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Liver Cancer: Effects, Safety, and Cost-effectiveness of Controlled-Release Oxycodone for Pain Control after TACE[1]

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Purpose: To evaluate the analgesic effect, safety, and cost-effectiveness of controlled-release oxycodone (CRO) to control postoperative pain in patients with liver cancer who are undergoing transarterial chemoembolization.

Materials and Methods: This randomized, double-blind, placebo-controlled, prospective clinical study received institutional review board approval. After written informed consent was obtained, 210 patients with liver cancer were randomized into three groups of 70 patients. Group 1 received 20 mg of CRO, group 2 received 10 mg of CRO, and group 3 received a placebo at 1 hour before transarterial chemoembolization (T_0) and 12 (T_{12}) and 24 (T_{24}) hours after T_0. Pain intensity on a numeric rating scale, percentage of patients with each degree of pain, quality of life, adverse reactions, analgesic costs, and hospital stays were evaluated and compared among the three groups.

Results: Numeric rating scale scores for pain intensity in group 1 and group 2 were significantly lower than those in group 3 at $T_{0–12}$ ($P < .001$); $T_{12–24}$ ($P < .001$); and $T_{24–48}$ ($P < .001$). When group 1 with group 2 were compared, numeric rating scale scores were significantly lower in group 1 than in group 2 during the period of $T_{0–12}$ ($P < .001$) but were not significantly different at $T_{12–24}$ ($P = .68$) and $T_{24–48}$ ($P = .10$). Analgesic cost and hospital stay were significantly lower in treated groups than in the placebo group. No significant difference was observed in quality of life and adverse events between the treated groups and the placebo group.

Conclusion: CRO is effective, safe, and cost-effective in the control of postoperative pain after transarterial chemoembolization for patients with inoperable liver cancer.

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Transarterial chemoembolization (TACE) has been proven effective in controlling tumor progression, improving quality of life, and prolonging survival time (1) and thus, has been used worldwide as the therapy of choice for patients with inoperable liver cancer. Each year, more than 3000 TACE procedures are performed in our department, and it is estimated that more than 100 000 TACE procedures are performed in China each year. Because of sudden obstruction of the major blood vessels that supply the tumor, subsequent local hepatic tissue swelling, and fast tumor necrosis, most patients experience pain of variable levels during and after TACE. The pain deteriorates patients' quality of life, prolongs hospital stay, and increases cost. According to our records, 75% of patients undergoing TACE experienced severe pain (in a three-grade mild, moderate, and severe classification), and 93% of patients required opioid treatment during the first 12 hours after TACE. Because of the complexity of the nature and severity of the pain, routine treatment was often inadequate (2).

Since 2004, we have used controlled-release oxycodone (CRO) in the management of moderate and severe postoperative pain in TACE therapy for patients with hepatocellular carcinoma and liver metastases of various origins. CRO is a semisynthetic opioid μ and κ agonist (3) that is two times more potent and three times higher in oral bioavailability than controlled-release morphine drugs (4). Compared with immediate-release opioids and other analgesics, CRO maintains a longer and more stable serum concentration, with an average duration of action of 8–12 hours (5,6). CRO treatment was noted to be associated with a lower incidence of adverse effects and earlier recovery of bowel function, compared with morphine (7). In addition, CRO use before surgery provided good control of postoperative pain (8–10) and substantially reduced postoperative opioid consumption (7–11).

The purpose of this randomized, double-blind, placebo-controlled, prospective clinical study was to evaluate the analgesic effect, safety, and cost-effectiveness of CRO in control of postoperative pain in TACE therapy for patients with liver cancer.

Advances in Knowledge

- Controlled-release oxycodone is effective in control of postoperative pain after transarterial chemoembolization therapy for inoperable liver cancers.
- Preoperative use of controlled-release oxycodone is sufficient to control postoperative pain due to transarterial chemoembolization.

