RESEARCH ARTICLE

Nausea and Vomiting after Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma: Incidence and Risk Factor Analysis

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Abstract

Background: Nausea and vomiting after transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) are common in clinical practice, but few studies have reported the incidence and risk factors of such events. Objective: The purpose of this study was to analyze the incidence and risk factors of nausea and vomiting after TACE for HCC. Methods: This study was a single-center retrospective analysis of a prospectively maintained database. Between May 2010 and October 2012, 150 patients with HCC were analyzed for incidence and preprocedural risk factors. Results: The incidence of postembolization nausea and vomiting was 38.8% and 20.9%, respectively, in patients with HCC. Patients who developed nausea had lower levels (<100 IU/L) of serum alkaline phosphatase (ALP) compared to those without nausea (123.04 ± 69.38 vs. 167.41 ± 138.95, respectively, *p*=0.044). Female gender correlated to a higher incidence of nausea as well (p=0.024). Patients who developed vomiting, compared to those who did not, also had lower levels (<100 IU/L) of serum ALP (112.52 ± 62.63 vs. 160.10 ± 127.80, respectively, *p*=0.010), and serum alanine transferase (ALT) (35.61 ± 22.87 vs. 44.97 ± 29.62, respectively, *p*=0.045). There were no statistical significances in the incidences of nausea and vomiting between male patients over 50 years old and female patients who have entered menopause (*p*=0.051 and *p*=0.409, respectively). Multivariate analysis by logistic regression analysis demonstrated that female gender and ALP>100 IU/L were the most independent predictive factors of postembolization nausea (odds ratio (OR): 3.271, 95% CI: 1.176-9.103, *p*=0.023 and OR: 0.447, 95% CI: 0.216-0.927, *p*=0.030, respectively). ALP>100 IU/L was also the most independent predictive risk factor of postembolization vomiting (OR: 0.389, 95% CI: 0.159-0.952, *p*=0.039). Conclusions: Postembolizaiton nausea and vomiting are common in patients with HCC. Recognition of the risk factors presented above before TACE is important for early detection and proper management of postembolization nausea and vomiting. Nevertheless, future studies are required.

Keywords: Hepatocellular carcinoma - nausea - vomiting - risk factors - transcatheter arterial chemoembolization

Asian Pac J Cancer Prev, **14 (10)**, 5995-6000

Introduction

In 2013, primary liver cancer is one of the most hazardous cancers worldwide with an estimated 30,640 diagnosis and 21,670 deaths in America (American Cancer Society, 2013). Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70% to 85% of the total liver cancer burden (Perz et al., 2006). Liver resection, liver transplantation, and percutaneous ablation are the potential curative treatments for patients with early-stage HCC (Forner et al., 2010). Unfortunately, over half of all HCCs are diagnosed at an intermediate or later stage when these treatment options are less effective (Bruix et al., 2001). Transcatheter arterial chemoembolization (TACE) is widely considered an effective treatment for most patients with HCC. Currently, it is the standard treatment option for patients with intermediate stage HCC (Forner et al., 2010). This treatment option usually leads to adverse events and complications, with nausea and vomiting being the major sources of patient discomfort. While parameters predictive of postembolization nausea and vomiting are greatly needed, few studies analyzing predisposing risk factors have been conducted thus far. In the present study, we retrospectively analyzed the incidence and preprocedural risk factors that may be helpful in predicting postembolization nausea and vomiting in patients with HCC.

