Biopsy was performed through intercostal approach in the first group and through subcostal approach in the second group. The intensity of pain 0, 2, and 4 h after the procedure was compared in two groups using a 100-mm visual analogue scale. All biopsies were performed without procedural IV sedation. If patients' discomfort demanded administration of IV analgesics during or after the procedure, then the patients were excluded from the study.
Results: In patients without routine procedural IV sedation, there was no significant difference in the pain level between the intercostal and subcostal groups immediately after the procedure ($p = 0.055$), but we found a significant difference in the pain level between the two groups 2 (7.5 mm, $p = 0.001$) and 4 (2 mm, $p = 0.001$) h after the procedure.
Conclusion: The minimum amount of change in the VAS score that is considered clinically important is 13 mm on a 100-mm scale. Pain differences at 2 and 4 h in the two groups in this study were statistically but not clinically significant. Therefore, the authors suggest the use of subcostal route for ultrasound-guided liver biopsy whenever possible, but the results do not warrant the routine use of post-procedure analgesics in whom biopsy is performed via intercostal route.

Key words: Image-guided biopsy—Pain—Ultrasonography

Despite recent advances in imaging modalities and the introduction of various MRI protocols for evaluating the liver parenchyma, core-needle liver biopsy (CNLB) still remains the gold standard for diagnosing focal and parenchymal liver diseases [1–3]. As an invasive procedure, it is associated with complications, among which, the most common are pain, hemorrhage, and pneumothorax [4]. Pain after CNLB is commonly mild and controllable and therefore has been ignored in numerous studies that have evaluated procedure-related complications of CNLB. However, effective pain control is important with regard to ethical considerations and patient's comfort. Patients' comfort during the procedure is of great importance, as their cooperation is needed should there be need for the procedure to be repeated. Pain is a known complication of CNLB and the most common cause of discomfort after the procedure [5]. The pain is usually at the biopsy site, sometimes radiating to the right shoulder. It is usually dull, mild, and brief in nature. Apart from frank trauma, adjacent organ injury, and severe bleeding, the mechanisms of prolonged post-biopsy pain are still debated [5, 6]. It is believed to be a nociceptor pain that originates from skin and liver capsule innervations [7]. The intensity of pain experienced during and after CNLB in the literature varies significantly, ranging from 1 to 50% of patients experiencing moderate to severe pain [5, 8, 9]. Pain is a subjective feeling with a complex nature, which complicates the study. The prospective assessment of pain in ultrasound-

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guided CNLB has rarely been addressed in the literature. Various factors have been reported to influence pain in ultrasound-guided CNLB; the operator's experience, patients' age and sex, type and dosage of preoperative analgesics, route of biopsy, and the size and type of needles so far have been suggested to cause pain, but the data available remain inconclusive [10–12].

Selecting the safest route is a major concern of any interventional radiologist while performing ultrasound-guided core-needle biopsy. The access route should be far from vital organs and should avoid unwanted transgression of adjacent structures. Two major approaches for performing CNLB are passing the needle through the intercostal and subcostal spaces. These two approaches are not necessarily applicable in all patients; downward displacement of liver as a result of lung hyperinflation makes the former route unavailable. In some cases, a distended transverse colon can render the latter dangerous. It has been suggested that the subcostal approach may result in less pain, as the intercostal nerves and muscles are not injured, and may be advisable in patients in whom it is applicable [13], but the supporting data are insufficient. In this randomized double-blind study, we compared post-biopsy pain in the patients undergoing CNLB using either of these two approaches.

Methods

Study settings

This clinical trial was approved by the Institutional Review Board with the approval number of 940539. The main objective was to compare the pain level based on the Visual Analogue Scale (VAS) in patients undergoing CNLB through subcostal access with those undergoing CNLB through the intercostal route.