Materials and Methods

Study Design

After we received approval from our institutional review board, written informed consent was obtained from 210 patients recruited for the study who were scheduled for TACE from May to July 2009 in our department. All patients had a confirmed pathologic diagnosis of liver cancer on the basis of biopsy findings, surgery findings, or both. Patients included in the study had tumors larger than 3 cm and smaller than 8 cm in diameter, and those with multiple tumors had no more than three. Patients with tumors larger than 8 cm in diameter were excluded because the complexity of pain caused by larger tumors would affect the accuracy of the study. Patients with the following conditions were excluded from the study: American Society of Anesthesiologists physical status greater than 3; known allergy to or intolerance of CRO; pregnancy; history of drug abuse, long-time opioid medication use, postoperative nausea and vomiting, or ileus; and liver dysfunction defined as elevation of serum alanine aminotransferase and serum aspartate aminotransferase three times above the reference range (12,13).

The patients (n = 210) were randomized into three groups of 70 patients, using a computer-generated random number table. In group 1, patients received 20 mg of CRO (Mundipharma Pharmaceutical, Beijing, China) 1 hour before TACE (T_0) and 12 (T_{12}) and 24 (T_{24}) hours after T_0. In group 2, patients were given 10 mg of CRO at the same intervals. The patients in group 3 received placebos of 100 mg of vitamin C (Xinyi Pharmaceutical, Shanghai, China). Every patient received three doses during the course of the study (Fig 1). The CRO and placebo were prepared in capsules with identical appearance. The physician, research nurse, and patients were not aware of the study group assignment. The pharmacist who prepared the medication for patients was aware of the study design; however, he was not allowed to communicate with other personnel involved in the study.

General Data Gathering

The day before TACE, the research nurse collected general information about the patients, including sex, age,

Implication for Patient Care

- Preoperatively planned use of controlled-release oxycodone is effective, safe, and cost-effective in the control of postoperative pain in patients undergoing transarterial chemoembolization.

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Abbreviations:
CRO = controlled-release oxycodone
NRS = numeric rating scale
TACE = transarterial chemoembolization

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Guarantor of integrity of entire study, B.Z., J.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, B.Z., Z.Y., Z.K.; clinical studies, B.Z., J.W., Z.Y., P.S.; experimental studies, B.Z., J.W.; statistical analysis, B.Z., P.S.; and manuscript editing, B.Z., J.W., P.S., Z.K.

Potential conflicts of interest are listed at the end of this article.

and type of tumor. The nurse also educated patients about the numeric rating scale (NRS), which patients used to rate pain from 0 (no pain) to 10 (the most severe pain).

During the TACE procedure, 5 mL of 2% lidocaine (Fuda Pharmaceutical, Shanghai, China) was injected for local anesthesia before the femoral artery was punctured. The catheter (Cook, Bloomington, Ind) was advanced superselectively into the artery that was feeding the tumor, and a mixture of iodized oil (Geubert, Roissy, France) and 30 mg of doxorubicin (Pfizer, San Francisco, Calif) was infused into the tumor followed by embolization with a gelatin sponge. The amount of the iodized oil used was recorded.

When an incident of acute pain occurred after TACE, the patient was given 10 mg of morphine subcutaneously. If pain continued, 10 mg of oral CRO or 20 mg or more of controlled-release morphine was given until the patient's pain was controlled. Fentanyl transdermal drugs were also used in the management of incident pain. The time and doses of the opioid drugs used were recorded, and the total amount of opioid analgesics used was converted to the amount of oral fast-releasing morphine for comparing analgesic consumption.

Efficacy Assessment

Patients assessed pain intensity by using an NRS (score of 0–10) every 4 hours starting from 1 hour before TACE (T_0) until 48 hours (T_{48}) after T_0. The whole study course was divided into three time periods: $T_{0\text{-}12}$, $T_{12\text{–}24}$, and $T_{24\text{–}48}$. In each time period, only the highest pain score was used for comparing the pain-controlling effects among the three groups. To further evaluate the analgesic results, pain scores of 0–3 were categorized as mild; 4–6, as moderate; and 7–10, as severe pain. The percentage distribution of patients whose pain score fell in each category was compared among the three groups during the three time periods.

