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Heamodynamic Doppler changes in portal pressure after trans-arterial chemoembolization of hepatocellular carcinoma.

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Abstract:

Aim: The goal of this study was to determine changes in portal pressure hemodynamics of HCC patients after their management using transarterial chemoembolization (TACE). Twenty five patients with HCC underwent TACE. Medical history in addition to investigations were carried out including Doppler ultrasound for assessment of portal hypertension (PHT)parameters, and then repeated 3 months after TACE. **Results:** TACE had resulted in a markedly increased liver vascular index with significant reduction in hepatic artery resistive index following therapy. TACE was accompanied by improvement of PHT parameters. Doppler ultrasound might be used as a reliable and efficient tool for assessment of PHT changes. **Conclusion:** Locoregional therapy has become increasingly pivotal for HCC patients as a result of advances in approaches, survival benefit, and a favorable safety profile, despite curative measures including surgical resection and liver transplantation are still the gold standard.

Keywords: Portal hypertension, HCC, Doppler ultrasound, TACE.

1. Introduction:

Hepatocellular carcinoma (HCC) is the 6th among the tumors occurring globally, and the 2nd principal factor to mortality caused by malignancies [1]. In fact, the incidence of HCC continuously increases all over the world, particularly as a result of the increase in the incidence of nonalcoholic fatty liver disease (NAFLD) in addition to the increase in the number of patients suffering hepatitis C-induced cirrhosis. Approximately 80% of HCC patients suffer cirrhosis [2].

Despite the advances in screening, diagnosis, as well as the treatment modalities has resulted in great improvement of the prognosis of HCC, HCC is still considered a catastrophic tumor due to the high risk of metastases and recurrence [3]. Nevertheless curative measures including surgical resection

and liver transplantation are still the gold standard. Nearly 70-80% of patients are poor candidates for these invasive approaches. Locoregional treatment has become of great importance for HCC patients due to advances in methods, survival benefit along with the favorable safety profile [4].

The occurrence of portal hypertension (PHT) is considered a crucial event in cirrhosis development [5]. PHT might occur following chemoembolization approaches of HCC that is considered a major complication after such techniques of intervention [6].
Since the vast majority of HCC patients have underlying liver cirrhosis along with impairment of liver function, the overall survival is markedly based upon the tumor control as well as preservation of liver function. It is recommended to carry out chemoembolization selectively when possible via the tumor-feeding arteries in order to maximize local tumor control in conjunction with minimizing hepatic damage [7].

Usually, the intra-arterial therapeutic options for HCCs depend upon that HCCs are exclusively supplied by hepatic arteries. Nevertheless, exclusive hepatic arterial supply can be detected only in case of well-encapsulated, nodular HCCs. In multistep hepatocarcinogenesis of HCC, portal vein continues in the early stage [8].

In advanced types of HCC with an infiltrative growth pattern, the leading edges of the enlarging tumor receive double blood supply from the hepatic artery as well as portal vein. In HCCs with moderate differentiation and having a pseudocapsule, portal veins surrounding the tumor become the drainage vessels. Microsatellites might arise in the area surrounding the tumor. The persistent portal venous supply or microsatellites might be an essential cause of incomplete management of HCCs by chemoembolization [9].

Lipiodol-based emulsion is beneficial for chemoembolization due to its physical criteria. It can pass via a fine tumor-feeding artery, hence reaching the tumor vessels, penetrating deep into the neoplasm capsule, to accumulate in these portal veins surrounding the tumor via either presinusoidal-arterioportal communication or the tumor drainage route [10].

In a retrospective analysis of the clinical outcome of cTACE, it has been demonstrated that local tumor recurrence is significantly decreased when more portal veins were visualized with Lipiodol during the approach. When such veins were markedly filled with Lipiodol, > 2/3 of small HCCs were entirely necrotized. Nevertheless, it should be taken in consideration that this ideal endpoint of “oily portogram” in cTACE is achieved case of selective catheterization of tumor-feeding arteries only. Thus, a superselective approach is crucial to get benefit of Lipiodol-based emulsion in cTACE [11].So,this study aimed to determine changes in portal pressure

hemodynamics of HCC patients after their management using TACE

2. Patients and Methods:

This study was a prospective interventional (Randomized Control Trial) study. It was conducted in the radiology Department of Beni-seuf University Hospital, Egypt.

