



Safety of Percutaneous Ethanol Injection as Neoadjuvant Therapy for Hepatocellular Carcinoma in Waiting List Liver Transplant Candidates

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ABSTRACT

Orthotopic liver transplantation (OLT) as therapy of hepatocellular carcinoma (HCC) improves the survival of a selected group of patients. Unfortunately, the progressive increase in waiting time for OLT may allow tumor progression. Percutaneous ethanol injection (PEI) has been proposed as neoadjuvant therapy for HCC in patients awaiting OLT, but its safety has not been defined.

Patients and Methods. During a 60-month period, 34 patients (27 men, overall mean age of 58.5 years, range 41–67) with HCC, were listed for OLT. Ultrasonography-guided PEI was delivered into 39 nodules at 117 sessions on an inpatient basis. Written informed consent was obtained from all patients before PEI. Doppler-ultrasonography was done before PEI, immediately after, and 4 weeks later. Noninvasive monitoring of arterial pressure, cardiac rate, and temperature was performed during the procedure and during a 24-hour period after each session. Pain was considered significant if analgesia was required or discontinuation of PEI necessary. Fever was defined as a temperature $\geq 37.5^{\circ}\text{C}$ after PEI.

Results. Minor complications included pain in 45 sessions (38.5%), fever in 17 (14.5%), arterial hypertension in 14 (12%), hypotension in 7 (7%), and vomiting in 2 (1.7%). The major complications were segmental liver infarction ($n = 3$), portal branch venous thrombosis ($n = 2$), ascites ($n = 2$), and one case each of subcapsular hematoma, duodenal ulcer, pneumonia, hepatic encephalopathy, and hepatic artery thrombosis. In all cases, clinical outcomes were favorable with conservative treatment. No evidence of tumor seeding in the needle track was reported and no PEI-related mortality observed.

Conclusions. PEI is a safe neoadjuvant therapy for HCC on waiting list liver transplant candidates. In our series, pain and self-limited fever were the most frequent complications. Clinically significant severe complications were uncommon, and nonconservative treatments were not required.

ORTHOTOPIC LIVER TRANSPLANTATION (OLT) is considered the best therapeutic option for patients with early hepatocellular carcinoma (HCC) in terms of survival and recurrence rate.¹ Nevertheless, the long time from indication to performance of OLT may cause tumor enlargement, vascular invasion, and extrahepatic spread, precluding some patients from undergoing this therapeutic procedure. One-year probability of HCC progression is 70%, resulting in a probability of exclusion after 6 months from waiting list after 6 months for OLT of 23% to 50%. This circumstance worsens

the outcomes in an intention-to-treat analysis of OLT.² Thus, safe, effective means to delay the progression of HCC are needed for liver transplant candidates. Percutaneous ethanol

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injection (PEI), radiofrequency ablation, and transarterial chemoembolization have been proposed to treat and delay HCC progression awaiting OLT.³⁻⁹ The safety of PEI as neoadjuvant therapy of HCC for patients awaiting for OLT has not been evaluated.

PATIENTS AND METHODS

During a 60-month period the 34 patients (27 men) with liver cirrhosis and hepatocellular carcinoma listed for OLT were treated with PEI. The overall mean age was 58.5 ± 6.8 years (range, 41-67). The etiology of cirrhosis was alcoholic in 14 patients (41.2%), hepatitis C virus infection in 11, hepatitis B virus infection in four, hemochromatosis in two, and cryptogenic in three patients. Pretreatment mean Child-Pugh score was 6.5 ± 1.7 . Twenty-one patients were Child-Pugh class A (61.8%), 10 Child-Pugh class B (29.4%), and three Child-Pugh class C (8.8%). Performance status test (PST) was 0 in 27 patients (79.5%), PST 1 in six (17.6%), and PST 2 in one patient (2.9%). HCC was single in 30 patients (88.2%). Mean maximal diameter was 31.6 ± 11.8 mm. Pretreatment mean serum AFP was 40.3 ± 177.4 ng/mL (range, 1-1042). Tumor stage according to modified TNM staging classification was T1 in three (8.8%); T2 in 27 (79.4%); and T3 in four cases (11.8%).