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Materials and Methods

Patients and enrollment

The study protocol was approved by the institutional review board at Fudan University Shanghai Cancer Center. Potential participants were identified by faculty in the Department of Integrative Oncology at Fudan University Shanghai Cancer Center, eligibility was assessed, and informed consent was obtained. Between May 2010 and October 2012, 150 patients with HCC were enrolled in the study and data was contained within a prospectively maintained database at the department of Integrative Oncology, Fudan University Shanghai Cancer Center. Inclusion criteria were as follows: 1) >18 years; 2) diagnosis of HCC based on cytology or the diagnostic criteria of the American Association of the Study of Liver Disease (Bruix and Sherman, 2005); 3) unavailable to resection or refused; 4) no contraindications for TACE; 5) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1 or 2; 6) Child-Pugh class A or B. The exclusion criteria included the following: 1) patient had an infection requiring antibiotic treatment; 2) patient had gastrointestinal bleeding.

TACE procedure

TACE was performed under conscious sedation and local anesthesia through the right femoral artery with a 5-F catheter according to Seldinger's technique (Seldinger, 1953). Hepatic and superior mesenteric arteriograms were carried out to define the location and size of tumor nodules. The arteries supplying the tumors were superselectively catheterized as close to the tumor as possible. When accessory hepatic arteries were present, they were catheterized successively followed by infusion of 200 mg of oxaliplatin, 60 mg of pirarubicin mixed with 1-20 ml of lipiodol. The dose of lipiodol depended on the size and vasculature of the tumor. Digital subtraction angiography (DSA) was used to plan the arterial treatment and to avoid injection of embolic material into nonhepatic arteries.

Follow-up after TACE

One month after TACE, tumor responses were evaluated by computed tomography (CT) or magnetic resonance imaging (MRI). Repeat TACE procedures were carried out based on tumor response and patient health.

Measures

Hepatitis B surface antigen (HBsAg) status, serum α-fetoprotein (AFP), complete blood count (CBC), and hepatic and renal function tests were performed prospectively in each patient. Tumor characteristics, such as size and location, were assessed in abdominal CT or MRI one week prior to TACE. Tumor staging was determined by Barcelona Clinic Liver Cancer (BCLC) classification (Llovet et al., 1999; Forner et al., 2010). The tumor response evaluation for this study was assessed by CT or MRI which was performed one week before and one month after TACE in each patient by the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009). According to RECIST criteria, complete response (CR) is defined as a disappearance of all recognizable tumors in the liver. Partial response (PR) is defined as a minimum reduction in the sum of the longest diameters of the lesions by 30%, taking as reference the baseline sum of the longest diameter. Progressive disease (PD) is considered either the appearance of new lesions or a minimum increase in the sum of the longest diameters by 20%, taking as reference the smallest sum of the longest diameters since the beginning of the study. Stable Disease (SD) is considered as neither enough shrinkage to qualify for PR nor a sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameters since the beginning of the study.

The Questionnaire used was the MD Anderson Symptom Inventory (MDASI) table which was surveyed for 5 days: on the same day before TACE, and on days 1, 2 and 4 after TACE. The data on the same day before TACE was analyzed in the study. MDASI measures on a 0 to 10 numeric rating scale, both the severity of symptoms and interference with patients' daily activities. Higher scores represent more severe symptoms and a greater interference with patients' daily activities. The MDASI measures 13 core symptom items, including nausea and vomiting in cancer patients. Six other items were used to assess interference to patients' daily activities.

Patients received anti-nausea or anti-emetic medications before and during chemoembolization.

Statistical analysis

Categorical variables were described using percentages. Continuous variables were expressed as means and standard deviations. Comparisons of categorical variables were made using the chi-square test or Fisher's exact test, where appropriate. Comparisons of continuous variables were carried out using a two-sided test or Mann-Whitney U-test, where appropriate. Pearson's correlation coefficient was used to determine the relationship between numerical variables, such as the tumor number and the degree of nausea or vomiting. To determine the risk factors associated with postembolization nausea or vomiting, patient and tumor-related variables including age, gender,

