Dexamethasone prevents TACE-induced adverse events
A meta-analysis

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Abstract
Background: While dexamethasone has been applied following transcatheter arterial chemoembolization (TACE) for years, its clinical effects have not been determined. In the current study, we aimed to evaluate the efficacy of dexamethasone in preventing adverse events induced by TACE.

Methods: Literature retrieval was conducted using globally recognized online databases, namely MEDLINE, EMBASE, and Cochrane Central, to identify randomized controlled trials (RCTs) of dexamethasone application in patients undergoing TACE. The relative odds ratios (ORs) of incidence rates of three adverse events, namely, fever, abdominal pain and nausea/vomiting, were calculated. The value of I2 was applied to evaluate the heterogeneity of the trials, and the overall publication bias was assessed with Egger test.

Results: Four RCTs containing 350 subjects were included for the pooled estimation. Dexamethasone significantly reduced the incidence rate of TACE-induced adverse events (OR = 1.237, 95% CI: 1.170–1.308, P < .001) with moderate heterogeneity (I2 = 46.0%). The result of Egger test revealed a publication bias for the included studies.

Conclusion: The current meta-analysis confirmed the efficacy of dexamethasone in preventing TACE-induced adverse events. To confirm the practicality of dexamethasone use with TACE, further studies with large sample sizes are warranted to update the evidence-based analyses.

Abbreviations: 5-HT3 = 5-hydroxytryptamine 3, CI = credible interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, OR = odds ratio, PES = postembolization syndrome, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, TACE = transcatheter arterial chemoembolization.

Keywords: dexamethasone, meta-analysis, transcatheter arterial chemoembolization

1. Introduction

Liver cancer is one of the most common malignant tumors and has the fourth highest cancer-related mortality rate worldwide.[1-2] Based on the developments of therapeutic procedures and further understanding of pathogenesis, the current treatments for liver cancer are multifarious and can be selected based on the characteristics of the tumor and systemic status of the patient.[3] In addition to surgical resection and traditional chemoradiotherapy, interventional therapy, such as transcatheter arterial chemoembolization (TACE), is widely performed in patients suffering from liver cancer.

TACE is recognized as an efficient and safe therapeutic procedure for unresectable multifocal and massive hepatocellular carcinoma (HCC).[4,5] By inducing ischemia and necrosis of tumor tissue through arterial chemoembolization, TACE efficiently suppresses the development of liver cancer and can be applied to recurrence, which occurs quite commonly in HCC; therefore, TACE contributes to tumor control and retreatment.[6,7] Given its feasibility and safety, TACE has been utilized for liver cancer for decades; nevertheless, postembolization syndrome (PES), which refers to a series of typical symptoms including fever, abdominal pain, and nausea/vomiting generally induced by TACE, turns out to be a notable clinical issue related to prognosis.[8] Presenting from 1 day to 5 days after the TACE
to meet the inclusion criteria (Fig. 1).[19] A total of 4 RCTs were identified to meet the inclusion criteria (Fig. 1). [15–22] The pooled quantitative analysis of the included studies was conducted following the principle of the PRISMA statement.[16] We registered the current meta-analysis in the PROSPERO database (CRD42020176322). To obtain access to the relevant trials, we searched electronic databases using the MeSH terms including liver neoplasms, chemotherapy, infusion, intraarterial, and dexamethasone. The studies of interest were initially screened by the inclusion criteria listed above and all relevant trials were collected separately and in combination to search the electronic databases recognized globally, including MEDLINE, EMBASE, and Cochrane Central. The studies of interest were initially screened by the inclusion criteria and their full-text versions were obtained. After an initial review, 4 RCTs were found to meet the inclusion criteria (Fig. 1).

2. Methods

2.1. Literature search and retrieval

Current meta-analysis was based entirely on previous published studies which had declared ethical approvals and no original clinical raw data was collected or utilized, thereby ethical approval was not conducted for this study. The current meta-analysis of the published studies of perioperative dexamethasone application for TACE-associated adverse events was conducted following the principle of the PRISMA statement.[16] We registered the current study online with PROSPERO (ID CRD42020176322). To obtain access to the relevant trials, we searched electronic databases using the MeSH terms including liver neoplasms, chemotherapy, infusion, intraarterial, and dexamethasone. The studies of interest were initially screened by the inclusion criteria of full text with English abstracts; there were no limitations according to full-text language or publication date.

2.2. Inclusion and exclusion criteria

The study inclusion criteria were as follows:

(1) studies conducted on adult participants;
(2) studies on liver cancer patients undergoing TACE;
(3) randomized controlled trials (RCTs);
(4) application of dexamethasone as an experimental intervention; and
(5) available targeted parameters reported in the form of data.