Quality-of-life factors of sleep, appetite, spiritual state, and fatigue were rated by patients at T_0 and T_{48} by using a five-point categoric scale (1 = worst, 2 = bad, 3 = mild, 4 = normal, 5 = very good). The differences in scores between T_{48} and T_0, indicating recovery of quality of life, were calculated and analyzed.

Safety Assessment

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (14), the percentage of patients who had adverse events referable to the use of CRO, such as nausea, vomiting, dizziness, constipation, dysuria, hypersomnia, and pruritus, during the study was calculated for each treatment group and compared among the three groups.

Cost-effectiveness Assessment

The cost-effectiveness analysis included comparisons of mean analgesic cost in Chinese yuan (renmimbi [RMB]) and hospital stay among the three groups. Morphine consumption was calculated by converting all CRO and other analgesics the patient had received into the sum of the morphine during the entire study course.

Statistical Analysis

CRO analgesic effect was assessed by comparing among the three groups the highest NRS scores and the percentage distribution of patients reporting scores in each pain category (mild, moderate, and severe) in each time period. The differences in the highest NRS scores among the three groups were analyzed by using repeated-measures analysis of variance (ANOVA), contrasting them with scores at T_0. Scores for group 1 and group 2 were compared using the same methods, applying a Bonferroni adjustment for multiple comparisons. The percentage distribution of patients in each pain category in the three groups was analyzed with the Cochran-Mantel-Haenszel χ^2 test, and then pain scores in group 1 and group 2 were compared.

To compare score differences in quality of life between T_0 and T_{48} and cost-effectiveness, the Kruskal-Wallis test or the Wilcoxon rank sum test was used for those with nonnormal distribution, and one-way ANOVA was used for continuous variables with normal distribution. A Bonferroni adjustment was also used for multiple comparisons.

Data are reported as mean ± standard deviation for continuous variables with normal distribution or as median (interquartile range, P_{25}–P_{75}) for those with nonnormal distribution, and number of patients and percentages for categoric variables. A P value of less than .05 was considered to indicate a statistically significant difference. All statistical analyses were conducted by using a statistical software package (SPSS; IBM, Armonk, NY).

Results

Patient and TACE characteristics of 210 patients who were divided randomly into three study groups are summarized in Table 1. No patient was excluded from the study after randomization. Information on patient age, sex, and tumor type; TACE operation time, and use of iodized oil in TACE showed no significant differences among the three groups.

Figure 1

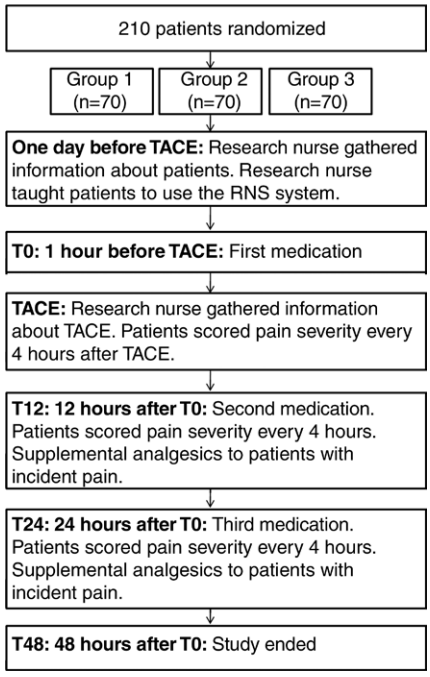

Figure 1: Flowchart shows course of the study.

Analysis of pain control revealed no significant difference among the highest pain scores in the three groups at T_0 (P = .71). The highest pain scores in group 1 and group 2 were significantly lower than the scores in group 3 during the periods of T_{0-12} ($P < .001$), T_{12-24} ($P < .001$), and T_{24-48} ($P < .001$). When group 1 and group 2 are compared, the highest pain score in group 1 was significantly lower than the that in group 2 during T_{0-12} ($P < .001$); however, the differences were not statistically significant during T_{12-24} (P = .68) and T_{24-48} (P = .10) (Table 2).