This study included 25 patients. They were treated with cTACE. All the patients were subjected to:

- Full history taking.
- Liver function tests (S.albumin level, S. Bilirubin level, and INR), serum alpha fetoprotein level (AFP).
- Triphasic abdominal CT.
- Color Doppler US for assessment of portal blood pressure.

All these investigations were carried out before & 3 months following cTACE.

After fasting for 8h, patients were subjected to Doppler US to measure portal pressure before & 3 months after treatment using GE logic P5 US machine, Using deep 4 MHZ transducer in order to image the portal vein, patients were supine, generally done at right longitudinal intercostal approach the same as that used to display the CHD. The hepatic artery indices were obtained from common hepatic artery that has been examined from oblique intercostal procedure, where it lies anteriorly to the portal vein inside the liver. Obtained Doppler US parameters included:

-Portal vein diameter.

-Portal vein velocity.

-Hepatic artery PI.

-Hepatic artery RI.

Also LVI (PV VEL/HAPI) ,CI (the ratio between the cross-sectional area of the vessel (cm2) and the blood flow (cm/s) in the portal vein) were estimated.

2.1 Inclusion criteria:

1. Patients exhibiting good compliance and providing informed consent.
2. Patients with primary HCC and naive to treatment.
3. Diagnosed patients confirmed by triphasic abdominal CT or dynamic contrast enhanced MRI. Diagnosis was carried out according to the identification of the typical hallmark of HCC (hypervascularity in the arterial phase with washout in the portal venous or delayed phases).
4. Patients with intermediate stage HCC (asymptomatic with limited unresectable multinodular lesion (< 3 lesions, and< 5 cm) with no vascular invasion or extrahepatic spread.
5. Patients with cirrhotic liver of Child-Pugh class A or B.
6. Received successful superselective TACE and no other treatment.

Exclusion criteria:

Liver cirrhosis of Child-Pugh class C, including :

- Clinical encephalopathy.
- Refractory ascites.
- Hepatorenal syndrome,

- Extensive tumor with massive replacement of both lobes.
- Renal insufficiency.

Those who had refused to participate in the study.

Statistical methodology

• Analysis of data were done by IBM computer using SPSS (statistical program for social science) as follows;

- Description of quantitative variables as mean, SD and range.

- Description of qualitative variables as number and % .

- Unpaired t-test was used for comparing quantitative variables, in parametric data (SD < 50 % mean)

• P value > 0.05 insignificant

• P < 0.05 significant

• P < 0.01 highly significant [20].

3. Results:

This study was a prospective interventional (randomized controlled trial) study, it was conducted on 25 patients diagnosed with HCC and treated by cTACE.

The study was approved by the ethical committee of Beni-suef University. An informed written consent in Arabic language was obtained from all participants.

Demographic data:

There were 19 males and 6 females, and their age ranged from 52 to 65 with the mean age of (58.88± 3.77)

According to Child –Turcotte-Pugh classification, 18 (72%) patients were classified as child A -and 7 (28%) as class B .Our patients performed TACE, all the patients survived to the date of follow –up with no major complication or morbidity.

Table (1): Liver function tests before and after ablation procedures

Measurement		Mean	Std. Deviation	P-value
Serum albumin	Pre	3.07	0.33	0.205
	Post	3.14	0.39	
Serum bilirubin	Pre	1.30	0.52	0.001*
	Post	1.16	0.43	
INR	Pre	1.22	0.21	0.006*
	Post	1.15	0.18	

Table (1): shows that, regarding liver function tests before and after ablation procedure, there were are significant changes Serum bilirubin and INR after treatment (p-value < 0.05). However, there were no significant changes in Serum albumin after treatment (p-value > 0.05).

