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Aspirin Is Associated With Improved Liver Function After Embolization of Hepatocellular Carcinoma

F. Edward Boas¹, Karen T. Brown¹, Etay Ziv¹, Hooman Yarmohammadi¹, Constantinos T. Sofocleous¹, Joseph P. Erinjeri¹, James J. Harding², Stephen B. Solomon¹

¹Department of Radiology, Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065

²Department of Medicine, Gastrointestinal Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

OBJECTIVE.—The purpose of this study was to assess the mechanism by which aspirin therapy improves survival when combined with transarterial chemoembolization or transarterial embolization (TAE) for hepatocellular carcinoma (HCC).

MATERIALS AND METHODS.—A retrospective review included 304 patients with HCC who were treated with TAE. The patients were divided into two groups on the basis of whether the patient took aspirin ($n = 42$) or did not take aspirin ($n = 262$) at the time of initial TAE. For each patient, response of embolized tumors, time to progression, initial site of progression, survival time, and liver function test results before and after embolization were evaluated.

RESULTS.—Patients taking aspirin and those not taking aspirin at the time of initial TAE for HCC had no difference in initial response rate (88% vs 90% complete response or partial response, $p = 0.59$), median time to progression (6.2 vs 5.2 months, $p = 0.42$), initial site of progression ($p = 0.77$), or fraction of patients dying with disease progression (88% vs 89%, $p = 1.00$). Before embolization, there was no difference in mean bilirubin level (0.8 vs 0.9 mg/dL, $p = 0.11$) for patients taking versus not taking aspirin. Among patients taking aspirin, bilirubin level was significantly lower 1 day (0.9 vs 1.3, $p < 0.001$), 1 month (0.9 vs 1.2, $p = 0.048$), and 1 year (0.8 vs 1.0, $p = 0.021$) after embolization. The median overall survival period after initial embolization was longer for patients taking aspirin (57 vs 23 months, $p = 0.008$).

CONCLUSION.—Aspirin use is associated with improved liver function test results and survival after TAE for HCC. It is not associated with differences in response or time to progression.

Keywords

aspirin; embolization; hepatocellular carcinoma; hepatoprotective; liver function

Retrospective studies have shown that aspirin use is associated with improved survival when combined with transarterial chemoembolization [1] or transarterial embolization (TAE) [2]

Address correspondence to F. E. Boas (boasf@mskcc.org).

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for hepatocellular carcinoma (HCC). Several theories have been proposed to explain these results [2]. First, aspirin is antiinflammatory. Chronic inflammation in the liver can result in cirrhosis and development of HCC. Retrospective studies have shown that aspirin reduces the rate of death of chronic liver disease [3] and reduces the risk of development of HCC [3]. Second, aspirin is antiangiogenic. It inhibits hypoxia-induced angiogenesis in in vitro models [4, 5], which might prevent TAE-induced ischemia from promoting angiogenesis and growth of the residual viable tumor [6, 7]. Third, aspirin is antiglycolytic. It decreases glucose consumption and the viability of tumor cells in vitro [8], which might make tumor cells less likely to survive TAE-induced ischemia [9].

To distinguish between these three mechanisms, we can examine response, recurrence, and liver function after embolization of HCC. If the antiinflammatory mechanism is dominant, we would expect patients taking aspirin to have better liver function and to be less likely to have new HCC develop. If the antiangiogenic mechanism is dominant, we would expect patients taking aspirin to have a longer time to progression after embolization. If the antiglycolytic mechanism is dominant, we would expect patients taking aspirin to have a higher rate of response to embolization.

The purpose of this study was to retrospectively compare response, time to progression, and liver function after embolization of HCC in patients taking versus those not taking aspirin to gain insights into the mechanism of improved survival among patients taking aspirin.

Materials and Methods

Patient Selection

This HIPAA-compliant retrospective study received institutional review board approval. A previously reported retrospective review [2] had identified 304 consecutively registered patients with HCC (232 [76%] men, 72 [24%] women; mean age at embolization, 69 years) who were treated with TAE between June 2009 and April 2016. Further analysis of this group of patients was conducted in the current study. Patients with prior ablation or radioembolization were excluded. Particle embolization was performed to stasis according to a standard published protocol [10].

Aspirin Use

According to hospital policy, the outpatient medication list (including over-the-counter medications) was reviewed with the patient at each outpatient or inpatient visit. Patients who reported taking aspirin 7 days before through 30 days after initial TAE ($n = 42$) were compared with patients who did not take aspirin ($n = 262$) during the same time interval. Aspirin doses were 81 mg orally daily (35 patients), 325 mg orally daily (five patients), 162 mg orally daily (one patient), and 81 mg orally every other day (one patient).