Comparison of the percentage distribution of patient pain severity showed that the percentages of mild and moderate pain were significantly higher in groups 1 and 2 than in group 3 ($P < .001$). When group 1 and group 2 are compared, the percentage of patients with mild and moderate pain was significantly higher in group 1 than in group 2 during T_{0-12} ($P < .001$), whereas there was no significant difference during T_{12-24} (P = .62) and T_{24-48} (P = .053) (Table 3).

Comparison of quality-of-life scores and score differences at T_{48} and T_0 showed that recovery of quality of sleep, appetite, spirit, and fatigue in group 1 and group 2 were both significantly better than in group 3 ($P < .001$). In a comparison of group 1 with group 2, there was no significant difference in sleep quality, spiritual state, and fatigue (P = .21, .02, .02, respectively), and appetite recovery was significantly better in group 1 than in group 2 (P = .001) (Table 4).

In the safety evaluation, numbers and percentages of patients who had adverse events referable to the use of CRO in group 1, group 2, and group 3, respectively, were nausea (57, 81%; 43, 61%; 55, 78%, P = .35), vomiting (40, 57%; 36, 51%; 41, 58%; P = .67), dizziness (22, 31%; 17, 24%; 18, 26%, P = .60), constipation (64, 91.4%; 57, 81%; 59, 84%; P = .22), dysuria (6, 8%; 4, 6%; 6, 8%; P = .76), hypersomnia (11, 16%; 10, 14%; 14, 20%; P = .64), and pruritus (6, 8%; 4, 6%; 3, 4%; P = .56). There was no statistically significant difference observed between each two groups among the three groups during the entire course of treatment (Fig 2).

In the cost-effectiveness analysis, analgesic cost was significantly lower in both group 1 and group 2 than in group 3 (P = .002). In a comparison of group 1 and group 2, the cost was significantly lower in group 2 than in group 1 (P = .001). Hospital stay was significantly shorter in both group 1 and group 2 than in group 3 ($P < .001$), but there was no statistically significant difference between groups 1 and 2 (P = .39) (Table 5).

The total morphine consumption in the three groups during the treatment periods is illustrated in Figure 3, which demonstrates that morphine consumption was lower in both group 1 and group 2 than in group 3 and lower in group 2 than in group 1 in all three treatment periods. Note that P values for these comparisons were not calculated, because each group had

Table 1

Patients and TACE Characteristics

Patient and TACE Characteristics	Group 1 (n = 70)	Group 2 (n = 70)	Group 3 (n = 70)	P Value*
Age (y)	53.4 ± 12.3	52.1 ± 9.1	50.2 ± 9.1	.18
Sex				.88
Men	58 (83)	56 (80)	56 (80)	
Women	12 (17)	14 (20)	14 (20)	
Tumor type				.97
HCC†	53 (76)	53 (76)	54 (77)	
Metastasis	17 (24)	17 (24)	16 (23)	
TACE time				.93
0–30 min	11 (16)	4 (6)	8 (11)	
30–60 min	50 (71)	62 (88)	55 (78)	
>60 min	9 (13)	4 (6)	7 (10)	
Iodized oil				.93
0–5 mL	24 (34)	18 (26)	22 (31)	
5–10 mL	30 (43)	44 (63)	33 (47)	
>10 mL	16 (23)	8 (11)	15 (21)	

Note.—Data are number of patients, with percentage in parentheses.

* Compares the difference among the three groups.

† HCC = hepatocellular carcinoma.

Table 2

Mean Highest Pain Scores among Study Groups in Each Treatment Period

Treatment Period	Group 1 (n = 70)	Group 2 (n = 70)	Group 3 (n = 70)	P Value*
T_0	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.7	.71
T_0–T_{12}†	3.8 ± 1.6	5.0 ± 1.8	7.8 ± 1.4	<.001
T_{12}–T_{24}‡	2.5 ± 1.2	2.4 ± 1.0	4.8 ± 1.2	<.001
T_{24}–T_{48}§	1.8 ± 1.1	1.4 ± 0.7	2.8 ± 1.4	<.001

Note.—Data are pain scores (range, 0–10) on an NRS.

