CLINICAL STUDY

Dexamethasone Prophylaxis to Alleviate Postembolization Syndrome after Transarterial Chemoembolization for Hepatocellular Carcinoma: A Randomized, Double-Blinded, Placebo-Controlled Study

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ABSTRACT

Purpose: To test the hypothesis that prophylactic administration of dexamethasone alleviates postembolization syndrome (PES) after transarterial chemoembolization for the treatment of hepatocellular carcinoma (HCC).

Materials and Methods: This prospective, randomized, double-blinded, placebo-controlled trial was conducted in a single center from August 2015 to June 2016. A total of 88 patients with intermediate-stage HCC were enrolled. After randomization, 44 patients were assigned to the dexamethasone group and the other 44 to the control group. In the dexamethasone group, 12 mg of intravenous dexamethasone was administered before chemoembolization. Nausea, vomiting, fever, pain, and alanine aminotransferase level elevation were evaluated after chemoembolization had been performed with the use of Lipiodol and doxorubicin.

Results: The incidences of PES were 78.0% in the dexamethasone group and 97.5% in the control group ($P = .008$). Mean hospitalization times after chemoembolization were 2.7 days ± 1.44 in the dexamethasone group and 2.9 days ± 1.83 in the control group ($P = .553$). Mean doses of antiemetic and analgesic agents were lower in the dexamethasone group than the control group (0.2 ± 0.58 vs 1.0 ± 1.89 [$P = .029$] and 0.6 ± 0.97 vs 1.92 ± 2.54 [$P = .006$], respectively). Prophylactic administration of dexamethasone was a significant factor that influences PES occurrence after chemoembolization (odds ratio = 10.969, $P = .027$).

Conclusions: This study demonstrates that the prophylactic administration of dexamethasone before chemoembolization is an effective way to reduce PES.

ABBREVIATIONS

ALT = alanine aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CTCAE = Common Terminology Criteria for Adverse Events, HCC = hepatocellular carcinoma, OR = odds ratio, PES = postembolization syndrome

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Tables E1–E5 are available online at *www.jvir.org*.

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Transarterial chemoembolization is the most commonly selected treatment option for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC) worldwide (1–4). However, postembolization syndrome (PES) can occur after chemoembolization in 60%–90% of cases, manifesting as fever, nausea, vomiting, or abdominal pain (5,6) Although the etiology of PES is not fully understood, it is thought to involve a systemic inflammatory response caused by cytolysis, ischemia, or necrosis of hepatocytes, with or without the systemic effect of the chemotherapeutic drug. PES is usually considered a self-limiting event that resolves within 24 hours, and it can be managed with the administration of analgesic, antiemetic, and antipyretic agents (7); however, some studies have reported that PES could persist for as long as 2 weeks (8,9). In addition, PES was reported to be associated with an increased duration of hospitalization and decreased quality of life in patients treated with chemoembolization (7).

Recently, a few studies have evaluated the effect of steroids for PES after chemoembolization for HCC (7,9,10). Kogut et al (10) reported the antiemetic effect of prophylactic and postprocedural steroids for PES after chemoembolization. However, they did not demonstrate an analgesic effect of prophylactic steroids for PES. A double-blinded, randomized control trial by Yinglu et al (9) demonstrated that prophylactic and postprocedural use of dexamethasone with ginsenosides was effective in reducing PES after chemoembolization, but they used multiple doses of steroids with ginsenosides, which can potentially cause serious side effects.

The present study was designed on the assumption that a single injection of 12 mg dexamethasone before transarterial chemoembolization could effectively reduce PES. The aim of this prospective, randomized, placebo-controlled, double-blinded trial is to evaluate the effect and safety of prophylactic dexamethasone for PES following chemoembolization.

MATERIALS AND METHODS

This is a prospective, randomized, placebo-controlled, double-blinded trial conducted in a single tertiary hospital, Seoul St. Mary's Hospital, from August 2015 to June 2016. The diagnosis and stage of HCC were assessed according to the American Association for the Study of Liver Disease guidelines (11) and the BCLC staging classification (1).

The inclusion criteria were as follows: (*i*) age 18–80 years, (*ii*) Eastern Cooperative Oncology Group performance status of 0, (*iii*) Child–Pugh class A disease, (*iv*) intermediate-stage HCC per BCLC staging classification (ie, BCLC stage B), (*v*) treatment with transarterial chemoembolization with doxorubicin (Adriamycin; Ildong, Seoul, Korea), and (*vi*) serum creatinine level lower than 1.5 mg/dL.

The exclusion criteria were as follows: (*i*) concurrent serious medical condition(s) such as underlying cardiac or renal disease, (*ii*) other concurrent primary malignancy, (*iii*) other chemotherapy such as hepatic arterial infusion chemotherapy or systemic chemotherapy, and (*iv*) chronic hepatitis B virus infection not treated with antiviral therapy. The latter criterion was adopted because steroids can induce viral reactivation in these patients.

The trial was registered in the Clinical Research Information Service, Republic of Korea (ID code KCT0002277), and conducted according to the Declaration of Helsinki, and the protocol was approved by the institutional ethics committee and the institutional review boards of The Catholic University of Korea (protocol number KC15MISI0445). Informed consent was obtained from all patients at enrollment before trial entry.

Study Endpoint

The primary endpoint of the present study is the effectiveness of prophylactic dexamethasone administration before chemoembolization for the reduction in severity of PES. Effectiveness was evaluated based on improvement of each constituent symptom of PES and by comparing the dexamethasone group with the control group.

Patients

From August 2015 to June 2016, a total of 88 patients with BCLC stage B HCC treated with chemoembolization were enrolled in the trial according to the inclusion and exclusion criteria. Among these patients, 44 were assigned to the dexamethasone group and 44 were assigned to the control group. In the dexamethasone group, a total of three patients were excluded after randomization. Among them, one withdrew consent after enrollment, one was not administered dexamethasone before chemoembolization, and one could not be fully evaluated for PES because of an early discharge 1 day after chemoembolization. In the control group, a total of four patients were excluded after randomization. Among them, two were excluded because of worsening of their Child–Pugh class from A to B after enrollment, one could not be fully evaluated for PES because of early discharge 1 day after chemoembolization, and one was excluded from the analysis because of a change in treatment plan after enrollment. The latter patient wanted to undergo a more curative treatment than chemoembolization after enrollment. In a multidisciplinary team conference, the surgery department recommended partial hepatectomy. The patient decided to undergo surgical treatment and was excluded from the analysis. Finally, a total of 165 tumors in 81 patients were analyzed (41 patients in the dexamethasone group and 40 in the control group; **Fig**).

Table 1 shows the baseline demographic data of all patients enrolled in the study. The mean age was 63.0 years ± 8.37; 67 patients were male and 14 were female. The most common cause of underlying liver disease was hepatitis B virus infection (76.5%). Fifty-nine patients had a Child–Pugh score of 5, and 22 patients had a Child–Pugh score of 6. All patients had BCLC stage B HCC. The modified Union for International Cancer Control (mUICC) stages were not significantly different between the