Retrospective Chart Review

For each patient, the following information was collected: response of embolized tumors, time to progression after initial embolization, initial site of progression (treated tumor, untreated liver tumor, or extrahepatic tumor), survival time, cause of death, and liver

function test results before and after embolization. Response of embolized tumors was evaluated by means of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [11] at contrast-enhanced CT or MRI performed 1 month after initial embolization. Time to progression at any site was evaluated with mRECIST after completion of the originally planned staged treatment (for example, right and left lobe embolization). The initial site of progression was classified as follows: progression of a treated liver tumor, new or growing tumor in the liver without progression of any treated tumor, or extrahepatic progression without intrahepatic progression. Images were reviewed by a board-certified radiologist with 8 years of experience in abdominal imaging who was blinded to the aspirin status of each patient at image review.

Mean liver function values (total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and international normalized ratio [INR]) at each time point after embolization were determined by examining the most recent laboratory values of patients who were still undergoing follow-up laboratory tests. Preprocedure liver function tests were performed within 30 days before the procedure. In the calculation of mean INR, 29 patients who underwent outpatient anticoagulation were excluded. Patients who received prophylactic inpatient heparin therapy were not excluded.

Statistical Analysis

Kaplan-Meier curves were compared by logrank test. Proportions were compared by Fisher exact test or chi-square test. Laboratory values were compared by two-tailed *t* tests and repeated-measures ANOVA. Statistical tests were performed with Mathematica 9 (Wolfram) and Excel 2016 (Microsoft). Values of $p < 0.05$ were considered significant.

Results

Survival

Prior analysis of these patients [2] showed that the median overall survival time after initial embolization was longer for patients taking aspirin (57 vs 23 months, $p = 0.008$). Before embolization, the group taking aspirin and the group not taking aspirin had no difference in American Joint Committee on Cancer (AJCC) stage, Child-Pugh score, cause of underlying liver disease, Eastern Cooperative Oncology Group performance status, prior sorafenib therapy, or prior liver resection [2]. There also was no difference in risk of postoperative death due to comorbidities (Charlson comorbidity index) for patients taking versus those not taking aspirin [2]. Indications for taking aspirin were coronary artery disease (15 patients), cardioprotective effect in the absence of documented coronary artery disease (one patient), atrial fibrillation (one patient), peripheral arterial disease (six patients), cerebrovascular disease (two patients), multiple vascular indications (five patients), arthritis (four patients), and unknown (eight patients).

Response

Four patients had no follow-up images, and two patients had no measurable lesions according to mRECIST. The other 298 patients had no difference in mRECIST response

between the aspirin and no aspirin groups (88% vs 90% complete or partial response, $p = 0.59$ by Fisher exact test (Table 1).

Progression

Median times to progression were 5.2 months in the no aspirin group and 6.2 months in the aspirin group ($p = 0.42$ by logrank test) (Fig. 1). Among patients with progressive disease, there was no difference in the initial site of progression ($p = 0.77$ by chi-square test) (Table 2).

Cause of Death

To determine the fraction of patients who died with disease progression, we examined patients who died and had either progression at imaging or no progression at imaging within 6 months of death. In the no aspirin group, 127 of 142 (89%) patients died with evidence of HCC progression at imaging. In the aspirin group, seven of eight (88%) patients died with HCC progression at imaging ($p = 1.00$ by Fisher exact test). For the 15 (11%) patients in the no aspirin group who died without documented HCC progression, the causes of death were liver failure (three patients), pneumonia (two patients), bleeding varices (one patient), and unknown (nine patients). For the one patient in the aspirin group who died without documented HCC progression, the cause of death was liver failure. None of the patients died of myocardial infarction or stroke.

Liver Function

Before embolization, there was no difference in mean bilirubin level (0.8 vs 0.9 mg/dL, $p = 0.11$) for patients taking versus not taking aspirin (Table 3 and Figs. 2 and 3). The bilirubin level was significantly lower for patients taking aspirin when it was measured 1 day (0.9 vs 1.3, $p < 0.001$), 1 month (0.9 vs 1.2, $p = 0.048$), and 1 year (0.8 vs 1.0, $p = 0.021$) after embolization.

Before embolization, there was no difference in albumin level or INR between the group taking aspirin and the group not taking aspirin. One and 4 months after embolization, the albumin level was significantly worse in the group not taking aspirin. The AST level was significantly worse in the group not taking aspirin both before and 1 month after embolization. The ALT level before embolization was significantly worse in the group not taking aspirin. Repeated-measures ANOVA confirmed that the changes in liver function test results after embolization were different for the groups taking aspirin and not taking aspirin (Table 4).

