Liver cancer has a poor prognosis and has become the second leading cause of death due to malignant neoplasms worldwide. Transarterial chemoembolization (TACE) is a standard treatment for intermediate stages of hepatocellular carcinoma (HCC) [1, 2]. The invasiveness of TACE is less than that of hepatectomy, but postembolization syndrome may be a problem [3]. During hepatocellular necrosis, which is a main cause of postembolization syndrome, alanine aminotransferase levels rise temporarily and abdominal pain and fever develop in a majority of HCC patients. Occasionally, liver and splenic abscess, acute cholecystitis, and bile duct necrosis occur, resulting in the development of ascites and hepatic encephalopathy, which are symptoms of hepatic failure.

Original Article

The Efficacy and Safety of Steroids for Preventing Postembolization Syndrome after Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma


Steroids are often administered at the time of transcatheter arterial chemoembolization (TACE), a standard treatment of hepatocellular carcinoma (HCC), with the expectation of preventing postembolization syndrome. Here we investigated the precise effects of steroids on TACE. We prospectively enrolled 144 HCC patients from 10 hospitals who underwent TACE. Three hospitals used steroids (steroid group, n = 77) and the rest did not routinely use steroids (control group, n = 67). The occurrence of adverse events and the algetic degree at 1-5 days post-treatment were compared between the groups. Fever (grades 0-2) after TACE was significantly less in the steroid group (56/21/0) compared to the control group (35/29/3, \( p = 0.005 \), Cochran-Armitage test for trend). The suppressive effect of steroids against fever was prominent in females \( (p = 0.001) \). Vomiting \( (G0/G1/G2-) \) was also less frequent in the steroid group (70/5/2) versus the control group (53/10/3), but not significantly \( (p = 0.106) \). The algetic degree and the grade of hematological adverse events, including hyperglycemia, did not differ between the groups. We conclude that the administration of steroids was useful for the prevention of adverse events after TACE in patients with HCC.

Key words: antipyretic, hepatocellular carcinoma, therapeutic chemoembolization, steroid
In Japan, gelatin sponge particles are frequently used as an embolic material [4]. Superselective TACE is usually performed to minimize damage to noncancerous liver tissue and to maximize the effect of the treatment, but postembolization syndrome still frequently occurs. There are no guidelines for the prevention of postembolization syndrome with preoperative and postoperative medications.

In daily practice, nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids are used empirically to relieve postembolization syndrome [5]. However, the use of these drugs is the treating physician’s choice, and protocols vary between institutions. In addition, the effects of steroid administration before and/or after TACE on the prevention of postembolization syndrome have not been demonstrated in detail, and there are only a few reports dealing with this topic.

We conducted the present study to examine the utility and safety of steroid use in the prevention of postembolization syndrome following TACE.

**Patients and Methods**

**Patients.** We conducted this prospective cohort study at Okayama University Hospital and 9 affiliated hospitals. We enrolled HCC patients with a Child-Pugh score of A or B who underwent TACE from April 2013 to December 2014. The eligibility criteria were as follows: (i) the diagnosis of HCC was confirmed by means of histology or noninvasive criteria according to the European Association of the Study of the Liver or the American Association for the Study of Liver Diseases guidelines [1,6]; (ii) steroids or NSAIDs were not given regularly for underlying disease; (iii) the patient did not have uncontrolled diabetes mellitus; (iv) there was no allergy to contrast media; and (v) hepatic failure or renal failure was not found in a biochemical blood examination.

We defined the steroid group as the patients who were administered pre-treatment or post-treatment steroids in the clinical protocol, and we defined the patients without steroid administration as the control group. The study profile is summarized in Fig. 1. Of the 158 patients enrolled, 14 patients were excluded because they did not follow the protocol. Consequently, 77 patients were enrolled in the steroid group, and 67 patients were enrolled in the control group.

We obtained informed consent from all patients who participated in this study. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the ethical committees of all institutions involved.

**TACE procedure.** TACE was performed according to the clinical protocol of each institution. The physicians who performed the procedures received training for a minimum of 2 years at Okayama University Hospital. We performed selective TACE [7] whenever possible in both groups. We used epirubicin (n = 110), doxorubicin (n = 14), cisplatin (n = 8), and miriplatin (n = 12) for the antineoplastic agent. We used 1- or 2-mm-diameter ready-made porous gelatin particles (Gelpart, Nippon Kayaku, Tokyo) in almost all cases for the embolic material. No other invasive treatment for HCC was performed within 1 week after the TACE.