Patient selection

All patients referred for ultrasound-guided CNLB between July 2017 and January 2018 to our interventional radiology department, which is located in a tertiary-level academic hospital, were possible candidates for the study. Inclusion criteria include patients older than 18 years with a normal coagulation profile. Exclusion criteria include patients with platelet level lower than 70,000/mL and International normalization ratio (INR) > 1.5, severe ascites, and bile duct dilatation. As it is proposed that culture shapes many aspects of the experience of pain [14], we excluded non-Iranian patients from the study to make this trial as controlled as possible. Also excluded were patients in whom biopsy was possible with only one of the two examined approaches and randomization was not possible. All patients were provided with an information sheet and written informed consent was obtained. Patients were randomly assigned to the intercostal (IC) (n = 60) or subcostal (SC) (n = 60) group. The sample size was calculated to achieve 80% power to detect a 0.6 standard deviation difference in the visual analogue score with an alpha of 0.05.

Randomization

The patients were randomized into two groups. Biopsy was performed through the intercostal approach in the first (IC) and through the subcostal approach in the second (SC) group.

The coagulation profile was verified twice in each patient before admitting them for ultrasound-guided CNLB. A randomized sequence of codes was prepared using a web-based randomization platform. The codes were placed in pockets and organized in a sequence. For each patient, a pocket was opened, and the approach was determined according to the assigned code. The patient, radiology resident who evaluated the pain, and statistical analyzer were blind to the procedural approach, but the interventional radiologist who performed the procedure was inevitably aware of the approach used.

Procedure

All procedures were performed under cardiac monitoring in sterile conditions and with local anesthesia using 10 mL of a 2% lidocaine (LIGNODIC; Caspian Tamin Pharmaceutical Co.) solution with a 25G needle. The anesthetic agent was injected from the subcutaneous tissue to the liver capsule. No intravenous sedation was administered (unless the patient expressed severe pain at the beginning of the procedure, in which case intravenous analgesics were administered and the subject was excluded from the study).

Biopsy was performed in the left lateral position in the first and in supine position in the second group. A skin nick was performed with a number 11 blade, followed by passing a semi-automated, 16G biopsy needle (BARD MISSION^{TM}) from the skin to the liver with the free-hand method. The needle was passed through the liver only once for each patient, and the depth of penetration into the liver before performing the biopsy was about 1 cm. All procedures were performed by a single interventional radiologist with 15 years of experience. Following the procedure, a simple dressing was applied on the skin incision and the patients were kept under observation for 4 h (with regular control of vital signs). If there was a severe pain, IV analgesics were administered (Pethedine, IV, 25 mg) (Caspian Tamin Pharmaceutical Co.) and the recording of relevant data was stopped.

Pain assessment

The pain level was evaluated using the VAS at the time of biopsy and 2 and 4 h later. VAS is a 100 mm line that is grade at 1 mm intervals. The line has two endpoints: one representing the "no pain at all" limit and the other representing "pain as bad as it could be" limit. The patients were asked to mark the intensity of their pain experienced. Pains at 0, 2 and 4 h were marked on separate VAS scales to prevent possible biases. Before starting the procedure, all patients were taught by a physician how to mark the VAS scale.

The primary outcome of this study was to compare the pain immediately after the procedure and 2 and 4 h later in patients who underwent ultrasound-guided CNLB with either the intercostal or the subcostal approach.

Statistical analysis

Statistical analysis was performed using student's t test or one-way ANOVA and multiple regression analysis. The statistical software SPSS^{TM} version 21 (IBM Corp., Armonk, NY) was used for data analysis. Pearson's statistical test was used to evaluate the correlation between quantitative variables. $p < 0.05$ indicated statistical significance. Student's $t$est and Mann–Whitney tests were used to compare the means between groups.

Results

Of the 176 patients referred to our interventional radiology clinic for ultrasound-guided CNLB, 120 were selected to participate in the study. All patients met the inclusion criteria. Four patients in the intercostal group complained of severe pain during the procedure and received intravenous analgesics. Two patients in each group received intravenous analgesics during the first 2-h period after the procedure. These patients were excluded from the study from the time of IV analgesic administration. The flowchart of participant selection is summarized in Fig. 1. Eventually, the pain was evaluated immediately after the procedure and 2 and 4 h later in 54 patients in the intercostal and 58 patients in the subcostal group. The demographics and clinical characteristics of the patients in each group are summarized in Table 1.