Discussion

Aspirin therapy is associated with both improved results of liver function tests and improved survival after TAE for HCC. It is not associated with any differences in response, time to progression, or initial site of progression (arguing against a direct antitumor effect). None of the patients died of myocardial infarction or stroke (arguing against a cardioprotective effect causing the improved survival). There was no difference in the predicted risk of postoperative mortality due to age or comorbidities in the group taking versus the group not

taking aspirin according to the Charlson comorbidity index (arguing against preferential use of aspirin by healthier patients). The groups taking aspirin and not taking aspirin also had no difference in AJCC stage, Child-Pugh score, or cause of underlying liver disease before TAE. These results suggest that aspirin is hepatoprotective for patients with HCC treated with embolization.

Previously published data also support our theory that aspirin improves survival by reducing liver inflammation and thus improving liver function [2, 3, 12, 13]. Other nonsteroidal antiinflammatory drugs (NSAIDs), most commonly, ibuprofen and naproxen, were also associated with improved survival when taken at the time of embolization for HCC [2]. Aspirin was not associated with survival differences after locoregional therapy for neuroendocrine tumors or colorectal liver metastases [2], probably because patients with these cancers are less likely to have cirrhosis. Retrospective studies have shown that patients with chronic liver disease who take aspirin have decreased liver fibrosis [12] and decreased risk of death of chronic liver disease [3]. An animal study [13] showed that aspirin and clopidogrel therapy decreased liver inflammation, liver fibrosis, and development of HCC in a mouse model of chronic hepatitis B.

Although the differences in liver function test results in the groups taking and not taking aspirin were small, standard biochemical liver function tests are insensitive to early cirrhotic changes. Perfusion imaging can be used to detect early cirrhotic changes that are predictive of survival but that are not reflected in the Child-Pugh score [14]. Results of biochemical liver function tests are not accurate predictors of the finding of fibrosis at liver biopsy [15]. Thus, a normal bilirubin level does not mean that the liver is normal; small changes in biochemical liver function test results might underestimate the degree of liver injury after embolization.

Improved liver function in the aspirin group was persistent for at least 1 year after embolization. A previous analysis by our group [16] showed that the patients taking aspirin were more likely to remain candidates for additional locoregional therapy. In the current study, the aspirin group had better AST results both before and after embolization, but bilirubin and albumin results were better only after embolization. This finding suggests that aspirin can improve liver function in patients with chronic liver disease but that the effect is more pronounced after TAE.

The lack of difference in response and time to progression argues against a substantial amount of antiglycolytic or antiangiogenic activity of aspirin in this patient population, most of whom took 81 mg of aspirin daily. In vitro experiments have shown antiangiogenic [4, 5] and antiglycolytic [8] effects of aspirin at concentrations higher than the typical peak plasma concentration of aspirin after an oral dose of 320 mg [17]. In addition, a case report [18] described HCC that responded to celecoxib, which is a selective cyclooxygenase 2 (COX-2) inhibitor (aspirin inhibits COX-1 and COX-2). Future experiments should examine the optimal dose, route (oral or intraarterial), and type of NSAID to achieve the optimal combination of antiinflammatory, antiglycolytic, and antiangiogenic effects.

The main limitation of this study was that it was retrospective; thus, a confounding variable may account for the improved survival among patients taking aspirin. However, the groups taking aspirin and not taking aspirin had comparable liver function, AJCC stage, comorbidities, and other clinical characteristics before embolization. In addition, published results of animal studies and retrospective human data support the connection between NSAID use and decreased liver inflammation. Aspirin and β -blockers are typically taken together [2], raising the possibility that β -blockers, not aspirin, could be responsible for the improved survival. However, β -blockers reduce blood flow in the portal vein and thus would not be expected to improve liver function [19]. The second limitation of this study was that the association between aspirin use and survival was identified in a prior study in which 29 different medications or medication classes were examined [2]. Although the connection between aspirin and survival remained significant after Bonferroni correction for multiple comparisons, the magnitude of the survival benefit was probably overestimated [20]. The third limitation of this study was that there were too few patients to assess the optimal dose of aspirin and the dosage timing or to analyze the effect of aspirin on subgroups of patients (such as those with hepatitis B versus hepatitis C virus infection).

Conclusion

Aspirin use is associated with improved liver function test results and survival after TAE for HCC. It is not associated with differences in response or time to progression. The results should be confirmed in a randomized controlled trial.