**Steroid use.** Three institutions used steroids routinely. Hydrocortisone succinic acid ester sodium was used as the steroid at all institutions. At institution 1 (n = 54), the patients were administered 100 mg of steroid on days 1-3. At institution 2 (n = 13), 300 mg of steroid was given on day 0 (before TACE). At institution 3 (n = 10), 100 mg of steroid was given on days 0-2. Seven institutions did not routinely use steroids. Among those institutions, NSAIDs were used on demand at six institutions, and 100 mg naproxen was given orally twice daily on days 1-3 at one institution (n = 9).

**Evaluation of adverse events.** For all patients, the severity of nausea, vomiting, and malaise were recorded, corresponding to the Common Terminology Criteria for Adverse Events (CTCAE) [8] version 4.0.
grade and based on a numeric rating scale (NRS) from 0 to 10 indicating the degree of pain on a daily questionnaire from before the treatment to 5 days after the treatment. We also examined the grade of fever before TACE to 5 days after TACE.

The primary endpoint was the grade of nausea, vomiting, fever, and malaise observed during the study period and the emergence of other adverse events associated with TACE. The secondary endpoint was the degree and duration of pain due to TACE.

**Statistical analysis.** We used t-tests for continuous data and chi-square tests, Fisher’s exact tests, and Cochran-Armitage’s tests for trends in categorical data. For the evaluation of nausea, vomiting, fever, and malaise, we calculated the incidence according to grade on each observation day. We calculated a maximum pain score and a cumulative pain score during the period of observation and then performed a t-test between the two groups. We compared the incidence of an NRS rating of ≥1 between the 2 groups on each observation day, as well as the number of days with an NRS rating of ≥1 between the 2 groups. We used JMP Pro 12.0.1 software (SAS Institute, Cary, NC, USA) for our statistical analyses.

**Sample size estimation.** Prior to this study, we performed 17 TACEs with and without steroids and evaluated the postembolization syndrome. We calculated that 66 cases per group were necessary to determine whether steroid use decreases the incidence of fever by one-half. We planned to enroll 75 cases in each group, with the prospect of a 10% dropout rate.

**Results**

**Patient characteristics.** The patients’ background factors are indicated in Table 1. There were more ascitic fluid cases in the steroid group, while the control group had more diabetes cases. Significant differences in characteristics were not observed between the steroid and control groups. There were no patients with severe diabetes showing glycated hemoglobin (HbA1c) > 8.5%.

**Symptoms.** The incidence of each grade of fever, vomiting, nausea, malaise, and other adverse symptom events is provided in Table 2. The grade of fever in the steroid group was significantly lower than that in the control group (p = 0.005). The grade of vomiting after TACE in the steroid group tended to be lower than that in the control group (p = 0.106). For nausea and malaise, there were no differences in their grade after TACE between the groups. In addition, extravasation at the infusion site was found in the steroid group, and stom- ach pain, hepatic failure, pleural effusion, and headache were recorded in the control group. These adverse symptoms occurred in small numbers, and thus a statistical examination was not performed.

Because fever, vomiting, nausea, malaise, and pain

### Table 1  Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Background Factors</th>
<th>Steroid Group (n=77)</th>
<th>Control Group (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73 (45–87)</td>
<td>74 (39–92)</td>
<td>0.359</td>
</tr>
<tr>
<td>Male (n)</td>
<td>50 (65%)</td>
<td>43 (64%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>22.2 (16.7–33.5)</td>
<td>22.3 (16.7–29.9)</td>
<td>0.921</td>
</tr>
<tr>
<td>Performance Status</td>
<td>0 66 (86%)</td>
<td>56 (85%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 11 (14%)</td>
<td>10 (15%)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.0 (0.4–2.4)</td>
<td>0.8 (0.3–3.0)</td>
<td>0.835</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.5 (2.4–4.6)</td>
<td>3.6 (2.5–4.9)</td>
<td>0.235</td>
</tr>
<tr>
<td>Ascites (present)</td>
<td>24 (31%)</td>
<td>11 (16%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Hepatic encephalopathy (present)</td>
<td>3 (4%)</td>
<td>4 (6%)</td>
<td>0.705</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>92 (41–123)</td>
<td>88 (40–133)</td>
<td>0.685</td>
</tr>
<tr>
<td>Child-Pugh Grade</td>
<td>A 51 (66%)</td>
<td>50 (75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 26 (34%)</td>
<td>17 (25%)</td>
<td>0.362</td>
</tr>
<tr>
<td>Diabetes (present)</td>
<td>15 (19%)</td>
<td>23 (34%)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Related Factors</th>
<th>Steroid Group (n=77)</th>
<th>Control Group (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main tumor size (mm)</td>
<td>20 (7–127)</td>
<td>21 (9–97)</td>
<td>0.443</td>
</tr>
<tr>
<td>Tumor number (single)</td>
<td>28 (36%)</td>
<td>19 (28%)</td>
<td>0.374</td>
</tr>
</tbody>
</table>