Table 1. Characteristics of Study Patients

Age (mean, range)	55.10±10.30 (28-74)
Gender (male/female)	120/19
HBsAg (positive/negative)	105/34
Liver function tests before TACE	
TB (μmol/l)	14.49±6.56
ALT (IU/l)	43.02±28.53
AST (IU/l)	54.72±41.88
ALP (IU/l)	150.17±118.63
LDH (IU/l)	251.45±293.33
AFP (ng/ml)	1110.72±1324.95
BCLC stage (A/B/C)	4/85/50
ECOG PS (0/1/2)	136/2/1
Tumor number(single/multiple)	75/64
Tumor size (cm)	7.17±3.74
Dose of iodized oil (ml)	8.23±4.71

HBsAg, hepatitis B surface antigen; TB, total bilirubin; ALT, alanine transferase; AST, aspartate transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Comparisons of Postembolzation with and Without Nausea and Vomiting

	With nausea	Without nausea	*p*-value	With vomiting	Without vomiting	*p*-value
No. of patients	54(38.8%)	85(61.2%)		29(20.9%)	110(79.1%)	
Age (years)	53.35±13.05	55.52±10.03	0.332	54.86±10.75	54.63±11.50	0.935
Gender (n, %)			**0.024**			0.075
Male	42(77.8%)	78(91.8%)		22(75.9%)	98(89.1%)	
Female	12(22.2%)	7(8.2%)		7(24.1%)	12(10.9%)	
HBsAg			0.423			0.639
Positive	43(79.6%)	62(72.9%)		23(79.3%)	82(74.5%)	
Negative	11(20.4%)	23(27.1%)		6(20.7%)	28(25.5%)	
Liver function tests before TACE						
TB (μmol/l)	14.79±6.30	14.30±6.74	0.394	14.59±6.81	14.47±6.52	0.896
ALT (IU/l)	37.35±21.76	46.63±31.69	0.081	35.61±22.87	44.97±29.62	0.045
AST (IU/l)	52.35±36.36	56.23±45.18	0.588	48.17±29.95	56.45±44.45	0.495
ALP (IU/l)	123.04±69.38	167.41±138.95	0.044	112.52±62.63	160.10±127.80	0.01
LDH (IU/l)	233.74±206.63	262.69±337.78	0.767	247.07±271.74	252.60±299.94	0.941
AFP (ng/ml)	1089.50±1335.15	1124.20±1326.20	0.848	1022.50±1287.52	1133.98±1339.44	0.999
BCLC stage (n,%)			0.589			0.51
A	1(2.6%)	3(3.0%)		1(4.8%)	3(2.5%)	
B	26(68.4%)	59(58.4%)		14(66.7%)	71(60.2%)	
C	11(28.9%)	39(38.6%)		6(28.5%)	44(37.3%)	
ECOG PS			1			1
0	53(98.1%)	83(97.6%)		107(97.3%)	29(100.0%)	
1	1(1.9%)	1(1.2%)		2(1.8%)	0(0.0%)	
2	0(0.0%)	1(1.2%)		1(0.9%)	0(0.0%)	
Tumor number	1.74±1.10	1.88±1.10	0.379	1.86±1.10	1.82±1.11	0.825
Tumor size (cm)	68.69±39.41	73.70±36.08	0.324	65.34±32.32	73.52±38.64	0.301
Dose of lipiodol (ml)	8.29±5.41	8.19±4.24	0.645	8.05±4.18	8.27±4.86	0.982

HBsAg, hepatitis B surface antigen; TB, total bilirubin; ALT, alanine transferase; AST, aspartate transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status

HBsAg, BCLC stage, ECOG PS score, tumor number, tumor size, and dose of lipiodol were gathered. Factors significant in the univariate logistic regression analysis were entered into a stepwise multivariate analysis to find the most significant risk factors. $P<0.05$ was considered significant for all tests. Statistical analysis was performed with SPSS 16.0 for windows (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Among 150 patients with HCC enrolled in the prospective study, 2 dropped out because they were unable to receive TACE treatment after signing informed consent, and 9 dropped out because of nausea or vomiting before TACE. Finally, a total of 139 patients were included in this study. Characteristics of all patients are listed in Table 1.

