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# Low-Dose Aspirin in Combination with Transarterial Chemoembolization in Treatment of Unresectable Hepatocellular Carcinoma

**Alshimaa Mahmoud Alhanafy[1], Naser M. Abd Elbary[1], Mohammed S. Elwarkky[2], Eman G. Esmail[1], Ashraf E Abd Elghani [1]**

[1]Departments of Clinical Oncology and Nuclear Medicine, Faculty of Medicine and [2]Medical Imaging and Interventional Radiology, National Liver Institute, Menoufia University, Egypt

***Corresponding author:** Alshimaa Mahmoud Alhanafy, **Mobile:** (+20)01006454574,

**E-mail:** Alshimaa_Alhanafy@yahoo.com, **ORCID Number:** 0000-0002-5452-5967

## ABSTRACT

**Background:** Various strategies under investigation aim to improve the outcome of transarterial chemoembolization (TACE). Aspirin demonstrated chemopreventive, antithrombotic and anti- inflammatory properties. Moreover, it has been reported that aspirin may reverse apoptosis resistance in hepatocellular carcinoma (HCC) cell lines.

**Objective:** To explore the clinical impact of adding aspirin with TACE in management of unresectable HCC patients.

**Patients and Methods**: This prospective randomized trial included 60 cases diagnosed as HCC indicated for TACE; who were simply randomized into two arms with ratio 1:1; to control arm and aspirin arm. Aspirin arm patients received 75 mg of aspirin daily for 3 months; we assessed aspirin toxicity and disease outcome.

**Results**: In this study most of side effects of aspirin were of grade I gastrointestinal side effect. 10% of patients in aspirin arm had complete response versus 6.7 % in control arm and 30% had partial response in aspirin arm versus 23% in control arm, 30% of patients in aspirin arm had disease progression versus 40% in control arm. The median progression free survival and Overall survival were not reached for aspirin arm versus 11 and 22 months for control arm (P=0.035 and P=0.036 respectively).

**Conclusions**: Low dose aspirin use in selected unresectable intermediate stage HCC undergoing TACE is tolerable and could be associated with survival benefit.

**Keywords:** Aspirin, Transarterial Chemoembolization, Hepatocellular carcinoma.

## INTRODUCTION

Although hepatocellular carcinoma (HCC) is the 5th most frequent cancer, it has the 3rd leading cause of cancer death worldwide [(1)]. Transarterial chemoembolization (TACE) is associated with improvement of median overall survival (OS) of cases from sixteen to twenty months for intermediate disease stage of HCC [(2)].

Patients who responded initially to TACE could progress if they developed TACE refractoriness [(3)]. There are several factors affecting treatment response as patient's general condition, liver functions, initial tumor stage, and the technique used. TACE refractoriness has recently drawn much attention as regard TACE failure that will affect disease outcome [(4)].

TACE and sorafenib combination in SOCRATES study was feasible and showed an improvement in overall survival and response [(5)]. There is less valuable combination regimens, which had lack of a clear benefit like thalidomide with TACE, which had no survival improvement, so there is a need for other agents combined with TACE [(6)].

HCC carcinogenesis had high levels of COX-2 and aspirin have inhibitory action of COX-2 [(7)]. Aspirin could prevent transarterial embolization induced ischemia from initiating angiogenesis and proliferation of the viable cancer cells [(8)]. Moreover, aspirin could overcome apoptosis resistance in all HCC cell lines [(9)].

In this trial, we aimed to explore the clinical impact of adding aspirin with TACE in management of unresectable HCC patients.

## PATIENTS AND METHODS

In this randomized prospective trial, we included HCC cases of intermediate stage, BCLC; Barcelona clinic liver cancer B stage.

**Inclusion criteria:** HCC patients diagnosed by biopsy or specific imaging patterns in triphasic computed tomography (arterial enhancement and wash out in portal venous phases) or dynamic magnetic resonance imaging. We included HCC cases of intermediate stage [(10)] eligible to TACE, with hemoglobin level more than 10 gm/dl, platelet count above 100,000, normal serum creatinine, prothrombin time, and compensated cellular and vascular liver functions. Previous local treatment of HCC was allowed.

**Exclusion criteria:**

Patients who had gastrointestinal tract (GIT) ulcers or any cause of bleeding, patients with portal hypertension and/or esophageal varices, and patients with allergy to aspirin or had any contraindication for aspirin.

All patients were initially had complete clinical history taking, full examination, laboratory investigation; CBC, alpha fetoprotein (AFP), complete liver and kidney functions, imaging: triphasic CT with contrast, metastatic work up and upper endoscopy.

