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CLINICAL INVESTIGATIONS

Intraarterial Lidocaine Administration for Relief of Pain Resulting from Transarterial Chemoembolization of Hepatocellular Carcinoma: Its Effectiveness and Optimal Timing of Administration

Sang Hoon Lee,[1] Seong Tai Hahn,[1] Seog Hee Park[2]

[1]Department of Radiology, St. Mary's Hospital, The Catholic University of Korea, 62, Youido-Dong, Yongdungpo-gu, Seoul 150-010, South Korea

[2]Department of Radiology, Kangnam St. Mary's Hospital, The Catholic University of Korea, 505, Banpo-Dong, Seocho-Ku, Seoul 137-040, Korea

Abstract

Purpose: Patients undergoing transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) commonly have significant post-procedural abdominal pain necessitating narcotic administration. It is known that intraarterial administration of lidocaine is effective in controlling the pain during the procedure. However, optimum timing of the lidocaine administration is not precisely known. The purpose of this study was to assess the efficacy of intraarterial lidocaine administration for control of pain resulting from TACE and to evaluate the optimal timing of administration.

Methods: In a prospective trial, 113 consecutive patients with HCC who underwent TACE were classified into three groups: those who received a lidocaine bolus intraarterially immediately prior to TACE (group A, $n = 30$), those who received lidocaine immediately after TACE (group B, $n = 46$), and those who did not received lidocaine (group C, $n = 37$). Incidence and degree of post-procedural pain was assessed using a subjective method (visual analogue scales scored from 0 to 10) and an objective method (amount of post-procedural analgesics).

Results: The incidence of post-procedural pain in group A (16.7%) was significantly lower than that of group B (38.3%; $p = 0.005$). The mean pain score was 3.0 in group A and 4.8 and 3.1 in groups B and C, respectively. The mean dose of analgesic used after the procedure in group A (25.0 mg) was significantly lower than those in group B (52.9 mg) and group C (41.0 mg; $p = 0.002$).

Conclusions: Pre-TACE intraarterial administration of lidocaine is much more effective than post-TACE administration in reducing the incidence and the severity of post-procedural pain. Furthermore, in order to reduce the incidence of post-procedural pain and dose of post-procedural analgesics, we recommend routine pre-TACE administration of lidocaine because post-procedural pain might developed even in patients who did not feel any pain during the TACE.

Key words: Anesthesia—Arteries, chemotherapeutic embolization—Liver neoplasms, therapy

Correspondence to: S.T. Hahn, M.D.; tel: +82-2-3779-1272, fax: +82-2-783-5288, e-mail: sthahn@cmc.cuk.ac.kr

In most institutions, transarterial chemoembolization (TACE) is considered an option when the patient is not a surgical candidate for the treatment of hepatocellular carcinoma (HCC) [1–5]. In most patients TACE commonly causes procedure-related abdominal pain either during or after the procedure, sometimes even in patients who did not experience pain during the procedure. The pain is severe enough to necessitate narcotic analgesia.

As suggested previously, intraarterial lidocaine administration during TACE has been known to reduce the severity of the pain resulting from TACE and to aid in a faster recovery [6, 7]. However, optimal timing of the lidocaine administration for maximum effect remains undetermined. The purpose of this prospective study was to assess the efficiency of intraarterial lidocaine administration and to determine the optimal timing of administration to obtain maximum effect.