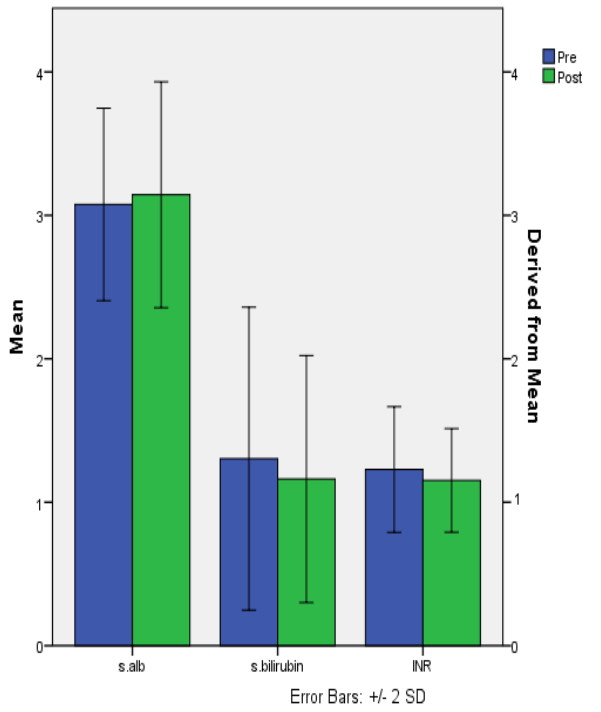

Fig. (1): Mean variation in the liver function tests pre and post cTACE.

The changes in Doppler US parameters TACE were shown in table (4,5). It demonstrate variable changes, after TACE the LVI remarkably increased (p=0.027).

There were significant changes in Portal vein velocity, HARI, HAPI and LVI in HCC patients after treatment (p-value < 0.05). However, there were no significant changes in Portal vein diameter and CI in those patients (p-value > 0.05).

Table (2): Descriptive measurements of ultrasound parameters and liver functions

Diameters (n=25)	Range	Minimum	Maximum	Mean	Std. Deviation
Pre TACE measurement					
Portal vein diameter	7	9	16	11.76	1.909
Portal vein velocity	8	8	16	11.04	2.222
HARI	0.11	0.66	0.77	0.69	0.02
HAPI	0.60	1.00	1.60	1.25	0.20
LVI	8.31	5.69	14.0	8.91	1.98
CI	.2190	0.001	0.22	.097	0.05
Serum albumin	1.1	2.4	3.5	3.07	0.33
Serum bilirubin	1.7	0.8	2.5	1.30	0.52
INR	.70	1.00	1.70	1.22	0.21
Post TACE measurement					
Portal Vein diameter	6	9	15	11.46	1.511
Portal Vein VEL	9	8	17	12.36	2.29
HA RI	0.08	0.62	0.70	0.66	0.024
HAPI	0.65	0.80	1.45	1.12	0.16
CI	0.12	0.03	0.16	0.08	0.02
Serum albumin	1.30	2.3	3.6	3.144	0.39
Serum bilirubin	1.60	0.70	2.30	1.16	0.43
INR	0.7	1.0	1.7	1.15	0.18

HARI: hepatic artery resistive index, HAPI: Hepatic artery pulsatility index, LVI: Liver vascular index, CI: Congestion index.

Table (3): Doppler US parameters before and after ablation procedures

Measurement (N=25)		Mean	Std. Deviation	P value
Portal vein diameter	Pre	11.76	1.909	0.06
	post	11.46	1.511	
Portal vein velocity	pre	11.04	2.222	0.001*
	post	12.36	2.298	
HARI	pre	0.69	0.02	0.001*
	post	0.66	0.02	
HAPI	pre	1.25	0.20	0.001*
	post	1.12	0.16	
	post	0.59	0.010	
LVI	Pre	8.91	1.98	0.001*
	post	11.23	2.68	
CI	pre	0.09	0.05	0.210
	post	0.08	0.02	

HARI: hepatic artery resistive index, HAPI: Hepatic artery pulsatility index, LVI: Liver vascular index, CI: Congestion index.