Total of 60 patients were randomized with ratio 1:1 into two groups: Control arm: TACE only and aspirin arm: TACE with combination of 75 mg oral



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tablet aspirin once daily given after meal, with proton pump inhibitors once daily before meal. The treatment continued for 3 months.

**During treatment:**

Every 3 weeks of treatment (CBC, liver, kidney functions) were done. After 3 weeks, triphasic CT was requested to assess response to treatment by using Modified (RECIST) criteria of HCC [(11)].

History and clinical examination were done every visit to assess treatment related toxicity using CTCAE version 5 [(12)]. At the treatment end we assessed treatment feasibility (number of patients completed the treatment) and number of TACE done. Patients' overall survival (OS) and progression free survival (PFS) were calculated.

**Ethical approval:**

**An approval from Ethical Committee at Faculty of Medicine, Menoufia University (IRB 12/2018onco38) was obtained, and all cases gave a written informed consent. The Helsinki Declaration was followed throughout the study's conduct.**

***Statistical analysis***

IBM SPSS version 20.0 (Armonk, New York: IBM Corp.) was utilized for the purpose of doing the data analysis. The qualitative information was conveyed through the use of number- and percentage-based descriptors. In order to determine whether or not the data follow a normal distribution, the Kolmogorov-Smirnov test was carried out on them. A number of statistical values, such as the minimum and maximum values, the mean, the standard deviation (SD), the median, and the interquartile range (IQR), were utilized to compile a summary of the quantitative data.

At the 5% level of analysis, it was determined that the results were statistically significant. The following tests were used to compare and contrast two different groups based on qualitative data: The chi-square, Fisher's exact, and Monte Carlo tests. The Mann-Whitney U test was the statistical method that was used in comparing two groups based on quantitative data that were not regularly distributed. Kaplan-Meier Survival curve was used for PFS and OS.

**RESULTS**

In this study the median age is 59 for both arms, we found statistically insignificant difference between the two studied arms regarding demographic data and co-morbidities (Table 1).

**Table (1): Comparing the two groups according to demographic data and comorbidities:**

| Data | Control Arm (n = 30) | | Aspirin Arm (n = 30) | | Test of sig. | P |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **Age (years)** | | | | | | |
| < 60 | 17 | 56.7 | 17 | 56.7 | $\chi^2$ = 0.000 | 1.000 |
| ≥ 60 | 13 | 43.3 | 13 | 43.3 | | |
| Min. – Max. | 35.0 – 64.0 | | 50.0 – 65.0 | | U= 443.0 | 0.915 |
| Mean ± SD | 56.63 ± 6.14 | | 57.70 ± 3.28 | | | |
| **Gender** | | | | | | |
| Male | 25 | 83.3 | 25 | 83.3 | $\chi^2$ = 0.000 | 1.000 |
| Female | 5 | 16.7 | 5 | 16.7 | | |
| **Co-morbidities** | | | | | | |
| No | 17 | 56.7 | 16 | 53.3 | $\chi^2$ = 0.067 | 0.795 |
| Yes | 13 | 43.3 | 14 | 46.7 | | |

SD: Standard deviation, IQR: Interquartile range, $\chi^2$: Chi square test, U: Mann Whitney test

Higher percentage: 80% of patients were HCV positive in aspirin arm compared to 56.7% in control arm. However, the difference didn't reach statistically significant level (p=0.052). Also, the difference between the 2 groups regarding antiviral treatment, liver cirrhosis, and previous local treatment (local ablative therapy and surgery) was insignificant (Table 2).

**Table (2): Comparing the two studied groups according to different parameters**

| Data | Control Arm (n = 30) | | Aspirin Arm (n = 30) | | $\chi^2$ | P |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **HCV infection** | 17 | 56.7 | 24 | 80.0 | 3.774 | 0.052 |
| **HCV therapy** | 14 | 46.7 | 13 | 43.3 | 0.067 | 0.795 |
| **HBV infection** | 1 | 3.3 | 0 | 0.0 | 1.017 | $^{FE}$p=1.000 |
| **HBV therapy** | 1 | 3.3 | 0 | 0.0 | 1.017 | $^{FE}$p=1.000 |
| **Cirrhosis** | 19 | 63.3 | 22 | 73.3 | 0.693 | 0.406 |
| **HCC Previous treatment** | 6 | 20.0 | 5 | 16.7 | 0.111 | 0.739 |
| **Local ablative** | 5 | 16.7 | 4 | 13.3 | 0.131 | $^{FE}$p=1.000 |
| **Surgery** | 1 | 3.3 | 1 | 3.3 | 0.000 | $^{FE}$p=1.000 |