* Compares the difference in the highest pain scores during each time period among the three groups.

† Group 1 vs group 2, $P < .001$.

‡ Group 1 vs group 2, P = .68.

§ Group 1 vs group 2, P = .10.

Table 3

Distribution of Pain Severity Scores

Time Period and Pain Severity	Group 1 (n = 70)	Group 2 (n = 70)	Group 3 (n = 70)
T_0-T_{12}			
Mild	42 (60)	18 (26)	2 (3)
Moderate	21 (30)	36 (51)	11 (16)
Severe	7 (10)	16 (23)	57 (81)
T_{12}–T_{24} †			
Mild	60 (86)	62 (88)	11 (16)
Moderate	10 (14)	8 (11)	54 (77)
Severe	0 (0)	0 (0)	5 (7)
$T_{24–48}$ ‡			
Mild	64 (91)	69 (98)	53 (76)
Moderate	6 (8)	1 (1)	16 (23)
Severe	0 (0)	0 (0)	1 (1)

Note.—Data are number of patients, with percentages in parentheses. Comparison of the difference among all groups was significant ($P < .001$).

* Group 1 vs group 2 ($P < .001$).

† Group 1 vs group 2 ($P = .62$).

‡ Group 1 vs group 2 ($P = .053$).

Table 4

Differences in of Quality-of-Life Scores between T_{48} and T_0

Quality of Life and Time Period	Group 1 (n = 70)	Group 2 (n = 70)	Group 3 (n = 70)
Sleep*			
T_0	4 (4,5)	4 (4,5)	5 (4,5)
T_{48}	4 (4,5)	4 (4,5)	3 (3,4)
Score difference	0 (0,0.2)	0 (-1,1)	−1 (-2,-1)
Appetite†			
T_0	4 (4,5)	4 (4,5)	4 (4,5)
T_{48}	4 (3,4)	4 (3,4)	3 (2,3)
Score difference	0 (-1,0)	−1 (-1,-0.8)	−1 (-2,-1)
Spiritual state‡			
T_0	4 (3.8,5)	4 (4,5)	3 (4,5)
T_{48}	4 (3,5)	4 (4,4)	3 (2,3)
Score difference	0 (0,0)	0 (-1,0)	−1 (-2,-1)
Fatigue§			
T_0	4 (3,4)	4 (3,4)	3 (3,4)
T_{48}	4 (3,4)	3.5 (3,4)	3 (2,3)
Score difference	0 (-1,0)	0 (-1,0)	−1 (-1.2,0)

Note.—Data are quality-of-life scores (range, 0–5) on an NRS. Data in parentheses are interquartile range. Comparison of the difference among all groups was significant ($P < .001$).

* Group 1 vs group 2 ($P = .21$).

† Group 1 vs group 2 ($P = .001$).

‡ Group 1 vs group 2 ($P = .02$).

§ Group 1 vs group 2 ($P = .02$).

different baseline morphine consumption according to study design.

Discussion

The study results demonstrated the effectiveness of CRO in the management of postoperative pain after TACE therapy for patients with inoperable liver cancer. Measurements of NRS pain scores, percentage of patients with each NRS pain degree, quality of life, adverse events, and cost-effectiveness were all significantly better in the treatment groups when compared with the placebo group. These results are inconsistent with those of previous evaluations of CRO in the management of pain from dental, abdominal, orthopedic, and gynecologic surgical procedures (12,13,15,16); cancers (17); and chronic pain from osteoarthritis (18,19), neuropathy (20), and other causes (21–23). To our knowledge, our report is the first in the literature to document the success of using CRO to control pain after TACE for liver cancer.