Table (3) shows that regarding Doppler US parameters before and after ablation procedure, there were significant changes in Portal vein velocity, HARI, HAPI and LVI in HCC patients after treatment (p-value < 0.05). However, there were no significant changes in Portal vein diameter and CI in those patients (p-value > 0.05).

4. Discussion:

Hepatocellular carcinoma is the commonest primary tumor of the liver [12]. The vast majority of the HCC patients are diagnosed in the late stage thus aren't candidates for curative options that include liver transplantation and surgical resection [13].TACE is considered one of the treatment techniques that firstly recommended for intermediate-stage (Barcelona Clinic Liver Cancer (BCLC) B class) HCC yet has lower necrosis rates [14]. systematic review from 217 articles that had been published between 1980& 2013 revealed that post-embolization syndrome (that is manifested by fever, abdominal pain, in addition to ileus) was the common treatment-related side effect, appearing in 47.7% of patients treated with cTACE [15].There was a transient elevation in

liver enzymes in 52% of patients, and the overall post- approach mortality rate was 0.6% [16]. Moreover, one of these risks is the development or the elevated degree of PHT after the ablative approach. The elevation in portal pressure might result in reduced effectiveness of the ablation process or the development of some other morbid conditions [17]. Using Doppler US for determination and monitoring of PHT is the commonest and the preferred methods as it is noninvasive, accurate, and costless [18].

Several studies [19] revealed that indices like HAPI, HARI, LVI and CI are considered indicative indices in patients with PHT, demonstrating that color Doppler US can be used as a noninvasive assessment technique for PHT degree. The changes in these indices accompanying the elevation in portal pressure might reflect hepatic resistance and hepatic artery capacity in an accurate method .

In the current study, color Doppler was used to evaluate particular and sensitive Doppler US parameters regarding PHT as, PVD, PVVel, HAPI, HARI, LVI, and CI along with liver function tests (S. albumin, S. bilirubin and INR). Twenty-five patients were assessed before &3 months after ablation.

Portal venous velocity was markedly decreased in patients with cirrhosis and esophageal varices (11.0 ± 2.4 cm/s vs. 15.9 ± 2.8 cm/s in controls, P <0.001) [20].This was in accordance wigh another study that revealed that PVVel was also significantly decreased in patients with advanced cirrhosis (15.1 ± 4.2 cm/s vs. 31.0 ± 1.4 cm/s in controls [21]. A significantly reduction in mean pPVVel was determined in cirrhotic patients (13.0 ± 3.2 cm/s vs. 19.6 ± 2.6 cm/s in controls). The value of 15 cm/s was considered the best cut-off value in determining PHT, ensuring high sensitivity & specificity [22].

This study showed that TACE was is associated with significant changes in Doppler US measures of PVVel (increased), HAPI (decreased), HARI (decreased), LVI (increased) after TACE procedure (p value< 0.05). This was in harmony with Zhang, Duan et al. 2007, El Sherbiny and AbdelRahman 2016 as regard HARI and LVI.

As regard PVVel our study was in agreement with findings by other study that documented a transient elevation in portal flow following transarterial embolization, which might compensate for the reduction in hepatic arterial blood flow..Another study on pediatric populations reported that doppler US is efficient method for hemodynamic monitoring and treatment of PV and the results is satisfactory when compared with CT angiography [23].

In contrast; a study by Taourel, Dauzat revealed that PVVel and flow didn't alter significantly after TACE. The peak systolic

velocity in the proximal hepatic artery showed a significant decrease (P < .01) and immediately after TACE then returned to the baseline values two days following TACE; the resistance index of the proximal hepatic artery is elevated significantly (P<.01) immediately following embolization, then returned to baseline values 2 days after TACE. Arterial signal in the distal hepatic artery was absent immediately after TACE, then it could be recorded two days after.