Values are median (range) unless otherwise noted.
Table 2  Adverse events observed after TACE

<table>
<thead>
<tr>
<th>Symptoms AEs</th>
<th>Steroid Group (n=77)</th>
<th>Control Group (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G0</td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Vomiting</td>
<td>70</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Fever</td>
<td>56</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Malaise</td>
<td>20</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Infusion site extravasation</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stomat pain</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hematologic AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP increased</td>
<td>73</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>ALT increased</td>
<td>32</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>AST increased</td>
<td>30</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>Hypalbuminemia</td>
<td>27</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>71</td>
<td>92</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>54</td>
<td>70</td>
<td>12</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>38</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>75</td>
<td>97</td>
<td>2</td>
</tr>
<tr>
<td>WBC decreased</td>
<td>68</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>60</td>
<td>78</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>56</td>
<td>73</td>
<td>17</td>
</tr>
</tbody>
</table>

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell. Values in parentheses are percentages. All statistical analyses were by the Cochran-Armitage test for trend.

were frequently observed as adverse events of TACE and effects of the steroids were expected, we evaluated these chronologically (Fig. 2a-e). Fever was most frequently observed on days 1 and 2 in the control group, while the incidence was significantly lower in the steroid group (days 1 and 3). The incidence was decreased almost to the baseline level on day 4 in both groups. When we analyzed the effect in different genders, there were no significant differences at any time points for the men, whereas a significant difference was found in the women on days 1 (p = 0.009) and 2 (p = 0.023) (Fig. 2a).

The frequencies of vomiting, nausea, and malaise were highest on day 1 and returned to the baseline on day 5. Vomiting was less frequent in the steroid group on day 2, but this difference was also observed before TACE (Fig. 2b). No difference in the frequency of nausea or malaise was observed between the steroid and control groups throughout the observation period (Fig. 2c, d).

For our analysis of pain, we excluded cases that showed an NRS rating of ≥ 2 before TACE to avoid the effect of pain that was unrelated to the treatment. The maximum NRS rating was 2.9 ± 2.6 (mean ± standard deviation) in the steroid group and 2.1 ± 2.6 in the control group; this difference was not significant (p = 0.116). The sum of NRS ratings from day 1 to day 5 was 5.8 ± 7.3 in the steroid group and 5.8 ± 8.7 in the control group (p = 0.977). For pain, we evaluated the frequency of an NRS rating of ≥ 2 chronologically; there were no significant differences between the two groups at any time point (Fig. 2e).

The body weights of the women were lower than those of the men, and to determine whether the difference in body weight was the reason for the gender differences in the effects of steroids on fever, we conducted a subanalysis for a group (33 men, 33 women) whose body weights matched at 1:1. The differences in fever incidence between the male and female groups from days 1 to 3 were still significant in this matched group of women (11% vs. 27% on day 1, 6% vs. 27% on day 2, and 6% vs. 29% on day 3 in the steroid group vs. the control group). This result suggests that the gender
(a) Fever (G1 to G3) all / female / male

(b) Vomiting (G1 to G3)

(c) Nausea (G1 to G3)

(d) Malaise (G1 to G2)

(e) Pain (NRS 1<)

Fig. 2 The degree of adverse events before and after TACE. A gender-specific difference was observed for fever. Solid line: The steroid group. Dashed line: The control group. *A significant difference in incidence between groups at that time point.
differences observed in the steroid effect were not due to the difference in body weight.

We conducted a subanalysis in the steroid group, and all adverse events except malaise were not significantly different among the 10 institutions. The incidence of malaise was low in 2 institutions where steroids were administered after TACE.

**Hematological disorders.** We compared 11 adverse hematological events (Table 2). There were no significant differences in the incidence of these events between the steroid and control groups. No patients in either group showed hyperglycemia over grade 2 after TACE.