The primary outcome of the study was pain level, which was evaluated using the VAS 0, 2, and 4 h after the procedure and was analyzed using Mann–Whitney U test. The median VAS scores (inter-quartile range) immediately after the procedure and 2 and 4 h later are summarized in Table 2. Six patients in the intercostal group (10%) and two patients in the subcostal group (3.33%) required intravenous analgesic administration within the first 4 h after the procedure (p value = 0.08, Mann–Whitney test); these were excluded from the final analysis. Due to the small number of patients excluded due to IV analgesics administration, no other statistical analyses were performed further. Figure 2 shows the graphical representation of the dynamic course of pain in these two groups.

There was no significant difference in the pain level between male and female patients. There was no significant difference in the pain level between the intercostal and subcostal groups immediately after the procedure ($p = 0.055$), but we found a significant difference in the pain level between the two groups 2 ($p = 0.001$) and 4 ($p = 0.001$) h after the procedure.

We also found no significant correlations between patient age and pain level at 0 ($p = 0.936$), 2 ($p = 0.285$), and 4 ($p = 0.617$) h postoperatively.

There was no significant difference in the pain level between patients who underwent parenchymal biopsy and those who underwent biopsy of a focal liver lesion.

Discussion

Liver biopsy is an essential procedure in evaluating acute and chronic parenchymal liver diseases [15]. Pain is the most common cause of patients' discomfort after CNLB. It is a subjective feeling and very difficult to evaluate objectively. Besides, it has a very complex nature that makes it difficult to be fully understood. Despite various studies, the variables that influence the intensity of pain during CNLB are still uncertain [5] We conducted a randomized, double-blind study to evaluate the pain level in patients undergoing ultrasound-guided CNLB either through the intercostal or the subcostal routes. The results showed that the immediate post-procedural pain level was not significantly different between the two groups, but there was a significant difference at 2 and 4 h postoperatively. The lack of significant difference in the pain level between the two groups immediately after the procedure may be attributable to the effects of local sedation. However, pain was most intense immediately after the procedure and gradually decreased in both groups (Fig. 2). In a similar study by Tan et al., the authors found no significant difference in the VAS score between the two groups, and did not show any difference in the analgesic requirements [5]. We believe that the observed discrepancy between Tan's study and ours is due to the procedural sedation used in the former. Tan et al. administered midazolam and fentanyl to all patients before the procedure, and this may explain why they did not find any significant difference in the VAS score between the two groups. Based on our results, pain dissipated faster with the subcostal, rather than the intercostal, approach within the first 2 h postoperatively. This may be due to irritation of the intercostal nerves or injury to the intercostal muscles, which are constantly active during respiratory movements, in the first group. Another explanation may be the greater possibility for