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Fig. 1—. Graph shows time to progression (any site) after initial transarterial embolization for hepatocellular carcinoma ($p = 0.42$).

Fig. 2—

Graphs show mean laboratory values before (Pre) and after initial embolization of hepatocellular carcinoma. Results of *t* tests comparing groups taking aspirin and groups not taking aspirin are as follows: not significant (NS; $p > 0.05$), * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

A, Total bilirubin level.

B, Albumin level.

C, Aspartate transaminase (AST) level.

D, Alanine transaminase (ALT) level.

E, International normalized ratio (INR).

Fig. 3—

Tukey box plots show laboratory values before (Pre) and after initial embolization of hepatocellular carcinoma (median, quartiles, and outliers). Whiskers show lowest value within 1.5 interquartile range (IQR) of lower quartile and highest value within 1.5 IQR of upper quartile. Results of statistical tests are shown in Figure 2 and Table 4.

A, Total bilirubin level.

B, Albumin level.

C, Aspartate transaminase (AST) level.

D, Alanine transaminase (ALT) level.

E, International normalized ratio (INR).

TABLE 1:
Response to Embolization of Hepatocellular Carcinoma 1 Month After Embolization

mRECIST Category	Aspirin	No Aspirin
Complete response	20 (48)	111 (43)
Partial response	17 (40)	121 (47)
Stable disease	0 (0)	11 (4)
Progressive disease	5 (12)	13 (5)
Total	42	256

Note—There was no significant difference between the aspirin group and the no aspirin group ($p = 0.59$). Values in parentheses are percentages, which owing to rounding do not total 100 in the no aspirin group. mRECIST = modified Response Evaluation Criteria in Solid Tumors.

TABLE 2:

Initial Site of Progression After Embolization of Hepatocellular Carcinoma

Site	Aspirin	No Aspirin
Treated lesion	21 (52)	102 (48)
Liver	16 (40)	88 (41)
Extrahepatic	3 (8)	23 (11)
Total	40	213

Note—No significant difference was found between the aspirin group and the no aspirin group ($p = 0.77$). Values in parentheses are percentages.

TABLE 3:
Laboratory Values Before and After Embolization of Hepatocellular Carcinoma Among Patients Taking and Not Taking Aspirin

Time After Initial Embolization (d)	No Aspirin			Aspirin		
	Mean	SD	No.	Mean	SD	No.
Bilirubin (mg/dL)						
Before	0.94	0.57	262	0.77	0.65	42
1	1.22	0.88	262	0.87	0.39	42
30	1.19	0.96	255	0.94	0.69	42
120	1.1	1.01	233	0.83	0.56	41
365	1.02	0.76	172	0.75	0.56	35
Albumin (g/dL)						
Before	3.9	0.47	262	4.03	0.39	42
1	3.66	0.45	262	3.76	0.36	42
30	3.54	0.52	255	3.71	0.34	42
120	3.7	0.50	233	3.93	0.44	41
365	3.76	0.52	172	3.91	0.45	35
International normalized ratio ^a						
Before	1.13	0.13	242	1.09	0.12	33
1	1.17	0.15	242	1.14	0.15	33
30	1.21	0.18	235	1.15	0.16	33
120	1.17	0.19	214	1.12	0.14	32
365	1.13	0.14	159	1.13	0.13	27
Aspartate transaminase (U/L)						
Before	72	57	262	53	32	42
1	386	610	262	287	562	42
30	115	161	255	75	73	42
120	94	147	233	72	78	41
365	76	111	172	64	46	35
Alanine transaminase (U/L)						
Before	62	49	262	50	31	42
1	254	423	262	192	336	42

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Time After Initial Embolization (d)	No Aspirin			Aspirin		
	Mean	SD	No.	Mean	SD	No.
30	112	161	255	82	77	42
120	79	119	233	66	68	41
365	61	71	172	59	41	35

Note—All patients had laboratory values before and 1 day after embolization.

^aIncludes only patients not undergoing anticoagulation.

TABLE 4:

Repeated-Measures ANOVA Results

Variable	<i>p</i>					
	Bilirubin	Albumin	Aspartate Transaminase	Alanine Transaminase	INR	
Aspirin	0.05	NS	NS	NS	NS	
Time	0.05	0.001	0.001	0.001	0.001	
Aspirin × time	0.05	0.001	0.001	0.001	0.001	

Note—Results show that liver function test results change over time after embolization (Time), and that the liver function test result changes over time are significantly different in the aspirin group compared with the no aspirin group (Aspirin × time). NS = not significant ($p > 0.05$).