PEI was applied to 39 nodules at 117 sessions. Mean volume of 12 ± 4.7 mL of ethanol injected by session. A mean of 3 ± 1.8 sessions and 38 ± 26.8 mL of ethanol was delivered to each nodule. In five patients an additional cycle of PEI was necessary due to incomplete radiologic response. PEI was performed via PAN-ETA (Gallini S.L., Mirandola, Italy) via 20-22G needles under sonographic guidance using a commercially available ultrasound scanner (Toshiba JustVision 400; Toshiba Medical Systems, Tokyo, Japan), with a 3.75 MHz convex probe. Written informed consent was obtained from all patients before PEI. A catheter introduced into a left upper limb vein guaranteed adequate vascular access. The procedure was performed under conscious sedation by intravenous administration of midazolam (Dormicum, Roche, Basel, Switzerland; 0.05-0.1, mg/kg), followed by an infusion of meperidine (Dolantina, Bayer AG, Leverkusen, Germany; 1 mg/kg). Drug dosage was adjusted in relation to patient compliance and according to the various phases of the procedure, seeking mild sedation and preserving the ability of the patient to cooperate. Mepivacain 2% (Scandinibsa, Inibsa, Barcelona, Spain) was used as the local anesthetic for a painless introduction of the PEI needle. An overnight hospital stay was scheduled after each session.

Noninvasive monitoring of arterial pressure, cardiac rate, and temperature was performed during the procedure and for 24-hours thereafter. Pain was considered significant if analgesia was required or discontinuation of PEI was necessary. Fever was defined as a temperature of 37.5°C or higher after PEI. Hypotension was considered when symptomatic or systolic arterial pressure was less than 90 mm Hg. Arterial hypertension was considered when systolic or diastolic arterial pressure were above 145 and 85 mm Hg, respectively, in the absence of previously diagnosed arterial hypertension. Doppler-ultrasonography using a digital ultrasound scanner (Hitachi EUB-6000; Hitachi Medical Corporation, Tokyo, Japan), with a 2.5 to 5.0 MHz convex probe, was performed before the procedure, after each session, and at 4 weeks after PEI to detect the presence of ascites, pleural effusion, hemorrhage, portal thrombosis, or liver infarction.

Baseline patient characteristics were expressed as mean values \pm SD. PEI-OLT interval and follow-up length were expressed as medians (ranges). Comparisons between adverse events and non-

Table 1. Minor Complications Occurred After 117 Sessions of PEI in a Series of 34 Patients With Hepatocellular Carcinoma Awaiting Liver Transplantation

Adverse Event	n (%)	Volume of Ethanol Injected by Session (mL) (mean \pm SD)	P
Pain	No: 72 (61.5%)	12.4 ± 4.5	.335
	Yes: 45 (38.5%)	13.4 ± 5	
Fever	No: 100 (85.5%)	12.7 ± 4.8	.479
	Yes: 17 (14.5%)	13.3 ± 4	
Arterial hypertension	No: 103 (88%)	12.7 ± 4.7	.497
	Yes: 14 (12%)	13.2 ± 4.9	
Hypotension, vagal syndrome, or both	No: 110 (94%)	12.9 ± 4.7	.631
	Yes: 7 (6%)	11.6 ± 5.8	
Nausea/Vomiting	No: 115 (98.3%)	12.9 ± 4.7	.104
	Yes: 2 (1.7%)	6.5 ± 4.9	

adverse event groups were performed using Mann-Whitney test. Statistical analysis was performed with the SPSS version 12 (SPSS, Chicago, Ill, USA).

RESULTS

During the follow-up, two patients were excluded from the waiting list for OLT due to tumor progression. Additionally, another patient was excluded due to clinical and performance status deterioration. Two patients died on waiting list due to complications of liver cirrhosis. Of the remaining 29 patients, 23 were transplanted, and six are awaiting transplantation. Median interval between PEI and OLT was 6 months (range 1-18).