Tumor responses after TACE

Of 139 patients, 107 had CT or MRI images available for retrospective evaluation of tumor responses. Inevitably, since the study was retrospective, 32 patients were unable to be evaluated for tumor responses due to absent images at the time of evaluation. Overall response rates were 1 patient with CR, 7 patients with PR (6.54%, 95% CI: 1.96-11.22), 71 patients with SD (66.36%, 95% CI: 57.40-75.31), and 28 patients with PD (26.17%, 95% CI: 17.84-34.50).

Nausea and vomiting after TACE and clinical features

On the first day after TACE, nausea occurred in 54 (38.8%) patients and vomiting occurred in 29 (20.9%) patients. Of the 54 nausea patients, 28 (51.9%) had vomiting, and of the 29 vomiting patients, 28 (96.6%) had nausea. A comparison of TACE procedures with and without nausea and vomiting is shown in Table 2. Patients who developed nausea, compared to those who did not, had lower levels of serum alkaline phosphatease (ALP) (123.04 ± 69.38 vs. 167.41 ± 138.95, p=0.044). Further, female gender was associated with a higher incidence of nausea as well (p=0.024). There were no statistical significances in the incidences of nausea and vomiting between male patients over 50 years old and

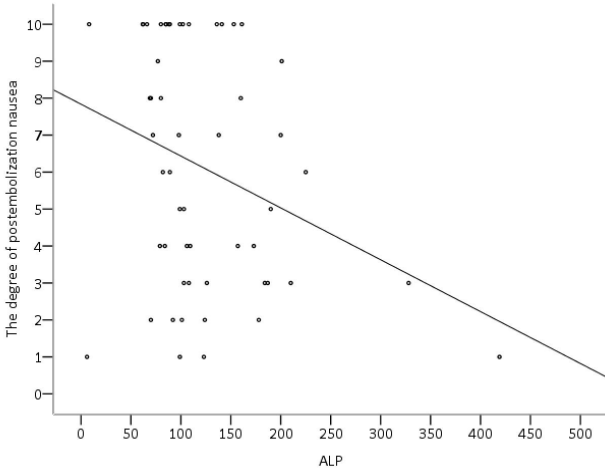

Figure 1. Correlation Between the Degree of Postembolization Nausea and the Level of ALP (r = -0.291, p = 0.033)

Table 3. Univariate Analysis of Potential Predictors of Postembolization Nausea and Vomiting

	Nausea			Vomiting		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Age (> 60 years)	0.5	0.233-1.070	0.074	0.888	0.368-2.142	0.791
Gender (female)	3.184	1.166-8.696	0.024	2.598	0.918-7.356	0.072
HBsAg (positive)	1.45	0.641-3.283	0.373	1.309	0.484-3.543	0.596
TB (>17.1 μmol/l)	1.135	0.533-2.415	0.742	0.776	0.302-1.995	0.598
ALT (>40 IU/l)	0.47	0.230-0.961	0.039	0.281	0.106-0.742	0.01
AST (>45IU/l)	0.745	0.376-1.479	0.401	0.568	0.246-1.314	0.186
ALP (>100 IU/l)	0.456	0.224-0.932	0.031	0.29	0.124-0.675	0.004
LDH (>215 IU/l)	0.855	0.421-1.738	0.666	0.852	0.362-2.007	0.714
AFP (>400 ng/l)	1.017	0.513-2.015	0.962	1.12	0.494-2.541	0.786
BCLC stage C	0.724	0.352-1.489	0.38	0.617	0.251-1.518	0.293
Tumor number (>1)	0.704	0.353-1.403	0.318	0.94	0.413-2.139	0.883
Tumor size (>7 cm)	0.556	0.275-1.121	0.101	0.41	0.167-1.004	0.051
lipiodol (>5 ml)	0.828	0.405-1.695	0.606	0.757	0.315-1.819	0.534

