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Original Article

Role of procalcitonin in diagnosis of bacterial infection in trans-arterial chemoembolisation treated hepatocellular carcinoma patients

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ABSTRACT

Background and study aim: Trans-arterial chemoembolisation (TACE) became the treatment of choice for multinodular hepatocellular carcinoma. The use of prophylactic antibiotics following intervention is controversial. This study aimed to assess the role of serum procalcitonin level in early diagnosis of bacterial infection following TACE to optimise antibiotic intake in those patients.

Patients and methods: This study was carried on HCC patients diagnosed according to AASLD who underwent TACE and developed post interventional fever within 48 h. Laboratory investigations including CBC, neutrophil count, C-reactive protein and ESR (pre and after intervention) were done. Cultures were done according to the suspected site of infection. Serum procalcitonin was done for all the included patients before and after TACE.

Results: Forty two TACE treated patients were included with post interventional fever within 48 h. Their ages ranged between 45 and 65 (mean 53.83 ± 5.23). All patients received antibiotic prophylaxis started 24 h pre intervention and for 5 days after according to the local protocol. Five patients (11.9%) had positive blood cultures post intervention. The analysis of laboratory results showed statistical significant correlation between procalcitonin levels and positive cultures, post interventional CRP and TLC and pre interventional INR and bilirubin, while there was statistical significant correlation between CRP and post interventional temperature, total leucocytic count and site of focal lesion.

Conclusion: Procalcitonin seems to be a promising marker for diagnosis of sepsis in TACE treated HCC patients to optimise the unnecessary use of antibiotics.

Introduction

During the past 20 years, the number of patients diagnosed with hepatocellular carcinoma (HCC) has increased worldwide [1]. In Egypt, annual proportion of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002 [2].

Trans-arterial chemoembolisation (TACE) has become the treatment of choice for multinodular hepatocellular carcinoma [3]. Chemoembolisation has played an important role in the treatment of large HCCs in patients who are not surgical candidates [4,5].

Procalcitonin (PCT) is a protein consisting of 116 amino acids with a molecular weight of 13 kDa. It can act as a hormone and a cytokine. It is produced by several cell types in response to pro-inflammatory stimuli, particularly bacterial infection. It is released under the stimulation of sepsis [6]. PCT levels rise within 6–12 h of bacterial infection. In patients with sepsis, severe sepsis, and septic shock, PCT levels can reach 1000 ng/ml once the bacterial infection is resolved; PCT levels rapidly decrease [7]. Several studies confirmed the value of procalcitonin in early prediction and diagnosis of sepsis [8,9]. Moreover; PCT can assist in identifying patients without serious bacterial infections and limit antimicrobial use [10].

This study aimed to assess the role of serum procalcitonin level in early diagnosis of bacterial infection following TACE to optimise antibiotic intake in those patients.

Patients and methods

This prospective study was carried out in HCC Clinic, Tropical Medicine Department; Ain Shams University Hospitals. After approval of the Research and Ethics Committee of Ain Shams University, Cairo, Egypt, the trial was registered with the federal clearinghouse for randomised trials; www.clinicaltrials.gov (NCT01518829).

The study was carried on HCC patients diagnosed according to AASLD who underwent TACE and developed post interventional

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fever within 48 h. Laboratory investigations including CBC, neutrophil count, C-reactive protein and ESR (pre and after intervention) were done. Cultures (blood, sputum, punctures site swab, etc, ...) were done according to the suspected site of infection. Serum procalcitonin level was done for all the included patients before and after TACE.

Inclusion criteria

Hepatocellular carcinoma patients (diagnosed according to AASLD) [11] who underwent TACE who developed post interventional fever more than 38 °C for more than 24 h.

Exclusion criteria

Hepatocellular carcinoma patients who did not develop fever after intervention, proven infection elsewhere (i.e. urinary tract infection, respiratory tract infection, ..., etc.), other tumours elsewhere. Patients who develop fever less than 38 °C or fever that resolved in the first 24 h following the procedure were excluded from the study.

According to the unit protocol, all the included patients received intravenous 3rd generation cephalosporin 1 g/12 h and oral metronidazole three times daily starting before the procedure and for 5 days after the procedure. Antibiotics intake is extended in those patients who develop fever.

TACE technique

Catheterisation of the hepatic artery was done through right femoral puncture. Diagnostic hepatic angiography was used for detection of tumour blush, then selective catheterisation of tumour feeding artery with injection of Adriablastin (1–2 mg/kg max 100 mg) and lipidol emulsion and embolisation of tumour bed and feeding artery by gel foam. After that post-embolisation hepatic angiography was done to detect disappearance of tumour blush.