**Severe adverse events.** Only one serious adverse event (pleural effusion) was reported in the control group. The patient was an 85-year-old male with multiple HCCs (maximum tumor diameter 27 mm), and his Child-Pugh score was 5 (Child-Pugh grade A). TACE using a 6.3-ml epirubicin emulsion was performed to A7, A8, and the lower right phrenic artery. The pleural effusion appeared 2 days after the treatment, and the patient’s respiratory status worsened. An albumin infusion and oxygenation relieved the respiratory status. We confirmed the disappearance of pleural effusion by computed tomography on the 36th day after TACE.

**Discussion**

In the steroid group, the incidence of fever was significantly lower than in the control group at 1 to 3 days after TACE. This tendency was particularly strong among the women. The incidence of vomiting in the steroid group also tended to be low, but no significant differences were found in nausea, malaise, or pain incidence between the groups. The risks of hyperglycemia and infection have been reported to increase with perioperative steroid administration [9]. However, we observed no significant differences in the incidence of adverse hematological events, including hyperglycemia, between the present steroid and control groups. In addition, we did not observe any other disadvantages associated with steroid administration.

When tumor tissue and the neighboring liver parenchyma are embolized by TACE, many cytokines and prostaglandin are produced, resulting in inflammation. Though selective TACE has become common in Japan for reducing postembolization syndrome, undesired effects cannot be avoided. Steroids block the effects of factors causing inflammation and suppress the function of leukocytes that elevate inflammation. The incidence of fever after TACE in the steroid group of the present study might have been reduced by this anti-inflammatory function of steroids. However, few studies have been conducted because of the difficulty in unifying the procedures of TACE. In addition, many physicians are wary of increasing their patients’ risk of infection and/or exacerbating hepatitis by the use of a steroid.

Steroids are widely used to prevent the nausea caused by anticancer drugs. In particular, dexamethasone, a strong and long-acting steroid, is used for anti-nausea purposes prior to the administration of various anticancer drugs [10-13]. Ho et al. reported that dexamethasone prevents nausea and vomiting after surgery [9]. In the present study, we examined the differences in the incidence of nausea and vomiting after TACE in the presence or absence of steroids. The incidence of vomiting was significantly lower in the steroid group, but the incidence of vomiting was already high before treatment in the control group. Therefore, we were not able to determine the effect of steroids on vomiting.

We used hydrocortisone succinic acid ester sodium, a short-acting steroid, to suppress inflammation after TACE. The incidence of nausea and vomiting may have been further decreased if a long-acting steroid had been used in this patient series. However, it is difficult to use strong, long-acting steroids for the purpose of relieving acute inflammation caused by TACE because many of the patients suffer from viral hepatitis. The exacerbation of hepatitis caused by the withdrawal of a steroid is sometimes dangerous, especially for cirrhotic patients with hepatitis B virus infection. In addition, it was reported that the side effects of steroids, such as gastrointestinal mucous membrane disorder, hyperglycemia, and psychic disturbance, occur more readily in strong steroid users [9]. Infection at the embolic site is another concern.

When we examined the post-treatment effect of steroids on fever, differences were revealed between the sexes in a gender-related subanalysis. There is reported evidence suggesting that gender is an important factor in pain modulation. According to Pueretti et al. [14], modulation of the endogenous opioid system and sex hormones are factors that influence pain sensitivity in males and females. We have found no reports about gender differences in the effects of steroids on fever;
this phenomenon might have happened by chance. A similar study was reported by Kogut et al. [15]. They compared the requirements for narcotic and antiemetic medications after TACE for HCC among three patient groups with differing dexamethasone administration regimens. Their results support our finding that vomiting after TACE is decreased by steroid administration. However, we cannot directly compare the Kogut study with our present investigation because their study evaluated the degree of symptoms of patients based on drug consumption, not on a rating scale.

Our study does have limitations. First, the TACE procedure was considered to be equal between the treatment groups, but our study was not a randomized controlled trial, so we cannot rule out the influence of technical differences. Second, the number of patients was not large enough to detect small differences in multiple adverse events. Third, the protocol for the steroid administration was not unified among the institutions.

Despite these limitations, the results of our analyses clearly demonstrated that steroid treatment before and after TACE for HCC was safe, and that it was useful for relieving postoperative fever. The effect seemed to be stronger in women than in men, but this needs further investigation.

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