HBsAg, hepatitis B surface antigen; TB, total bilirubin; ALT, alanine transferase; AST, aspartate transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer

Table 4. Multivariate Analysis of Potential Predictors of Postembolization Nausea and Vomiting

	Nausea			Vomiting		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Female gender	3.271	1.176-9.103	0.023			
ALP (>100 IU/l)	0.447	0.216-0.927	0.03	0.389	0.159-0.952	0.039

ALP, alkaline phosphatase

female patients who have entered menopause (p=0.051 and p=0.409, respectively). Patients who experienced vomiting, compared to those who did not, also had lower levels of both serum ALP (112.52 ± 62.63 vs. 160.10 ± 127.80, p=0.010) and serum alanine transferase (ALT) (35.61 ± 22.87 vs. 44.97 ± 29.62, p=0.045). A strong negative correlation was found between serum ALP and the degree of nausea (r= -0.291, p=0.033) as shown in Figure 1.

Univariate analysis of predictors of postembolizaiton nausea and vomiting

The univariate analysis of possible factors correlated with postembolization nausea and vomiting using univariate logistic regression analysis is presented in Table 3. Serum ALT and ALP were associated with postembolization nausea and vomiting. Female gender was also associated with postembolization nausea (OR: 3.184, 95% CI: 1.166-8.696, p=0.024). There was no difference in the tumor responses between patients with and without nausea. No differences were found between patients with and without vomiting.

Multivariate analysis of predictors of postembolization nausea and vomiting

Stepwise multivariate analysis by logistic regression analysis demonstrated that female gender and ALP>100 IU/L were the most independent predictive factors of postembolization nausea (OR: 3.271, 95% CI: 1.176-9.103, p=0.023 and OR: 0.447, 95% CI: 0.216-0.927, p=0.030, respectively). ALP>100 IU/L was also the most independent predictive factor of postembolization vomiting (OR: 0.389, 95% CI: 0.159-0.952, p=0.039). The result of multivariate analysis is presented in Table 4.

Discussion

TACE is widely accepted as an effective treatment for unresectable patients with HCC. TACE procedure was performed by selectively embolizing tumor-feeding arteries with lipiodol and infusing chemotherapeutic agents to attain the ultimate goal of tumor necrosis and shrinkage. However, the treatment usually results in adverse reactions and complications, the most distressing of which are nausea and vomiting (Coates et al., 1983). A meta-analysis showed that the incidence of nausea and vomiting ranges from 32.9% to 100% (Han and Zhang, 2007). Nausea and vomiting after TACE are so common that they are usually expected and inevitable in many cases. By definition, nausea has been described as a subjectively unpleasant sensation with awareness of the urge to vomit, and vomiting has been described as the forceful expulsion of upper gastrointestinal contents via the mouth caused by the powerful sustained contraction of the abdominal muscles (Watcha and White, 1992). Both nausea and vomiting are responses to stimuli. There are only a few published studies about nausea and vomiting after TACE; hence, the etiology of these symptoms is still unclear and considered complicated. Until now, there have been no studies demonstrating simple and effective parameters for predicting postembolization nausea and vomiting. It is of importance to determine predisposing risk factors for such symptoms.

In our study, we showed that postembolizaiton nausea and vomiting are common events and we demonstrated for the first time, female gender and ALP as the major risk factors predicting postembolization nausea. Many recent surgical reports showed that gender differences in prevalence of postoperative nausea and vomiting (PONV)

