Assessment of Pain Severity after Radiofrequency Ablation in Patients with Hepatocellular Carcinoma

Araya Ongiem BNS*,
Arunotai Siriussawakul MD*, Aungsumat Wangdee BNS*,
Saowanee Homsud BNS**, Tassanee Jaiyen BNS*

** Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Nursing Division, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To find the incidence of moderate to severe pain after percutaneous radiofrequency ablation (RFA) in patients with hepatocellular carcinoma and to identify the factors affecting unwanted pain scores.*
Material and Method: *This prospective study was conducted on patients who underwent percutaneous radiofrequency ablation under intravenous sedation and local anesthesia. The pain scores were obtained from 18 to 24 hours after the procedure. Moderate to severe pain was defined as a value of 4 or more on the Numeric Rating Scale (NRS). Data on patients' factors, tumor characteristics, procedural factors, anesthetic management, postoperative treatment and perioperative complication was collected.*
Results: *A total of 190 patients were enrolled, comprised of 134 men (70.5%) and 56 women (29.5%). The mean age of the patients was 63.3±11.1 years. The incidence of moderate to severe pain on movement (an NRS value equal to or greater than 4) was 11.6% (22 out of 190 patients). A univariate analysis revealed that two factors - patients with multiple tumors (more than two tumors), and an ablation time of greater than 30 minutes - seemed to be related to an NRS equal to or greater than 4. Nevertheless, after entering those two factors into a multiple regression model, neither factor was associated with the moderate to severe pain scores.*
Conclusion: *The incidence of undesired pain scores after percutaneous radiofrequency ablation in our institution was around 10%, and the rate of complication was very low.*

Keywords: *Postoperative pain, RFA liver, Hepatocellular carcinoma*

J Med Assoc Thai 2016; 99 (5): 572-7
Full text. e-Journal: *http://www.jmatonline.com*

Mortality rates from hepatocellular carcinoma (HCC) have increased substantially over the past two decades. Hepatocellular carcinoma was the leading cause of death for males and the fifth for females, and it is predicted to increase further to a plateau in 2015-2020[1]. The rising prevalence of obesity and diabetes could be a contributing factor for the rising incidence of HCC in Thailand[2]. Surgical resection offers the only chance for curative treatment and long-term survival after hepatic resection; Shimozawa et al reported that the 3-, 5-, and 10-year disease-free survival rates were 49%, 30%, and 8%, respectively[3]. However, only 20% of patients with HCC are suitable candidates for surgery. Percutaneous radiofrequency ablation (RFA) is an alternative treatment for otherwise inoperable liver tumors. Electrodes are inserted percutaneously into the tumor, and a current is applied to generate local heating and thereby destroy tissue. However, the heat destroying the tumor through the application of the radiofrequency current causes pain and discomfort for patients, and they cannot tolerate the procedure. Sedation with either a local anesthesia or a general anesthesia has been provided to patients in order to complete the ablation. Post procedural pain may persist for several days. Identifying the risk factors for post procedural pain would help anesthetic personnel to provide optimal pain management for the target population.

Currently, information on post operative pain after RFA is scant. A few studies have described periprocedural pain in detail. Lee et al reported intra-procedural pain and postoperative pain in patients who had undergone RFA under conscious sedation with intravenous pethidine and local anesthesia.

Correspondence to:
Siriussawakul A, Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4197990, Fax: +66-2-4113256
E-mail: arunotai.sir@mahidol.ac.th

Supplemental opioids were administered to 22.8% of the patients within the 24-hour, postoperative period. Possible factors related to periprocedural pain were large tumor size, previously untreated tumors, tumors adjacent to the parietal peritoneum, multiple ablations, and a long duration of the ablation[4]. Hori et al also reported that a long ablation was associated with severe pain, with 14.1% of the 99 patients requiring a supplemental dose of analgesic drug within the 24-hour, postoperative period[5]. The incidence of intense pain after RFA reported by Hsieh et al was 38.2%. The higher level of the pain scores was related to general anesthesia, postoperative nausea vomiting, and abnormal blood test results[6].

We conducted this prospective study with two objectives. Firstly, to ascertain the incidence of moderate to severe pain of post percutaneous RFA in patients with hepatocellular carcinoma, and secondly, to determine the factors affecting unwanted pain scores.

Material and Method

This prospective, cohort study was reviewed and approved by the Institution Review Board of the Faculty of Medicine, Siriraj Hospital. Informed consents were obtained from all participants. The inclusion criteria were adult patients (aged >18 years) who had been diagnosed with hepatocellular carcinoma, and who were to be treated with radiofrequency ablation. Those patients who were not able to communicate or cooperate well were excluded.