The elevated PHT might be explained also on the basis of severe necro-inflammation of blood vessels and nearby tissue as a result of the nature of the therapeutic chemical substance used in ablation causing vascular obliteration, elevated tissue resistance, and finally PHT .

Nevertheless, HCC chemoembolization might result in improvement of portal circulation, removal of malignant debris from vascular tissue, preventing seeding of micrometastatic foci, and improving PHT consequently as detailed in the results of this study.

Besides, CI reveals a statistically significant difference between patients with cirrhosis and controls (0.180 ± 0.107 cm/s vs. 0.070 ± 0.029 cm/s) [24].The CI considers the elevated cross sectional area of the portal vein and the markedly decreased blood flow velocity both in cirrhosis and PHT [25].

Iwao 2010 [11], showed that the HAPI was is significantly elevated in patients with cirrhosis and PHT. This finding was in coherence with another study that proved that the HAPI and HARI were significantly increased in cirrhotic patients (HAPI: 1.30 ± 0.29 vs. 0.89 ± 0.09 in controls, HARI: 0.71 ± 0.07 vs. 0.59 ±0.04 in controls) [26].

Reciprocal hemodynamic relationship between hepatic artery and portal vein in forementioned study demonstrated that the liver vascular index is elevated in cirrhotic patients when compared with healthy controls. For the diagnosis of liver cirrhosis and/or PHT the best cut-off value of the liver vascular index is12 cm/s with high sensitivity & specificity [27].

In another study the arterio-portal velocity ratio was markedly elevated in cirrhotic patients in comparison with controls, using a cut-off value > 3.0 the ratio had a high sensitivity & specificity [28].

The HAPI and LVI are indicative indices in patients with PHT, indicating that color Doppler US can be used as a noninvasive assessment technique for PHT degree. The alterations in the HAPI, LVI, and HBI that associate the elevation in portal pressure can denote hepatic resistance and hepatic artery buffer capacity in an accurate method. Liver functions:

The current study showed that S. bilirubin was significantly reduced following the ablation approach, the literature revealed number of studies that have been carried out internationally with variable results. In a prospective study as regard the complications of TACE in HCC patients, increased S.bilirubin following TACE was proved to be accompanied by the high dosage of chemotherapeutic agent and stage of cirrhosis[28]**.** The same study demonstrated that patients complained acute hepatic decompensation following TACE approach were ~20% of the whole studied 197 patients and patients with irreversible hepatic decompensation were more prone to have increased pre-TACE bilirubin level and comparable results as regard post TACE bilirubin was determined [29].and this indicate that bilirubin levels might predict acute hepatic failure following TACE in HCC patients. Thus, there are contradictory results in literature regarding elevation or reduction in bilirubin level after TACE [30].

Regarding Albumin level, our study showed that there was no significant difference between S. Albumin level pre and post TACE approach. Generally, [31].evaluation of the efficacy&safety of TACE in patients with unresectable HCC determined that no treatment-related mortality occurred within one month of treatment technique and concluded that the intervention is considered safe, tolerable in patients with unresectable HCC and repeated TACE might prevent rapid progression of the disease . Another study by [32] showed that TACE induced preservation of functional hepatic parenchyma and this explains the improvement in the survival rate determined in such patients .

5 .Conclusion and Recommendations :

- TACE is a useful technique for palliative as well as curative treatment of HCC. It is generally safe with few complications in patients with early cirrhosis.
- TACE is accompanied by improved PHT parameters.
- Doppler us could be used as a reliable and efficient modality of assessment of PHT post TACE intervention.
- Improvement of PHT should be considered when deciding to continue TACE or switch to systematic management .
- TACE is beneficial management of HCC in patients with fair liver function
- PHT should be considered as a crucial prognostic factor to guide the decision for management with cTACE in addition to the available scores or AFP, further studies on layer scale with higher number of patients is required.

6. References:

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