The exclusion criteria were established as follows:

(1) non-RCTs;
(2) inadequate raw data of interest;
(3) replicated studies;
(4) basic science or animal experiment studies;
(5) study protocols, comments, reviews, case reports, or conference summaries.

2.3. Parametric data selection and extraction

In the current study, we evaluated the capability of dexamethasone to reduce TACE-associated adverse events. Considering the complicated connotation of adverse events, the 3 main outcomes were determined to estimate the relative efficacy of dexamethasone compared with the control group. The I² index was calculated to evaluate the heterogeneity among the included studies. A fixed-effects model was used to estimate the overall ORs if I² < 50%, which indicates that no significant heterogeneity exists. In contrast, a random effects model was applied when I² ≥ 50%.[18] The interpretation of heterogeneity was roughly defined as follows: I² values of 0% to 30% represented homogeneity that might not be important; I² values of 30% to 60% represented moderate heterogeneity; I² values of 60% or more represented considerable heterogeneity. Moreover, Egger test was conducted to assess publication bias, and a value of P < .05 was identified as an indication of significant publication bias. The statistical manipulation and graphic rendering for this meta-analysis were accomplished utilizing the STATA software package (Version 15.0).

2.4. Quality assessment

The quality assessment of the included trials was carried out independently by 2 investigators using the Cochrane Risk of Bias assessment tool.[17] The relative risks of bias for individual trials was determined by the following items:

(1) selection bias;
(2) performance bias;
(3) detection bias;
(4) attrition bias;
(5) reporting bias and
(6) other bias.

The grades from the bias assessment were summarized in a graphical representation utilizing Review Manager software (version 5.3).

2.5. Statistical analysis

Pooling the results of individual studies together, the overall odds ratios (ORs) and their 95% confidence intervals (CIs) regarding the 3 main outcomes were determined to estimate the relative efficacy of dexamethasone compared with the control group. The I² index was calculated to evaluate the heterogeneity among the included studies. A fixed effects model was used to estimate the overall ORs if I² < 50%, which indicates that no significant heterogeneity exists. In contrast, a random effects model was applied when I² ≥ 50%.[18] The interpretation of heterogeneity was roughly defined as follows: I² values of 0% to 30% represented homogeneity that might not be important; I² values of 30% to 60% represented moderate heterogeneity; I² values of 60% or more represented considerable heterogeneity. Moreover, Egger test was conducted to assess publication bias, and a value of P < .05 was identified as an indication of significant publication bias. The statistical manipulation and graphic rendering for this meta-analysis were accomplished utilizing the STATA software package (Version 15.0).

3. Results

3.1. Study characteristics and quality assessment

After screening the 3442 papers obtained initially, 4 RCTs were identified to meet the inclusion criteria (Fig. 1). [15–22] A total of
350 subjects were ultimately included in the pooled comparison. The 2 RCTs were conducted in China and contained multiple groups; thus, we compared the experimental groups that applied dexamethasone (alone or in combination with other ingredients) with the control group. The general information about the studies and the primary characteristics are listed in Table 1.

For the assessment of bias, an overall high quality of the 4 RCTs was recognized, as exhibited in Figure 2. All of the trials were designed to assign subjects by means of random sequence generation and utilized blinding methods in the intervention and outcome detection processes.

3.2. **Dexamethasone significantly reduces adverse event after TACE**

To evaluate the efficacy of dexamethasone on reducing TACE-associated adverse events, we performed the current quantitative synthesis of individual results based on a fixed effects model. The pooled results indicated that dexamethasone significantly reduced the incidence of adverse events after TACE ($P<.001$). The overall OR was 1.237 (95% CI: 1.170–1.308) (Fig. 3). Additionally, the ORs specific to each of the 3 outcomes were calculated. The incidence rate of nausea/vomiting decreased with an OR of 1.187 (95% CI: 1.093–1.288, $P<.001$). Moreover, dexamethasone turned was associated with less risk of fever (OR = 1.291; 95% CI: 1.167–1.428; $P<.001$) and alleviation of postoperative abdominal pain (OR = 1.263; 95% CI: 1.170–1.308; $P<.001$). Regarding heterogeneity, the overall $I^2$ of the main result indicated moderate heterogeneity ($I^2 = 46\%$). Specifically, high heterogeneity was observed in the nausea/vomiting outcome subgroup with $I^2 = 68.6\%$, while the other outcome subgroups for fever and pain revealed insignificant heterogeneity with $I^2 = 4.9\%$ and $I^2 = 0\%$, respectively.
3.3. Publication bias

Egger test was applied to assess the overall publication bias, and the regression line is exhibited in Figure 4. The P value of bias was <0.05, implicating an obvious publication bias for the included studies.