Anesthetic protocol

Standard monitors, including a non-invasive blood pressure monitor, an electrocardiograph, and a pulse oximeter, were used. Patients were placed in a supine or a lateral position, depending on the tumor's location. All patients received supplemental oxygen via an oxygen cannula or an oxygen face mask. Around 5-10 ml of 2% lidocaine was provided by a percutaneous injection from the skin to the liver capsule along a specified insertion route. A radiologist measured the distance between the middle point of the largest tumor and the parietal peritoneum. Subsequently, all patients were sedated with midazolam, propofol and narcotics, aiming for moderate to deep sedation levels, which were at the discretion of an anesthesiologist and the radiologist. Whenever patients complained of intolerable pain during the ablation, additional doses of narcotics and propofol were administered. Following the ablation procedure, all patients were transferred to the post anesthetic care unit (PACU) and observed for one to two hours. Intravenous pethidine, ordered by the radiologist, was administered for postoperative pain control. The discharge from the PACU was based on stable vital signs, the Numeric Rating Scale (NRS) $\leq$3, and no evidence of surgical bleeding.

Outcomes

The primary outcome of our study was the proportion of patients who reported moderate to severe pain, defined as an average NRS value of 4 or higher. Under the NRS, the severity of pain intensity is classified as follows: 0 = no pain, 1-3 = mild pain, 4-7 = moderate pain and 8-10 = severe pain. The patients' pain scores were collected by a research nurse within 24 hours of the ablation procedure. As for the secondary outcomes, six possible factors were associated with moderate to severe pain: tumor size (>3 cm; 3-4 cm; >4 cm); the number of tumors; first time treatment with RFA; the distance between the tumor and the parietal peritoneum (<2 cm; >2 cm); multiple ablation sessions (<10; >10); and the duration of the ablation (<30 minutes; $\geq$30 minutes). Other outcomes collected were the additional types of narcotics employed for postoperative pain control; the non-pharmacological methods utilized to relieve pain; any periprocedural adverse events (respiratory depression, nausea, vomiting, urinary retention); and patient satisfaction with the postoperative pain management.

Statistical analysis

The sample size was based on information from a literature review, which reported that around 23% of patients who underwent RFA required additional doses of narcotics during the 24-hour, postoperative period[4]. To obtain a 95% confidence interval (CI) of 6%, a sample of 189 subjects was required. Regarding the second objective, around 130 to 260 patients were needed to identify the possible factors of moderate to severe pain after RFA.

Descriptive statistics were used to examine the incidence of moderate to severe pain after RFA; the number of adverse events; and the patients' demographics, such as gender, age, co-existing diseases and medications. The Pearson Chi-square test or Fisher's exact test, as appropriate, was used to examine all categorical risk factors in a univariate analysis. Factors with *p*-value less than 0.20 in the univariate analysis were then entered into a multiple logistic regression model of moderate to severe pain. A statistical analysis was conducted using the software

program, SPSS (version 18, SPSS Inc., Chicago, Illinois, USA). Data were presented as mean ± standard deviation (SD), number (percent), median (minimum, maximum), and adjusted odds ratios (95% CI), as appropriate. The $p<0.05$ was considered to indicate statistically significant differences.

Results

190 patients were enrolled between September 13, 2011 and July 8, 2013. Most were male (70.5%), with an average age of 63.3. Almost patients (96.3%) had a coexisting disease, the most common being diabetic mellitus and hypertension. Most cases of HCC were secondary to a viral hepatitis infection, with hepatitis A, B, and C rates of 0.8%, 61.9%, and 37.3%, respectively. The severity of cirrhosis was classified using the Child-Pugh score, with class A, B and C being 80.0%, 16.8%, and 3.2%, respectively. Around one-third of patients had a recurrent tumor, and almost all patients (98.4%) had been treated with RFA before this admission. Besides RFA, enrolled patients had been previously treated by percutaneous transarterial oily chemo-embolization (TOCE), transarterial chemo-embolization (TACE), percutaneous ethanol injection (PEI), hepatectomy, or wedge resection (Table 1).

All patients were sedated to moderate or deep levels with an intravenous continuous infusion propofol, and/or an intermittent dose of midazolam, fentanyl, pethidine, or ketamine. The median ablation time was 30 minutes (minimum: 5 minutes; maximum: 180 minutes), and the median ablation session was 4 (minimum; 1 session; maximum: 20 sessions). The median anesthetic time was 75 minutes (minimum: 15 minutes; maximum 215 minutes).