$\chi^2$: Chi square test, FE: Fisher Exact test

Toxicity profile in aspirin group ranged from grade (G) 0 to II. It only reported gastrointestinal tract adverse event; gastritis, abdominal pain, vomiting and nausea. In aspirin arm; gastritis was found in 10% of cases with grade I in 6.7% and grade II in 3.3%. Abdominal pain grade I, vomiting grade I and II were observed in three and two patients respectively with insignificant difference between both groups (Table 3). There were no renal, hematological and hepatic toxicity; and aspirin didn't cause any GIT bleeding.

**Table (3): Comparing the two groups according to toxicity.**

| GIT Toxicity | | Control Arm (n = 30) | | Aspirin Arm (n = 30) | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| Gastritis | No | 30 | 100.0 | 27 | 90.0 | 3.158 | FEp= 0.237 |
| | Yes | 0 | 0.0 | 3 | 10.0 | | |
| | G 0 | 30 | 100.0 | 27 | 90.0 | 2.718 | MCp= 0.244 |
| | G I | 0 | 0.0 | 2 | 6.7 | | |
| | GII | 0 | 0.0 | 1 | 3.3 | | |
| Abdominal pain | No | 30 | 100.0 | 27 | 90.0 | 3.158 | FEp= 0.237 |
| | Yes | 0 | 0.0 | 3 | 10.0 | | |
| | G 0 | 30 | 100.0 | 27 | 90.0 | 3.158 | FEp= 0.237 |
| | GI | 0 | 0.0 | 3 | 10.0 | | |
| | GII | 0 | 0.0 | 0 | 0.0 | | |
| Nausea | No | 30 | 100.0 | 27 | 90.0 | 3.158 | FEp= 0.237 |
| | Yes | 0 | 0.0 | 3 | 10.0 | | |
| | G0 | 30 | 100.0 | 27 | 90.0 | 3.158 | FEp= 0.237 |
| | G I | 0 | 0.0 | 3 | 10.0 | | |
| | G II | 0 | 0.0 | 0 | 0.0 | | |
| Vomiting | No | 30 | 100.0 | 28 | 93.3 | 2.069 | FEp= 0.492 |
| | Yes | 0 | 0.0 | 2 | 6.7 | | |
| | G0 | 30 | 100.0 | 28 | 93.3 | 1.938 | MCp= 0.499 |
| | G I | 0 | 0.0 | 1 | 3.3 | | |
| | GII | 0 | 0.0 | 1 | 3.3 | | |

$\chi^2$: Chi square test, FE: Fisher Exact test, MC: Monte Carlo test.

Regarding treatment response, there was no significant difference between both groups. Also regarding the site of disease progression (local progression including portal vein thrombosis and distant progression) the difference was also statistically insignificant between both arms (Table 4).

**Table (4): Comparing the two groups according to treatment response.**

| Response | Control Arm (n = 30) | | Aspirin Arm (n = 30) | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| CR | 2 | 6.7 | 3 | 10.0 | 0.985 | MCp= 0.806 |
| PR | 7 | 23.3 | 9 | 30.0 | | |
| SD | 9 | 30.0 | 9 | 30.0 | | |
| DP | 12 | 40.0 | 9 | 30.0 | | |
| DP | | | | | | |
| No | 18 | 60.0 | 21 | 70.0 | 0.659 | 0.417 |
| Yes | 12 | 40.0 | 9 | 30.0 | | |
| **Progression** | **Control Arm (n = 30)** | | **Aspirin Arm (n = 30)** | | $\chi^2$ | p |
| | No. | % | No. | % | | |
| No | 18 | 60.0 | 21 | 70.0 | 0.659 | 0.417 |
| Local | 8 | 26.7 | 6 | 20.0 | 0.373 | 0.542 |
| Distant | 4 | 13.3 | 3 | 10.0 | 0.162 | FEp 1.000 |
| PVT (local progression) | 6 | 20.0 | 2 | 6.7 | 2.308 | FEp 0.254 |

$\chi^2$: Chi square test, MC: Monte Carlo test, FE: Fisher Exact test. PVT: Portal vein thrombosis

Among cases Mr. M E, 54 years old, was diagnosed as HCC and had microwave ablation then presented with recurrent HCC lesion and serum alpha fetoprotein was high (455 ng /dl), we enrolled him in our trial and he had TACE with aspirin and after 3 weeks triphasic CT showed complete remission (Figure 1).