Materials and Methods

One hundred thirteen consecutive, randomized patients (86 men and 27 women; age range: 33–78 years) with HCC underwent TACE during a recent 9-month period. Patients who had repeat TACE during this period were not included in this study. Fifty-one of the 113 patients had undergone one or two TACEs before this study. The underlying causes of liver disease in the patients were viral hepatitis-related cirrhosis in 78 patients (69%) and alcoholic-related cirrhosis in 22 (19%). In 13 patients (12%), no clinical or radiologic signs of cirrhosis were found. Five patients had undergone resection of HCC 12–25 months before the TACE, but none after the TACE. All patients were premedicated with intramuscular injection of 25 mg of pethidine hydrochloride (Demerol; Keuk-Dong Pharmacy, Inchon, Korea) approximately 30 min before the procedure. TACE was performed by injecting an emulsion of 5–50 mg of doxorubicin hydrochloride (Adriamycin; Dong-A Pharmacy, Seoul, Korea) mixed with 2–15 ml of Lipiodol (Guerbet, Villepinte, France) after placing the catheter tip in the distal feeding arteries as close to the tumor as possible using either the standard 5 Fr catheter or a 3 Fr coaxial catheter when necessary. The volume of Adriamycin (range 5–50 mg) and Lipiodol (range 2–15 ml) injected depended on the size of the tumors. The emulsion was prepared by mixing the two fluids (Adriamycin and Lipiodol) using two syringes connected through a three-way stopcock. After injecting the emulsion, embolization was performed under fluoroscopic guidance by injecting 1-mm-square gelatin sponge pledgets (Gelfoam; Pharmacia and Upjohn, Kalamazoo, MI, USA) mixed with 3–8 ml of contrast agent. In all patients, the arterial supply to the gallbladder was preserved to avoid severe abdominal pain. We infused oily emulsion only, without Gelfoam embolization, in 36 patients with portal vein thrombosis or portal hypertension or no definite tumor staining. The study patients were classified into three groups, at random: those who received lidocaine intraarterially immediately prior to TACE (group A, $n = 30$), those who received lidocaine immediately after TACE (group B, $n = 46$), and those who did not received lidocaine (group C, $n = 37$). In group A and B, 5 ml (100 mg) of 2% lidocaine bolus was injected into the feeding vessel. No other medical treatments were performed on the patients during the procedure. All patients were asked about subjective pain by using a visual analogue scale (VAS) [8] based on a scale of 0 (no pain) to 10 (excruciating pain) the next morning. The person asking the questions was blinded as to the patient's group. We consider a pain score more than 5 as meaningful, necessitating medical treatment for the patient. Only Demerol was administered. The dose of Demerol used in each patient was recorded, and the mean doses of Demerol for the groups were compared. The means of the VAS score among the three groups were also compared. Statistical analyses were performed with the chi-square test and ANOVA with multiple comparison using SPSS. The study was approved by our institutional review board and written informed consent was obtained from all patients before the TACE.

Results

The incidence of post-procedural pain with a score greater than 5, the mean pain score, and the mean dose of Demerol for the three groups are listed in the Table 1. Pain incidence in group A was significantly lower than that of group B ($p = 0.005$) and mean dose of Demerol in group A was significantly lower than those of group B and C ($p = 0.002$). The mean pain (VAS) scores are not significantly different among the three groups. One patient in group B had a transient (about 10 min) decrease of blood pressure (from 120/80 mmHg to 90/60 mmHg) after lidocaine injection. There were no other serious side effects resulting from intraarterial lidocaine administration. There were no significant differences in age, size of HCC, Child's class, dose of Adriamycin, dose of Lipiodol, or the rate of portal vein thrombosis among the three groups (Table 2).

Table 1. Incidence of post-procedural pain, mean VAS pain score and mean dose of Demerol for the three groups

Outcome	Group A (pre-TACE, $n = 30$)	Group B (post-TACE, $n = 46$)	Group C (no lidocaine, $n = 37$)
Pain incidence[a]	16.7%	38.3%	32.4%
Mean VAS pain score	3.0 ± 2.1	4.9 ± 2.0	3.1 ± 2.8
Mean dose of Demerol	25.0 ± 4.7 mg	52.9 ± 6.5 mg	41.0 ± 6.2 mg

VAS = visual analogue scale
[a]Pain score greater than 5

Discussion

Our result indicates that intraarterial lidocaine administration is highly effective in reducing pain and dosage of analgesics, as suggested previously [6, 7]. Previously, we investigated various times of administration and amounts of lidocaine, ranging from 20 to 100 mg per procedure. We found that there was a remarkable reduction in pain when 100 mg of lidocaine were injected intraarterially 30 sec prior to TACE; additional analgesics for pain control during the procedures were not required in many of these patients. Therefore a prospective study was considered to assess the optimal timing of lidocaine administration for maximum effect.

Hartnell et al. [7] injected the lidocaine at varying intervals before and during TACE up to four times. The dose of lidocaine used in their study (maximum 105 mg injected over 10–20 min) was safe and effective. Therefore we used a single bolus injection of 100 mg lidocaine in our study. In group B, most patients complained of right upper abdominal or periumbilical pain immediately after TACE, which was rapidly deminished by lidocaine administration.