Procalcitonin test principle

The RayBio Human Procalcitonin ELISA (Enzyme-Linked Immunosorbent Assay) kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human procalcitonin in serum, plasma, cell culture supernatants and urine. This assay employs an antibody specific for human Procalcitonin coated on a 96-well plate. Standards and samples are pipetted into the wells and procalcitonin present in a sample is bound to the wells by the immobilised antibody. The wells are washed and biotinylated anti-human procalcitonin antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and colour develops in proportion to the amount of procalcitonin bound. The Stop Solution changes the colour from blue to yellow, and the intensity of the colour is measured at 450 nm (*RayBio Human Procalcitonin ELISA Kit Protocol*).

Statistical analysis

IBM SPSS statistics (V. 19.0, IBM Corp., USA, 2010) was used for data analysis. Data were expressed as mean ± SD for quantitative parametric measures in addition to Median, Percentiles for quantitative non-parametric measures and both number and percentage for categorised data. Student's *t*-test, Wilcoxon Rank Sum test, Ranked Spearman correlation test, and Chi square test were used. The probability of error 0.05 was considered significant.

Results

TACE was done in 196 patients according to BCLC guidelines for HCC management [12]. Forty two (21.4%) of TACE treated HCC patients developed post interventional fever within 48 h after the manoeuver and were included in the study. They were thirty three males and nine females. Their ages ranged between 45 and 65 (mean 53.83 ± 5.23). Prior to TACE, twenty three patients were Child A and nineteen patients were Child B; their mean MELD was 11.48 ± 3.52. Post intervention, eighteen patients (42.9%) had ascites compared to fourteen (33.3%) pre-intervention with statistical significant difference ($p = 0.00$). As regards MELD score it ranged between 6 and 20 (mean 12.55 ± 3.69). Seventeen patients (40.5%) were Child class A, twenty four patients (57.1%) were Child class B and one patient (2.4%) became Child class C and this mount statistical significant deference between the pre and post interventional Child classification and MELD of the studied patients ($p = 0.00$).

The analysis of the laboratory results showed statistical significant increase in post interventional TLC, neutrophils%, HB, AST, ALT, Bilirubin, CRP and procalcitonin ($p < 0.5$) (Table 1).

Although all patients received antibiotic prophylaxis 24 h pre intervention and for 5 days after according to our unit local protocol, five patients had positive blood cultures post intervention (Klebsiella pneumonia was the most common pathogen). Those 5 patients were 2 males and three females, their ages ranged between 49 and 62 years. Two of them were child A and 3 were Child B. Three of them had single focal lesion in the right lobe from 5 to 6 cm in diameter. The other 2 had 2 hepatic focal lesions 5–9 cm in diameter. Those 5 patients stayed in the hospital for 9–14 days after culture results antibiotics were shifted according to culture results and they showed a good clinical response and were discharged with complete resolution of infection.

Post interventional procalcitonin levels were significantly higher in patients with positive blood culture (1.2 ± 0.31) than those with negative cultures (0.38 ± 0.23) ($p =$ **0.00).** While, there were non significant differences as regards total leucocytic count, neutrophil count, CRP, ESR, site or size of focal lesions between patients with positive and patients with negative blood cultures ($p > 0.05$).

Correlation between serum procalcitonin level and CRP level with the studied parameters is summarised in Table 2. There was statistical significant correlation between procalcitonin levels and positive cultures, post interventional CRP levels and TLC, while there was statistical significant correlation between CRP levels and post interventional temperature, total leucocytic count and site of focal lesion.

Table 1
Comparison between pre and post interventional laboratory results.

Variable	Pre intervention	Post intervention	*t*	*p*
TLC cell/cmm	5.22 ± 1.99	7.96 ± 3.10	7.92	0.00
Neutrophils %	56.55 ± 8.98	74.40 ± 9.75	9.46	0.00
HB g/dl	12.54 ± 1.55	11.80 ± 1.55	3.27	0.00
PLT/cmm	113.67 ± 76.34	106.98 ± 75.70	0.91	0.37
AST u/l	53.60 ± 12.66	72.62 ± 15.96	5.07	0.00
ALT u/l	51.00 ± 10.67	86.31 ± 20.26	9.86	0.00
BIL mg/dl	1.43 ± 0.48	2.22 ± 0.92	4.42	0.00
ALB g/l	3.05 ± 0.39	2.98 ± 0.48	0.82	0.42
INR	1.27 ± 0.27	1.34 ± 0.28	1.08	0.29
ESR	55.48 ± 36.72	59.57 ± 37.47	0.82	0.42
CRP mg/ml	11.69 ± 16.05	28.76 ± 28.71	3.93	0.00
Procalcitonin ng/ml	0.33 ± 0.19	0.48 ± 0.36	2.95	0.01