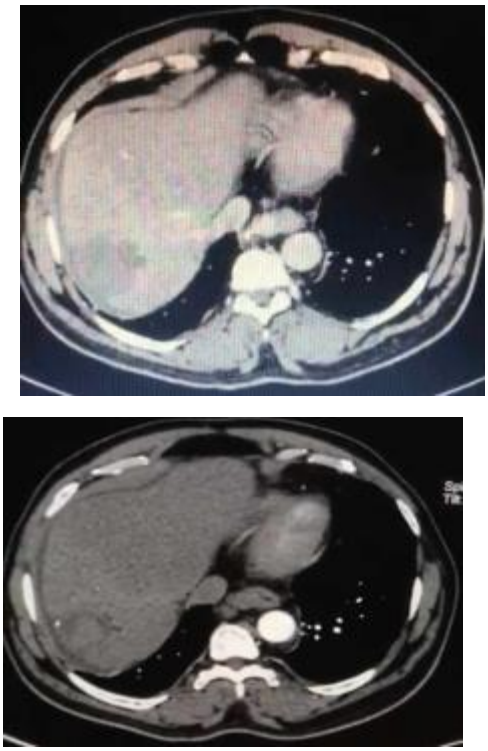

**Figure (1):** Triphasic CT shows complete remission of HCC lesion after TACE with aspirin (previous microwave ablation noted in lower image).

Regarding treatment compliance, TACE refractoriness and the number of TACE; there was no significant difference between both groups (Table 5).

**Table (5): Comparing the two groups according to treatment feasibility.**

| Feasibility | Control Arm (n = 30) | | Aspirin Arm (n = 30) | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **Compliance to aspirin** | | | | | | |
| No | – | – | 2 | 3.7 | – | – |
| Yes | – | – | 28 | 93.3 | | |
| **Compliance to TACE** | | | | | | |
| No | 3 | 10 | 2 | 3.7 | 0.069 | 0.793 |
| Yes | 27 | 90 | 28 | 93.3 | | |
| **TACE number** | **Control Arm (n = 30)** | | **Aspirin Arm (n = 30)** | | **U** | **p** |
| **Min. – Max.** | 1.0 – 5.0 | | 1.0 – 5.0 | | 364.5 | 0.179 |
| **Mean ± SD.** | 2.57 ± 0.94 | | 2.93 ± 1.08 | | | |
| **Median (IQR)** | 2.0 (2.0 – 3.0) | | 3.0 (2.0 – 3.0) | | | |

$\chi^2$: Chi square test, SD: Standard deviation, IQR: Interquartile range, U: Mann Whitney test.

The median overall follow-up duration was 14 months; the median progression free survival/month was 11 in control arm; however, it was not reached in aspirin arm (Figure 2). The median OS/month was 22 months in control arm and it was not also reached in aspirin arm (Figure 3).

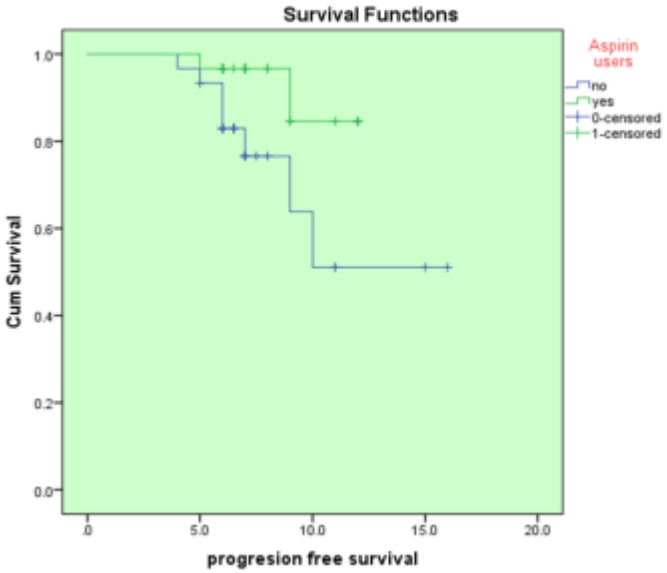


**Figure (2):** Kaplan-Meier curve of PFS shows median of control group of 11 month, while it was not reached in aspirin group (P = 0.035).