Owing to variable individual tolerability and other influences, the appropriate dose of CRO in pain control, especially for postoperative pain, has been a difficult and controversial issue. In a study to assess efficacy and tolerability, Koizumi et al (17) reported that 5 mg of CRO every 12 hours offered stable and adequate pain control for cancer patients, and the pain was significantly relieved as early as 1 hour following the initial dose intake. Pan et al (24) reported that an initial dosage of 5–10 mg of CRO every 12 hours with a daily dosage of 10–30 mg is well-tolerated and effective in controlling moderate to severe cancer pain in Chinese patients. In a dosing survey study of CRO for chronic pain, Marcus et al (23) reported the effective dosage of CRO as 60–120 mg daily. The majority of studies on pain relief suggested that doses of 10–30 mg twice daily are sufficient for management of variable pain (13,16,25). In our study, we compared doses of 20 and 10 mg of CRO, and the results were mixed. NRS pain scores and the percentage of patients with each degree of pain suggested that 20 mg of CRO was superior to 10 mg of CRO in reducing both pain intensity and the number of patients who required pain treatment during $T_{0\text{-}12}$, but there was no difference during the later periods of $T_{12–24}$ and $T_{24–48}$. Nevertheless, analgesic cost and morphine consumption were higher in group 1 than in group 2.

Figure 2

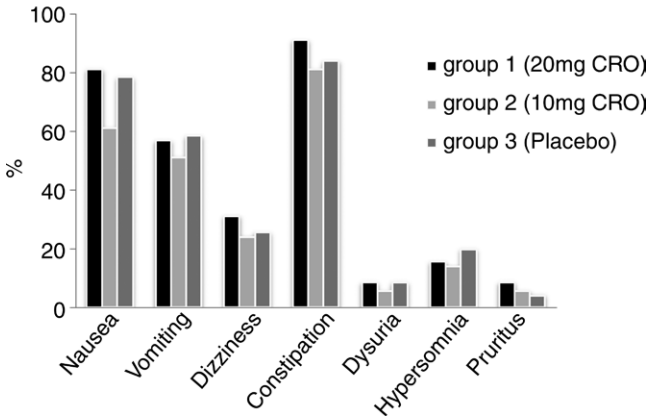

Figure 2: Graph of percentages of patients who experienced adverse events during TACE. No statistically significant difference was observed among the three groups.

Table 5

Cost-effectiveness Analysis

Analgesic Cost and Hospital Stay	Group 1 (n = 70)	Group 2 (n = 70)	Group 3 (n = 70)	P Value*
Analgesic cost (RMB)				
Median (IQR)†	37.0 (18.5, 43.7)	19.6 (9.8, 22.8)	43.4 (5.6, 90.4)	.002
Hospital stay(d)‡	4.2 ± 0.4	4.3 ± 0.4	5.1 ± 1.1	<.001

* Compares the analgesic cost in Chinese yuan (RMB) and hospital stay in days among the three groups.

† Group 1 vs group 2 (P < .001). Data in parentheses are interquartile range.

‡ Data are mean ± standard deviation. Group 1 vs group 2 (P = .39).

Figure 3

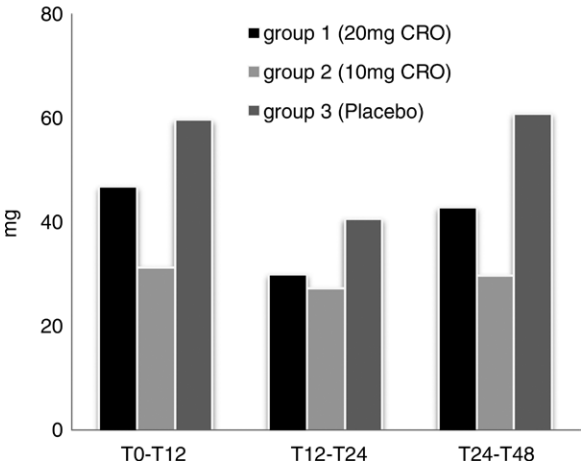

Figure 3: Graph shows that total morphine consumption was lower in both group 1 and 2 than in group 3. Total morphine consumption was lower in group 2 than in group 1. P values were not calculated because of different baseline morphine consumption in the three groups.

