Study of the Efficacy of Combined RadioFrequency Ablation and Percutaneous Acetic Acid Injection in the Management of Hepatocellular Carcinoma

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Abstract*:* Hepatocellular carcinoma (**HCC**) is one of the most commonly occurring solid tumors globally and is the most frequent cause of cancer death in some parts of the world such as China and sub-Saharan Africa and the prognosis without treatment is poor . There is an apparent increase in the number of HCC patients in Egypt. In Egypt liver malignancies were the 3rd most common cancer in men and the 6th in women in National Cancer Institute (NCI), Cairo University. The male to female ratio in these studies was 4:1 to 5: 1 and the mean age was 50-60 years old. Among the various local percutaneous ablative therapies, radio-frequency ablation (RFA) has attracted the greatest interest because of its effectiveness and safety in the treatment of small HCCs, with a 3-years survival rate of 62% – 68%, a treatment-associated morbidity rate of 0%–12%, and a treatment-related mortality rate of 0%–1%. However, complete tumor necrosis rate with RFA for tumors larger than 5 cm is less favorable, and local recurrence rate can be as high as 20%, even for HCCs smaller than 3.5 cm. Percutaneous acetic acid injection (**PAI**) has been used as a potential alternative to Percutaneous ethanol injection (PEI) for therapy of small (less than 3 cm) HCC**.** It is reported that it has a strong cytotoxic effect than ethanol. It causes tissue necrosis by the same mechanisms of dehydration and protein denaturation. Its low pH induces swelling of the fibers and promotes dissociation of intermolecular collagen. The aim of this work was to evaluate the efficacy of combined RFA and PAI compared to PAI alone the management of HCC of relatively large size 5-8 cm in diameter. 30 patients with single lesions of HCC measuring 5-8 cm in diameter were divided into 2 groups, each composed of 15 patients. Each group was subdivided into 2 subgroups according to the size, group 1a =7 patients (5-6.5 cm in diameter) & group 1b =8 patients (6.6-8 cm) while group 2a=8 patients (5-5.6 cm) & group2b=7 patients (6.6-8 cm). Group1 was treated by 2-3 sessions of intralesional injection of 6 ml of 50% acetic acid using 21 gauge spinal needle, 1 week apart. Group2 was treated by one setting of RFA using RF needle with that expand on deployment up to 5 cm in diameter plus 2-3 sessions PAI as in group1. Complete ablation was achieved in 46.6% of group 2 treated by combination of RFA and 2-3 sessions of PAI, compared to 20% of group1 treated by 2-3 sessions of PAI with highly significant difference. Dividing the groups into 2 subgroups according to HCC diameter, subgroup a of 5-6.5 cm and subgroup b of 6.6-8 cm in diameter, complete ablation was achieved in 62.5% of subgroup 2a compared to 28.5% of subgroup 1a **In conclusion** combination therapy of PAI plus RFA is needed if better ablation is seeked.

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related death **(Llovet *et al.,* 2003**).

With 500,000 new cases diagnosed yearly. The age-adjusted worldwide incidence varies by geographic area, increasing from 5.5/100,000 of the population in the United States and Europe to 14.9/100,000 in Asia and Africa **(Bosch** *et al.,* **1999)**

The higher incidence observed in Europe during the past decade probably reflects the increasing number of cases of hepatitis C infection (**Tanaka** *et al.,* **2002 and El-Serag** *et al.,* **2003)** and liver cirrhosis, both strong predisposing factors for HCC (**Colombo, 2003**). In most parts of Asia and Africa, hepatitis B virus infection is most relevant **(Liaw** *et al.,* **1986).** In the West and Japan hepatitis C virus infection is the main risk factor (**Tsukuma** *et al.,* **1993 and Bruno & Silini., 1999),** although patients with alcoholic cirrhosis or haemochromatosis are also at increased risk (**Niederau** *et al.,* **1985**). Older patients are more likely to develop HCC (**Colombo, 2003**). In contrast, in developing countries HCC more frequently affects younger individuals who have chronic hepatitis B (**Zhou** *et al.,* **2001),**

In Egypt liver malignancies were the 3rd most common cancer in men and the 6th in women in National Cancer Institute (NCI), Cairo University. Its incidence rate, however, has been increasing over the last two decades of the 20th century. Cirrhotic patients have a higher risk than non-cirrhotic patients with annual HCC incidences 2-6.6% and 0.4% respectively. Unfortunately most of our Egyptian

patients are discovered late, especially when symptoms like persistent pain or deep jaundice or even pulging tender epigastric or hypochondrial masses are evident. **(El-Attar, 2002)**

Alpha fetoprotein (AFP) is the most widely studied screening test used as a tumor marker for HCC. A level more than 200 ng/ml is usually regarded as diagnostic **(Ryder, 2003).**

The treatment of hepatocellular carcinoma depends on the extent of the disease, the presence or absence of cirrhosis and the degree of hepatic dysfunction **(Farmer** *et al.,* **1994)**. Few therapies are currently considered to be able to achieve complete tumor ablation (**Llovet and Beaugrand, 2003**).