Minor complications included pain in 45 sessions (38.5%), fever in 17 (14.5%), transitory arterial hypertension in 14 (12%), hypotension or vagal syndrome in seven (7%), and vomiting in two sessions (1.7%). Additional minor complications included catheter-induced phlebitis in four patients. Administration of intravenous flumazenil (Anexate, Roche, Basel, Switzerland) was necessary in four patients due to a midazolam-induced consciousness low level. No relationship between the occurrence of adverse events and the volume of injected ethanol by session was observed (Table 1).

Major complications observed were segmental liver infarction in three patients, portal branch venous thrombosis in two, ascites in two, and one case each of subcapsular hematoma, duodenal ulcer, pneumonia, hepatic encephalopathy, and hepatic artery thrombosis. Liver infarction was clinically significant in only one patient, resulting in increased levels of transaminases and liver function deterioration. In the remaining two patients, liver infarction was a pathologic finding after the examination of explanted liver. Clinical outcome was favorable with conservative treatment in all cases. No evidence of tumor seeding in the needle track was observed at transplantation or in the explant.

Four patients (17.4%) died during the posttransplant follow-up: due to sepsis at 27 days, cardiac failure at 35

days, intrahepatic and ganglionic recurrence of HCC at 6 months, and chronic rejection at 21 months. No PEI-related mortality was observed. The remaining 19 patients are alive and recurrence-free at a median follow-up of 21 months (range 3–60).

DISCUSSION

The most frequently reported complications of PEI include abdominal pain, fever, and acute ethanol intoxication.^{10–12} In one study, pain was observed in 48% of procedures.¹³ Usually, the pain is well tolerated without treatment, but administration of nonopioid analgesics may be required. Discontinuation of PEI due to pain is uncommon. In one study, 13.5% of the patients required analgesics, and severe pain experienced during the maneuver led to discontinuation of the procedure in 3.7% of patients.¹⁴ Interestingly, the presence of pain was related to higher doses of injected ethanol.¹³ Increased body temperature may be observed after PEI, secondary to ethanol-induced tumor necrosis. Reported prevalence of fever is 24%.¹⁴ Temperature values above 38°C are uncommon. Fever is usually well-tolerated, and no treatment is required. Nausea, vomiting, and vagal syndrome are additional potential adverse events of PEI. In our series, pain and self-limited fever were the more frequent complications. No relationship was observed between injected volume of ethanol and prevalence of minor complications. A larger series may be required to assess this association.

Major complications of PEI include intraabdominal hemorrhage, right pleural effusion, obstructive jaundice, cholangitis, liver abscess, portal venous thrombosis, liver infarction, gallbladder or intestinal injury, arterio-portal shunt, pneumothorax, and shock.^{10,12} Neoplastic seeding in the needle track has been reported, mainly of >2 cm diameter, moderately differentiated hepatocellular carcinomas.^{12,14} The reported prevalence of severe complications is 1.3 to 3.2%.^{11,12,14} Conservative measures are usually sufficient for resolution of complications in most cases. In the present study, eight patients (23.5%) presented major complications. Nevertheless, only in one case of liver infarction was there hepatocellular dysfunction, development of ascites, hepatic encephalopathy, and pneumonia, requiring discontinuation of the therapy. Prospective clinical and ultrasonographic search for potential complications may be the explanation for the large prevalence of major adverse events in our series. No neoplastic seeding in the PEI needle track was reported.

PEI-related mortality is low; no death was observed among series of 1623 patients.¹² A multicenter study of about 1066 patients reported one death (0.09%) due to intraperitoneal bleeding and hepatic encephalopathy.¹⁴ Two additional cases of death secondary to massive liver

necrosis have been reported.^{15,16} In our study, no PEI-related mortality was observed.

In conclusion, our data suggested that PEI was a safe therapeutic procedure for neoadjuvant therapy of HCC for patients on the waiting list for OLT. Pain and self-limited fever were the more frequent complications. Clinically significant severe complications were uncommon, and non-conservative treatments were not required.

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