4. Discussion

The current meta-analysis evaluated the efficacy of dexamethasone in preventing TACE-induced adverse events by pooling data from 4 RCTs. The pooled results revealed that the cumulative incidence rate of 3 outcomes, namely fever, abdominal pain and nausea/vomiting, was significantly reduced by dexamethasone. Furthermore, the effects of dexamethasone on each individual outcome were consistent with the main result.

TACE, which was first proposed by Professor Yamada in 1978, has been utilized for unresectable and recurrent liver neoplasms for decades due to its feasibility and therapeutic safety. Due to improvements in radiography and anticarcinogenic medication, TACE technology has become recognized as a superior treatment in HCC worldwide. The rationale for TACE includes selective embolization with intra-arterial infusion of lipiodol and chemotherapeutic drugs, which then block the blood supply of the tumor, thus inducing the shrinkage and necrosis of tumor tissues.[23,24] With increased concerns about the survival quality of patients suffering from HCC, the management of TACE-induced adverse events tends to be taken seriously. According to a systematic review of the efficacy and safety of TACE, approximately 47.7% of patients undergoing TACE were diagnosed with PES.[10] In addition, the incidence rates of fever, abdominal pain and nausea/vomiting were highest among TACE-induced adverse events;[10] these events were selected as the main outcomes in the current meta-analysis. The duration of hospitalization after TACE ranges from 12 hours to 6 days owing to individual and regional diversities,[25-27] which also impacts differences in outcomes resulting from post-TACE management.

It is thought that the cytolysis and necrosis of tumor cells following chemoembolization may lead to inflammatory cytokine release and a systemic stress response. Simultaneously, intra-arterial infusion can cause ischemia and injury of normal hepatic tissues due to differences in the operation. Moreover, the invasive procedures and side effects of chemotherapeutic drugs inevitably influence the homeostasis of patients.[14,20] Therefore, TACE-induced PES is mainly controlled with symptomatic treatments due to indeterminate etiopathogenesis at present. The application...
of a 5-HT3 receptor antagonist was proven to treat TACE-induced nausea and vomiting efficiently, and postoperative pain could be controlled by analgesic agents, such as oxycodone.\(^{[28,29]}\) Considering the metabolic load on the liver caused by multiple medications, dexamethasone, which has promising anti-inflammatory effects and inhibits immunoreactions, was expected to prevent PES. Several retrospective and prospective clinical trials have confirmed the function of dexamethasone in reducing TACE-induced adverse events.\(^{[15,22]}\) Targeting the glucocorticoid receptor dexamethasone plays an important role in inflammatory and immune responses through the genetic effects of inhibiting the expression of inflammatory mediators and inducing the apoptosis of immunocytes. Furthermore, the membrane-stabilizing action of dexamethasone has been recognized for a long time. In addition to the capability of maintaining lysosomal membrane integrity, dexamethasone could also regulate vascular permeability by strengthening cell-to-cell contacts.\(^{[30,31]}\) Based on the powerful effects of stabilizing the endothelium, dexamethasone plays an important role in both local and systemic inflammatory responses. Regarding antiemetic efficacy, it was reported that dexamethasone could prevent chemotherapy-induced cerebral nausea and vomiting,\(^{[32]}\) suggesting its potential in the management of PES. In the RCT by Ogasawara et al.,\(^{[21]}\) prophylactic dexamethasone treatment improved post-TACE recovery and protected HCC patients from postoperative fever, anorexia, and nausea/vomiting. Moreover, the application of dexamethasone in patients with diabetes or impaired glucose tolerance maintained the beneficial effects, and there was no significant change in either hemoglobin A1c or glycol-albumin over the course of 12 weeks. For the subjects with current or prior hepatitis B virus (HBV) infection, no reactivation of HBV was induced by dexamethasone in the follow-up period.
In conclusion, the results of this quantitative synthesis demonstrated that prophylactic dexamethasone treatment prevents adverse events induced by TACE. The current meta-analysis was an initial attempt to evaluate the efficacy of dexamethasone in patients undergoing TACE, providing an evidence-based suggestion and research direction for future studies on this topic. More high-quality clinical trials with large sample sizes and prolonged follow-up are expected to verify the safety and effects of dexamethasone with respect to the prevention of TACE-induced adverse events.

**Author contributions**

Tao Guo and Lei Chang and Wei Wang designed the research; Tao Guo, Lei Chang, Wei Wang, Nanhui Jiang, Fengying Rao, Cheng Gong, Ping Wu, Jian Yang and Zhiwu Liu performed the research and data collection; Lei Chang, Wei Wang contributed analytic tools and data analysis; Tao Guo and Lei Chang wrote the paper.

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**Figure 4.** Egger publication bias plot of adverse events.
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