The pain scores were collected between 18 and 24 hours after the RFA procedure. Moderate to severe pain occurred in 22 patients (11.6%). The pain scores were asked both when patients experienced pain on movement, and while at rest. The data are at Table 2. Six factors which were probably associated with an NRS ≥4 were included in the univariate analysis and the multiple logistic regressions analysis. In the case of the univariate analysis, patients with multiple tumors (odds ratio (OR) 5.5, 95% confidence interval (CI) 0.87, 34.92, $p = 0.071$) and an ablation time >30 minutes (OR 2.07, 95% CI 0.82, 5.19, $p = 0.122$) seemed to be related to an NRS ≥4. However, after entering those factors into a multiple regression model of an NRS ≥4, neither factor was associated with moderate to severe pain (Table 3).

Most patients did not require an additional dose of analgesic drug during the post procedural period. However, 31 patients (16.1%) received supplemental doses of paracetamol, tramadol or pethidine. Non-pharmacological methods which could alleviate pain were used with seven patients (4.7%). The methods were reading books, listening to music, and watching television. As for adverse events, there was minimal pneumothorax in four patients, suspected aspiration pneumonia in one obese patient, and nausea and vomiting in six patients. All patients had improved after treatment within 24 hours of the procedure. Satisfaction scores for pain management after the

Table 1. Demographic data of 190 patients

Variables	Mean ± SD or Number (%)
Age (years)	63.3±11.1
Gender; male: female	134 (70.5): 56 (29.5)
Body mass index (kg/m^2)	25.0±4.4
Hypertension	80 (42.1)
Diabetes mellitus	75 (39.5)
Cirrhosis	125 (66.8)
Viral hepatitis	126 (66.3)
Recurrent tumor	52 (27.4)
Number of RFA treatments	
Never	3 (1.6)
1	128 (67.3)
2	40 (21.1)
3	15 (7.9)
4	4 (2.1)
Treated tumor	124 (65.3)

SD = standard deviation; kg/m^2 = kilogram/meter^2; RFA = radiofrequency ablation

Table 2. Data of post-procedural pain scores

Pain score	Number of patients (%)	
	At rest	On movement
0	112 (58.9)	81 (42.6)
1	38 (20.0)	38 (20.0)
2	15 (7.9)	27 (14.2)
3	20 (10.6)	22 (11.6)
4	1 (0.5)	5 (2.6)
5	3 (1.6)	11 (5.8)
6	-	3 (1.6)
7	-	1 (0.5)
8	1 (0.5)	2 (1.1)

Table 3. Factors associated with moderate to severe postprocedural pain

Variables	Number (%)		Univariate analysis		Multivariate analysis	
	NRS <4 (n = 168)	NRS ≥4 (n = 22)	Crude OR (95% CI)	Wald *p*-value	Adjusted OR (95% CI)	*p*-value
Size (cm)						
<3	130 (89.0)	16 (11.0)	1	0.627	1	0.898
≥3	38 (86.4)	6 (13.6)	1.28 (0.47, 3.51)		1.07 (0.37, 3.14)	
No. of tumor						
≤2	165 (89.2)	20 (10.8)	1		1	
>2	3 (60.0)	2 (40.0)	5.50 (0.87, 34.92)	0.071	4.98 (0.65, 38.24)	0.122
treated tumor						
No	56 (84.8)	10 (15.2)	1		1	
Yes	112 (90.3)	12 (9.7)	0.60 (0.24, 1.47)	0.265	0.63 (0.25, 1.57)	0.316
distance (cm)						
≤2	38 (86.4)	6 (13.6)	1.28 (0.47, 3.51)	0.627	1.41 (0.49, 4.02)	0.523
>2	130 (89.0)	16 (11.0)	1		1	
Session						
<10	148 (89.2)	18 (10.8)	1		1	
≥10	20 (83.3)	4 (16.7)	1.64 (0.51, 5.35)	0.409	0.94 (0.24, 3.68)	0.934
Ablation time (min)						
<30	91 (91.9)	8 (8.1)	1		1	
≥30	77 (84.6)	14 (15.4)	2.07 (0.82, 5.19)	0.122	1.90 (0.73, 4.94)	0.191

OR = odds ratio; CI = confidence interval; NRS = numerical rating scales; n = number of patients; cm = centimeter; min = minute

ablation procedure was 9.6 out of 10.