It is interesting that many of the patients of group C, who did not feel any pain during the TACE, complained of a significant degree of pain requiring a considerable amount of analgesics after the procedure possibly due to postembolization syndrome. This result might emphasize the importance of prophylactic lidocaine administration.

Postembolization syndrome, including abdominal pain, fever and vomiting, is a self-limiting condition; nevertheless, it is a major complication of hepatic TACE causing longer hospitalization. Many authors attribute the pain in hepatic TACE to the following mechanisms: acute ischemia of liver parenchyma, transient hepatic swelling causing tension on

Table 2. Patient data analysis

Parameter	Group A (n = 30)	Group B (n = 46)	Group C (n = 37)
Age (years)	40–78 (mean: 58.7)	33–78 (mean: 53.1)	35–74 (mean: 53.7)
Type of HCC			
Single, nodular	14	18	18
Massive	14	23	15
Diffuse	2	5	4
Child's class			
A	12	21	21
B	16	20	14
C	2	5	2
Dose of Lipiodol (ml)	2–10 (mean: 4.1)	2–15 (mean: 6.6)	2–15 (mean: 6.9)
Dose of Adriamycin (mg)	5–40 (mean: 16.6)	5–40 (mean: 22)	5–50 (mean: 19)
Cases of PV thrombosis	4	9	5

PV = portal vein

the liver capsule, and gallbladder ischemia due to inadvertent embolization of the cystic artery [6, 7, 9–12]. However, these mechanisms cannot completely explain the pain occurring immediately after TACE. Molgaard et al. [6] suggested another mechanism for pain, arising from the hepatic arteries themselves. Reporting on an experimental study on cats, Moore and Singleton [13] suggested that injection of an irritating solution into the hepatic arteries was responsible for immediate pain. Although not proved, we experienced more excruciating pain in patients in whom a large amount of emulsion was used and was injected rapidly. Therefore, we think Moore and Singleton's suggestion that chemical irritation by the anticancer drug-Lipiodol mixture leads to abrupt pain in most patients seems to be the most reliable explanation for procedure-related pain.

In a study by Coldwell et al. [14], excellent analgesia during hepatic TACE was achieved with a celiac plexus block. However this method seems to be hazardous and time-consuming. Therefore we recommend intraarterial lidocaine administration because it might be a much easier and less time-consuming method than the celiac plexus block.

The mechanism for the analgesic effect of intraarterial lidocaine in hepatic TACE is unclear. Hartnell et al. [7] suggested that it has a direct local effect after diffusion into the arterial wall and liver parenchyma, and this effect will be prolonged in tumors where blood flow is occluded, preventing washout of the agent.

Lidocaine hydrochloride is a Class I antiarrhythmic drug and is the most widely used agent for the treatment and prevention of ventricular ectopic activity associated with myocardial infarction [15, 16]. In addition lidocaine is a potent vasodilator of the arterial system [17], although there is a case report of paradoxical vasospasm during femoral angiography [18]. Since most of our patients had cirrhosis of varying degree, the vasodilator effect, as well as analgesic effect, for these patient groups remains undetermined. However, although there was only one patient who revealed transiently decreased blood pressure, our results indicate that the amount of lidocaine used in our study (100 mg) might be a safe dose, as suggested previously [7, 15, 16], even in patients with hepatic dysfunction. However, the optimal dosage of lidocaine to produce the best therapeutic effect should be investigated further.

Our study has a few limitations. A few patients had variable degrees of portal vein thrombosis with arterioportal or arteriovenous shunt (A: 4, B: 9, C: 5); therefore pre-TACE lidocaine administration might have had both a systemical and local effect. Furthermore, the levels of analgesia resulting from lidocaine administration vary by patient. Patients in our study who had portal vein thrombosis or no definite tumor staining were treated only with chemo-infusion, without gelfoam embolization. This might have influenced our results to some extent. These concerns should be addressed by further study.

In conclusion, patients who received lidocaine immediately before TACE experienced minimal discomfort and needed smaller amounts of post-procedural analgesics than those who received lidocaine immediately after TACE. Our results indicates that pre-TACE lidocaine administration is much more effective than post-TACE administration in reducing post-procedural pain and the dose of analgesics. In addition, post-procedural pain could developed even in those patients who did not feel any pain during TACE. Based upon these results, it would be reasonable to adopt routine pre-TACE lidocaine administration to reduce the incidence of post-procedural pain and the amount of analgesic required.

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