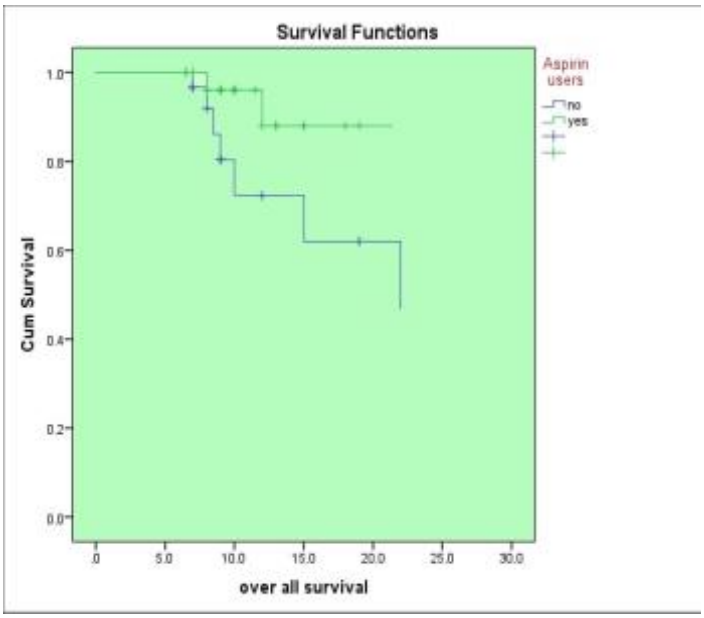


**Figure (3):** Kaplan-Meier curve of overall survival shows that median of control group was 22 months, while it was not reached in aspirin group (P = 0.036).

## DISCUSSION

The antiplatelet oral therapy has shown to have a role in prevention of HCC and improvement patients' disease outcome [13]. Furthermore, aspirin was accompanied by significant improvement of survival when taken as adjuvant with embolization for patients with HCC (p=0.00036) [14]. In current study, we studied adding aspirin to TACE for treatment of unresectable hepatocellular carcinoma.

There was insignificant difference between the 2 arms regarding both demographic and disease features indicating homogeneity of the sample. Current study had included all patients of Child Pugh A, normal liver and renal function and platelets > 100,000 in both arms, unlike **Li *et al.*** [15] study; the investigators had included patients with platelets <100,000, the percentage of platelets less than 100,000 in aspirin users was 28.3% versus 33.3% in non-aspirin users. Also, the percentage of Child A in aspirin users was equal to non-aspirin users; both 98.3%, and furthermore, our study is randomized prospective study unlike their study, which was retrospective in nature.

Regarding response to treatment, in current study, there was statistically insignificant difference between 2 arms (P = 0.659), that may be attributed to the low dose aspirin used; as aspirin potential antiangiogenic and antiglycolytic effects could be more obvious after oral dose of 320 mg [16].

Similarly, as for patients included in **Boas *et al.*** [17] study, there was no difference regarding response according to mRECIST with 88 percent had CR or PR for aspirin arm compared with 90 percent in non-aspirin arm (p = 0.59) and there was shorter time to disease progression with median/months of 5.2 in non-aspirin arm vs. 6.2 in aspirin arm (p = 0.42), which is supporting our results. Also in their trial, the mean initial serum bilirubin level of 0.8 Vs 0.9 mg/dL, (p = 0.11) were similar for cases received versus cases didn't receive aspirin. Regarding adverse effects and treatment compliance, in our study, aspirin adverse effect was GIT adverse effects; there are no recorded GIT bleeding, renal or hepatic toxicity, which is in agreement with **Li *et al.*** [15] study, in which only 1 case in aspirin arm discontinued oral aspirin due to GIT bleeding.

In current study there was a survival benefit with use of aspirin with TACE in management of unresectable HCC, median PFS in control arm was 11 (95% CI) months while in aspirin arm was not reached (p=0.035), also there was oversurvival benefit, the median of OS in control arm was 22 (95% CI) months while in aspirin arm it was not reached (p = 0.036).

Similarly, **Li *et al.*** [15]**,** results showed an improvement of overall survival (P = 0.050), with median OS/months of 32.5 in aspirin arm vs. 20.3 in non-aspirin arm. To our knowledge, their trial is one of the earliest trials to evaluate the role of aspirin in combination with TACE.

**Study limitation:** The low dose of aspirin used and the relatively short treatment duration.

## CONCLUSION

Low dose aspirin use in selected unresectable HCC intermediate stage undergoing TACE is feasible, tolerable, and could be associated with survival benefit.


- **Financial support and sponsorship:** Nil
- **Conflict of Interest:** Nil

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