Discussion

Post RFA pain is a distressing feeling caused by tissue damaging stimuli and inflammation. Unremitting pain may adversely affect the physical and psychological changes that increase morbidity and mortality. Persistent pain exerts profound impacts on the respiratory, endocrine, cardiovascular, and gastrointestinal systems. Ineffective pain control causes patients not to ambulate, resulting in deep vein thrombosis, pulmonary embolism, changes in bowel movements, nausea, and vomiting. These complications have economic and medical implications, such as long hospital stays, increasing mortality, and patient dissatisfaction.

Our study found that the incidence of moderate to severe post-RFA-pain on movement (NRS ≥4) within 18 to 24 hours was 11.6% (representing 22 patients). Comparing this lower incidence with previous literature, it could be explained by the unclear definition of pain, different procedural techniques, and different anesthetic techniques among the studies. A low incidence of pain was reported in the postoperative period more than in the intra-operative period. A local anesthetic injection (before puncturing the skin and ablating tumors) combined with a sedation technique seemed to be an effective method of relieving postoperative pain. As for the secondary outcomes, a tumor adjacent to the parietal peritoneum, a large tumor size, a long duration of ablation, and an untreated tumor had been identified as significant factors for pain in other published papers[4,5]. In contrast, no factor was associated with moderate to severe pain in the presented study; this may be because the number of cases of moderate to severe pain was insufficient. The sample size should therefore be inflated in any future study to obtain at least 30 patients with an NRS ≥4.

A combination of the WHO analgesic-ladder approach and non-pharmacological methods of pain control probably yield the most effective pain relief for patients. While analgesics drugs are used for treating the physiological and emotional dimension of the pain, non- pharmacological methods aim to treat the affective, cognitive, behavioral, and socio-cultural dimensions of the pain. Gelinas et al reported that four, non-pharmacological interventions, including music therapy, distraction, simple massage, and family-

presence facilitation - were accepted by Intensive Care Unit (ICU) nurses, patients, and family members as useful methods for pain management in ICU patients[7]. Topcu et al introduced relaxation exercises to patients undergoing upper abdomen surgery[8]. Pain levels reported by most patients enrolled in that exercise decreased dramatically even though some patients had experienced severe pain before participating in the activity. Therefore, we recommend that non-pharmacological methods, which are low cost, easy to provide, and safe, should be included in a pain management program for post RFA patients.

The common side effects of hepatic RFA include pain, shoulder pain, asymptomatic pleural effusion, asymptomatic perihepatic fluid or hemorrhage, minimal thermal damage to adjacent organs, and post ablation syndrome. The major complications are RFA needle track seeding, infection, hemorrhage, hepatic infarction, gastrointestinal perforation, hemothorax, pneumothorax, and death[9-11]. At our institution, the complications reported were minimal pneumothorax, suspected aspiration pneumonia, and nausea and vomiting. All patients improved after treatment and within 24 hours of the procedure.

Our study had some limitations. Firstly, the data on the complications in our study were low compared with other studies. It might be because those previous studies had followed-up patients for 30 days, whereas we monitored patients for only 24 hours. Secondly, we did not have clear details of the non-pharmacological methods utilized by our institution.

In conclusion, liver RFA in our institution was safe. The incidence of undesired pain scores was around 10%, and the rate of complications was very low. However, a further study should be designed to find the risk factors for moderate to severe pain in order to improve the quality of postoperative pain control.

What is already known on this topic?

Periprocedural pain in patients who had undergone RFA under conscious sedation with local anesthesia was mild. A large tumor size, previously untreated tumors, tumors adjacent to the parietal peritoneum, multiple ablations, and a long duration of ablation were factors related to more severe pain.

What this study adds?

A low incidence of moderate to severe pain was reported in the post procedural period. A sedation technique combined with a local anesthetic injection before puncturing the skin and ablating the tumors seemed to be an effective method for relieving postoperative pain.

Acknowledgements

This study was supported by Siriraj Research Development Fund (managed by Routine to Research –R2R). The authors thank Trongtum Tongdee for his advice and information; Miss Nichapat Sooksri, a research assistant, for help with the paperwork; and Chulaluk Komoltri for her statistical assistance.

Potential conflicts of interest

None.