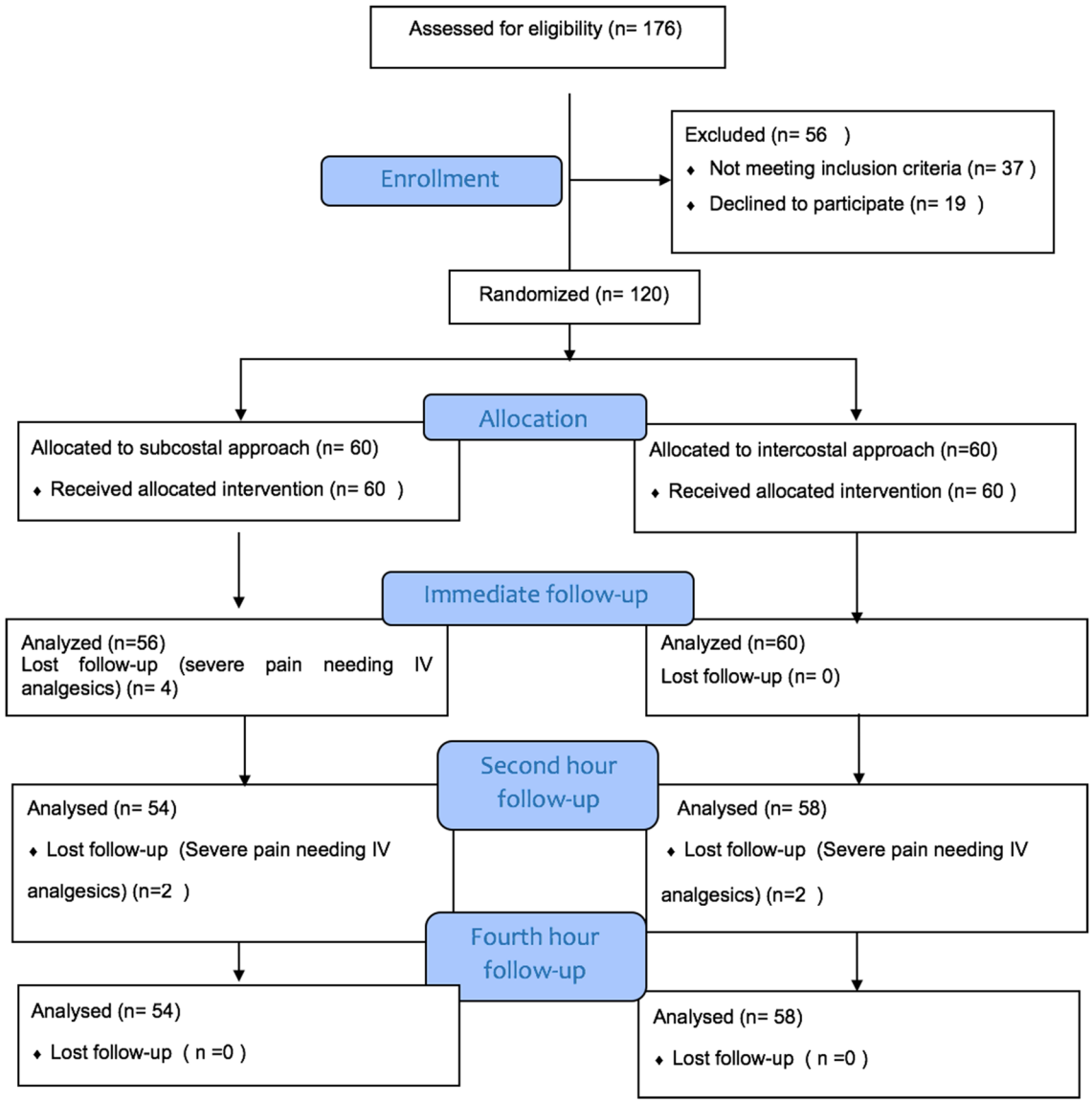

Fig. 1. The flowchart of participant selection.

Table 1. Demographics of patients undergoing ultrasound-guided CNLB

Characteristic	Intercostal $n = 54$ (48.2%)	Subcostal $n = 58$ (51.8%)	p value
Age ± SD	52.09 ± 12.7	49.8 ± 11.85	NS (0.346)
Sex ratio (female/male)	27/27	39/19	NS (0.65)
previous liver biopsy	5 (9%)	6 (10%)	NS (0.849)
Focal liver mass/Parenchymal disease	11/43	14(/44	NS (0.636)

CNLB, core-needle liver biopsy; SD, standard deviation; NS, not significant

subcutaneous hemorrhage in the first group, as there is a greater risk for intercostal-vessel damage. According to these findings, it is advisable to favor the subcostal approach whenever possible. VAS is a validated and recommended method for evaluating the intensity of pain and provides a method for objective evaluation of pain [16]. But it should be noticed that the minimal change in VAS that is considered clinically important is 13 mm on a 100 mm scale and any change less than 13 mm may be statistically, but not clinically, significant [17]. Although the difference in the VAS scores between the two groups in this study was statistically significant, the observed

Table 2. Reported pain after liver biopsy

	Intercostal group	Subcostal group	*p* value	Male patients	Female patients	*p* value	Parenchymal CNLB	CNLB for focal lesion	*p* value
Number	54	58		46	66		87	25	
Immediate pain*	16 (4.75–31.2)	12 (2–18)	0.055**	12 (3–23)	15 (3–31)	0.615**	15 (3–26)	13 (3–32)	0.889**
2-h pain*	9.5 (2–26)	2 (1–5.2)	0.001**	3 (1–14)	5 (1–13)	0.647**	3 (1–14)	4 (1–12)	0.894**
4-h pain*	3 (1–11)	1 (0.0–2.2)	0.001**	1 (0–7)	2 (0–6)	0.362**	2 (0–8)	1 (0–3)	0.134**
Anxiety level+	45.09 (9.57)	40.60 (10.06)	0.017++	39.59 (9.10)	44.98 (10.12)	0.004++	42.59 (10.60)	43.40 (7.93)	0.68++