(Huppe et al., 2013; Moreno et al., 2013). Furthermore, ALP was the predisposing risk factor for postembolization vomiting as well. A strong negative correlation was found between serum ALP and the degree of nausea. There were no statistical significances in the incidences of nausea and vomiting between male patients over 50 years old and female patients who have entered menopause. The incidence of postembolization nausea and vomiting was more likely in younger women, just as reported in PONV (Thompson, 1999).We speculated that both phenomena above have similar etiology. Honkavaara et al. (1991) concluded that the highest incidence of PONV occurs during the luteal phase. This was in contrast to a retrospective study which demonstrated that the incidence of nausea and vomiting was higher on the first eight menstrual days (Beattie et al., 1991). A recent prospective study showed that patients in the luteal phase of their menstrual cycle might have a decreased risk of PONV after laparoscopic gynecological surgery in the early postoperative period (Simurina et al., 2012). Coburn et al. (1993) showed that the likelihood of vomiting was related to the peak plasma oestradiol level.

ALP, a phosphate monoester hydrolase, relating to bone metabolism in human body, catalyzes the hydrolysis and transfer of phosphate groups in alkaline conditions (Harris, 1990). Elevated levels of ALP may indicate metabolic disorders, such as bone disease or hepatic impairment. In our study, few patients had bone diseases; therefore, the elevation of ALP can be attributed to hepatic impairment. It is interesting to find that lower levels of ALP (< 100IU/L) was a risk factor of postembolization nausea and vomiting. We observed that lower levels of ALP (<100IU/L) occurred more frequently in patients with lower levels of ALT, AST and LDH (p=0.002, p=0.000 and p=0.001, respectively), and smaller tumor size (p=0.001). The mechanism explaining why patients with good liver function were susceptible to postembolization nausea and vomiting remains unclear to us.

There was no difference in tumor responses between patients with and without nausea, or between patients with and without vomiting. A possible explanation may be because there is no correlation between postembolizaiton nausea/vomiting and tumor response in reality. As illustrated in tumor responses after TACE, the majority of patients in the study were SD (66.36%, 95% CI 57.40-75.31). In our study, most HCC patients with inadequate liver reserves had liver cirrhosis because of hepatitis B. The amount of chemotherapeutic agents and lipiodol used during TACE was proportional to tumor size. However, in actual clinical practice, the dose of chemotherapeutic agents and lipiodol are usually reduced because of inadequate liver reserve, despite tumor size. The corresponding result was that the tumor response was unsatisfactory.

No differences were seen between doses of lipiodol in patients with and without nausea, as well as, vomiting. A possible explanation may be nontarget embolization. Unfortunately in clinical practice, minimal amounts of nontarget embolization are sometimes unavoidable, despite superselective catheterization (Dhand and Gupta, 2011). Chemotherapeutic agents can be inadvertently directed into gastrointestinal mucosa via gastric or duodenal branches (Sakamoto et al., 1998). Another possible explanation may be contributed to the dose reduction in chemotherapeutic agents and lipiodol, in participants with inadequate liver reserve. These participants might not have had doses sufficient enough to cause postembolization nausea and vomiting.

Postembolization nausea and vomiting was self-limiting. Standard of care treatment, including intravenous and oral antiemetic, was required until mild or complete symptom resolution occurred. Changes in dietary regimens were also needed, as patients couldn't tolerate oral intake due to nausea and appetite loss. Because few studies about the treatment of postembolization nausea and vomiting have been published, it was difficult to predict whether it would be necessary to administer antiemetic preventively. In our study, we were able to demonstrate risk factors of postembolization nausea and vomiting. Understanding these risk factors is an important strategy to ensure patients at highest risk receive appropriate preventive measures prior to TACE.

In conclusion, postembolization nausea and vomiting was common in patients with HCC. Patients with ALP<100IU/L were at a higher risk for postembolizaiton nausea and vomiting. Female gender was also a risk factor of postembolization nausea for younger women who were still menstruating. Recognition of these risk factors before TACE is important for early detection and proper management of postembolization nausea and vomiting. Due to limited sample size and non-multicenter study, the results of the study may not reflect the overall incidence of postembolization nausea and vomiting in HCC patients. Thus, future studies are required.

Acknowledgements

The author (s) declare that they have no competing interests.

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