References

1. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005; 40: 225-35.
2. Chitapanarux T, Phornphutkul K. Risk Factors for the Development of Hepatocellular Carcinoma in Thailand. J Clin Transl Hepatol 2015; 3: 182-8.
3. Shimozawa N, Hanazaki K. Longterm prognosis after hepatic resection for small hepatocellular carcinoma. J Am Coll Surg 2004; 198: 356-65.
4. Lee S, Rhim H, Kim YS, Choi D, Lee WJ, Lim HK, et al. Percutaneous radiofrequency ablation of hepatocellular carcinomas: factors related to intraprocedural and postprocedural pain. AJR Am J Roentgenol 2009; 192: 1064-70.
5. Hori M, Tanaka M, Suzuki Y, Fukao M, Shimizu H, Mikoshiba N, et al. Periprocedural pain of radiofrequency ablation for hepatocellular carcinoma. Gastroenterol Nurs 2011; 34: 129-34.
6. Hsieh YC, Yap YS, Hung CH, Chen CH, Lu SN, Wang JH. Factors related to postoperative pain among patients who underwent radiofrequency ablation of hepatocellular carcinoma. Clin Radiol 2013; 68: 600-7.
7. Gelinas C, Arbour C, Michaud C, Robar L, Cote J. Patients and ICU nurses' perspectives of non-pharmacological interventions for pain management. Nurs Crit Care 2013; 18: 307-18.
8. Topcu SY, Findik UY. Effect of relaxation exercises on controlling postoperative pain. Pain Manag Nurs 2012; 13: 11-7.
9. Howenstein MJ, Sato KT. Complications of radiofrequency ablation of hepatic, pulmonary, and renal neoplasms. Semin Intervent Radiol 2010; 27: 285-95.

10. Venkatesan AM, Gervais DA, Mueller PR. Percutaneous radiofrequency thermal ablation of primary and metastatic hepatic tumors: current concepts and review of the literature. Semin Intervent Radiol 2006; 23: 73-84.

11. Ohmoto K, Yoshioka N, Tomiyama Y, Shibata N, Kawase T, Yoshida K, et al. Comparison of therapeutic effects between radiofrequency ablation and percutaneous microwave coagulation therapy for small hepatocellular carcinomas. J Gastroenterol Hepatol 2009; 24: 223-7.

การศึกษาระดับของความเจ็บปวดในผู้ป่วยหลังได้รับการรักษาโดยการใช้คลื่นวิทยุจี้ทำลายเนื้องอกที่ตับ

อารยา องค์เอี่ยม, อรุโณทัย ศิริอัศวกุล, อังศุมาศ หวังดี, ทัศนีย์ ใจเย็น, เสาวนีย์ หอมสุด

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์และปัจจัยเสี่ยงของความปวดระดับปานกลางถึงมากหลังการจี้ทำลายเซลล์เนื้องอกที่ตับด้วยคลื่นวิทยุภายใน 18-24 ชั่วโมง*

วัสดุและวิธีการ: *เป็นการศึกษาแบบไปข้างหน้าในผู้ป่วยที่เข้ารับการรักษาด้วยการจี้ทำลายเซลล์เนื้องอกตับด้วยคลื่นวิทยุ ภายใต้การระงับความรู้สึกทางหลอดเลือดดำร่วมกับการใช้ยาชาเฉพาะที่ การประเมินความปวดใช้ Numerical Rating Score ข้อมูลที่เก็บรวบรวมได้จากการสอบถามและจากบันทึกการรักษาเกี่ยวกับลักษณะของเนื้องอก วิธีทำหัตถการ วิธีการระงับความรู้สึก การรักษาหลังทำหัตถการและการเกิดภาวะแทรกซ้อนภายใน 18-24 ชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *มีผู้เข้าร่วมโครงการทั้งหมด 190 คนเป็นเพศชาย 134 คน (70.5%) และเพศหญิง 56 คน (29.5%) อายุเฉลี่ย 63.3±11.1 ปี พบอุบัติการณ์ของระดับความปวดปานกลางถึงมากร้อยละ 11.6 (22 รายจากผู้ป่วย 190 ราย) ปัจจัยที่อาจเกี่ยวข้องกับระดับความปวดปานกลางถึงมากได้แก่ มีเนื้องอกมากกว่า 2 แห่งและระยะเวลาจี้ทำลายเซลล์เนื้องอกมากกว่า 30 นาที อย่างไรก็ตามเมื่อใช้การวิเคราะห์แบบ multiple logistic regression แล้วกลับไม่พบปัจจัยเกี่ยวข้องกับระดับความปวดในการศึกษานี้*

สรุป: *อุบัติการณ์ระดับความปวดปานกลางถึงมากผู้ป่วยกลุ่มนี้พบค่อนข้างน้อย คือประมาณร้อยละ 10 และมีภาวะแทรกซ้อนเกิดขึ้นน้อยมาก*