CNLB, core-needle liver biopsy
*Reported as the median score [inter-quartile range]
**Mann–Whitney *U* test
+Reported as mean (standard deviation)
++Student's *t* test

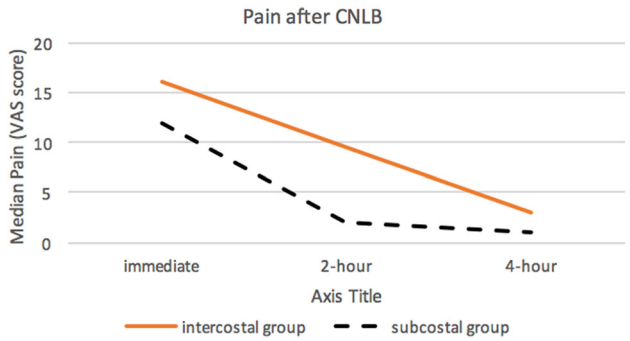

Fig. 2. Pain dissipation after percutaneous core-needle liver biopsy.

median VAS score difference at 2 h and 4 h (7.5 mm and 2 mm, respectively) may not be considered clinically significant and does not warrant routine administration of postoperative analgesics in the IC group.

Another noticeable finding was that the mean pain level in our study was 17.86 that is considerably lower than that reported in other studies. In the study by Eisenberg et al. [9], the mean pain level was 42. The analgesics protocol for this study was 5 mg diazepam (per os) 1 h before the procedure and all biopsies were performed with a 16G Trucut needle. In a study by Cadranel et al. [8], the mean pain level was 28. The lowest pain level after CNLB was reported by Castera et al. [6] who used an inhalation mixture of nitrogen oxide and oxygen for sedation and performed all biopsies with the aspiration technique and a needle with 1.8 mm diameter. In this study, all subjects received 10 mL of subcutaneous 2% lidocaine solution as a preoperative analgesic. Routine use of a 2% analgesic solution may be a possible cause of the lower level of pain in our patients, as numerous other studies had used 1% lidocaine solution for analgesia. In the present study, an experienced interventional radiologist performed all procedures with ultrasound guidance and carefully anesthetized the entire area from the subcutaneous tissue to the liver capsule. Although this issue remains debatable [18], the operator's experience could have a significant effect on the pain experienced by the patients. When the procedure is performed by an inexperienced operator, liver capsule infiltration may be insufficient or the biopsy needle may enter a different route than the anesthetized one. We also excluded eight patients who required intravenous analgesic administration within the first 4 h. Although the number of excluded patients was low, it may have influenced the medial VAS score reported in this study.

Despite the findings reported by Eisenberg et al. [9], we did not find a significant difference in the pain level between men and women. We also did not find a significant difference in the pain level between patients undergoing parenchymal and those undergoing focal-mass biopsy. Therefore, the only significant influencing factor affecting pain in this study was the approach used for the procedure.

The subjective nature of pain is a limitation in this study. As pain perception is a subjective and complex entity, we assume that the lower level of pain reported in this study may also be in part associated with ethnic and cultural differences [10].

Considering the limited number of patients as another limitation, we suggest that the same study should be applied prospectively to a large number of patients to verify its validity and evaluate its generalizability.

In conclusion, we found a statistically, but not clinically significant difference in the pain level 2 and 4 h postoperatively between patients undergoing CNLB via the intercostal or subcostal route. Based on this finding, we do not suggest routine administration of postoperative analgesics when either of these two approaches is used for CNLB.

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Compliance with ethical standards

Funding This randomized, parallel, double-blind study was approved by the Chancellor for Research of Mashhad University of Medical Sciences, Mashhad, Iran. The registration code of IRCT20180106038249N1 was assigned to this trial.

Conflict of interest The authors declare no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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