Our study results demonstrated that premedication 1 hour before TACE with either 20 or 10 mg of CRO provides efficient control of postoperative pain. During $T_{0\text{-}12}$, when the pain intensity is the highest, 20 mg of CRO is better than 10 mg of CRO in reducing pain. There was no difference in pain relief between 20 and 10 mg of CRO during $T_{12\text{-}24}$ and $T_{24\text{–}48}$, which may suggest that CRO doses could be reduced without decreasing the effectiveness of pain control after T_{12}. It is also economical to use CRO preoperatively. Analgesic costs in CRO groups 1 and 2 were significantly lower than those in the placebo group (P = .002). During the study, we had to double the dosage of opioids to achieve a similar analgesic effect in patients who did not take CRO before TACE. We suggest that this may be attributed to multifold reasons such as delayed drug absorption in the presence of decreased gastric emptying, frequent nausea or vomiting, patient asking for more drug because of anxiety about pain, and the necessity to use transdermal fentanyl and morphine injections in patients who have difficulty taking drugs orally after TACE. Dickenson (26) and Woolf and Wall (27) have suggested that preoperative analgesic treatment has the advantage that it may create a "preemptive" analgesic effect, and the dose needed may be as low as one-tenth the dose required once the pain has developed. In cost-effectiveness comparisons, average analgesic cost was significantly lower and hospital stay was significantly shortened in the CRO groups than in the placebo group. Between groups 1 and 2, analgesic cost was lower in group 2, but no difference was found in hospital stay.

Treatment with opioid analgesics often causes adverse reactions that may make continuous use difficult. CRO produces relatively constant serum opioid levels (6). Reuben et al (8,9) and Kaufmann et al (11) have reported that less postoperative nausea and vomiting were demonstrated in patients receiving CRO during surgical interventions. Blumenthal et al (12) suggested that earlier return of bowel function with CRO treatment helps reduce the fear of potential gastrointestinal reaction. Our data were in agreement with the previous reports. Measures of percentages of patients with adverse reactions of nausea, vomiting, dizziness, constipation, dysuria, hypersomnia, and pruritus during the entire course of treatment demonstrated that taking 20 mg of CRO or 10 mg of CRO did not increase adverse effects, and the incidence of adverse

effects in groups 1 and 2 was not significantly different.

Our study had some limitations. Assessments of pain score, quality of life, incidence of adverse events, and satisfaction were conducted by patients who, for the most part, did not have experience with the rating system, and their assessments could have varied during the course of treatment. In addition, the study was limited in clinical observation without looking into the mechanisms involved; therefore, we are currently planning a study to correlate the pain control effects with blood levels of CRO for accurate dosing for pain management. Finally, the study design for the dosage used was somewhat subjective; patients may have taken more analgesics than necessary, especially during the period of T_{24-48}.

In conclusion, our study results demonstrated the effectiveness of CRO in the control of postoperative pain after TACE for patients with inoperable liver cancer. It also demonstrated that 20 mg of CRO given 1 hour preoperatively is sufficient to control pain during the first 12 hours after TACE, and the dose could be reduced to 10 mg without affecting the therapeutic results. In addition to the benefits of lowering pain scores during the entire postoperative period, CRO use in our study resulted in less analgesic consumption and cost, shorter hospitalization, better quality of life, and the same incidence of adverse effects, compared with the control group. Our study results indicate that patients undergoing TACE or other interventional procedures that are associated with prolonged pain would benefit from receiving preoperative oral CRO.

Disclosures of Potential Conflicts of Interest:
B.Z. No potential conflicts of interest to disclose.
J.W. No potential conflicts of interest to disclose.
Z.Y. No potential conflicts of interest to disclose.
P.S. No potential conflicts of interest to disclose.
Z.K. No potential conflicts of interest to disclose.

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