Radio Frequency Thermal Ablation (RFA) is a local ablation technique designed to destroy the tumor by heating, in patients with unresectable liver tumors. The technique is safe and effective **(Azab** *et al.,* **2007&2008).**

Radiofrequency ablation (RFA) is becoming the most commonly used and perhaps most promising modality for tumor ablation (**Choti, 2000**). The rationale for **RFA** of liver tumors is evident **(Azab** *et al.,* **2007**). Firstly, this approach often allows for greater preservation of uninvolved hepatic parenchyma, directing treatment specifically to the tumor location. This feature is particularly beneficial in patients with hepatocellular carcinoma in the background of cirrhosis, where hepatic reserve is often limited. In cases of metastatic disease, tumors that are multiple, bilobar, centrally located, or in areas not technically respectable are potentially well suited for this approach **(Azab** *et al.,* **2007**).

Percutaneous acetic acid injection (PAI) may have good penetration into cancer cells in the tumor capsule or intratumoral septa. **(Okada, 1999)** and it is better than ethanol in this respect **(Azab** *et al.,* **2009)**

Percutaneous acetic acid injection (**PAI**) has been used as a potential alternative to PEI for therapy of small (less than 3 cm) HCC**.** It is reported that it has a strong cytotoxic effect than ethanol. It causes tissue necrosis by the same mechanisms of dehydration and protein denaturation. Its low pH induces swelling of the fibers and promotes dissociation of intermolecular collagen **(Ohnishi** *et al.,* **1994 and Azab** *et al.,* **2007&2009).**

Moreover, in HCC nodules, injected acetic acid may have good penetration into cancer cells in the tumor capsule or intratumoral septa, whereas ethanol cannot penetrate them. Therefore in PAI, it is expected that the number of treatment sessions may be reduced and local recurrence rates may decrease as compared with PEI. The preliminary reports suggested the efficacy of PAI for HCC smaller than 3 cm; all tumors could be treated successfully with PAI, and none of the PAI treated tumors developed local recurrence (**Okada, 1999**). **Ohnishi** *et al.* **(1998**) performed a randomized trial comparing PAI with PEI conducted in patients with one to four HCC nodules smaller than 3 cm. Although all tumors were treated successfully by either therapy, local recurrence was significantly less common with PAI compared with PEI (2 year local recurrence rate, 10% vs. 44%). Moreover, PAI showed a more favorable prognosis than PEI (2 year survival rate, 92% vs. 63%). It was found that the capability of 50% AA to necrotize hepatocytes is assumed to be more than 3 times that of absolute ethanol (**Ohnishi** *et al.,* **1998**).

2. Patients and methods

This study was carried out on 30 patients with HCC who attended the Tropical Medicine Department Al-Hussein University Hospital from December 2010 to October 2011, they were diagnosed by imaging techniques including abdominal ultrasound that shows focal lesion in cirrhotic liver followed by Triphasic spiral C T scan which shows early enhancement in the arterial phase and rapid washout in the delayed venous phase or by elevated alpha fetoprotein beyond the cut off level (200 ng /ml) or liver biopsy confirming HCC.

Inclusion criteria:

-Presence of a single focal lesion 5-8 cm in diameter.
-Absence of extra hepatic spread.
-Absence of portal vein thrombosis.
- Absence of ascites.
-Patients should be child A or B according to Child Pugh classification.
-Platelet count should be ≥ 60.000/cmm and Prothrombine concentration ≥ 60 %.
-The patients must be aware of therapy and sign consents.

These patients were classified into two groups: Each group was subdivided into 2 subgroups according to the size of the tumor,

Group 1a:-included 7 patients (5-6.5 cm in diameter) managed by 2-3 sessions of PAI only, 1 weeks apart

Group 1b:-included 8 patients (6.6-8 cm) managed by 2-3 sessions of PAI only, 1weeks apart

Group 2a:-included 8 patients (5-6.5 cm) treated by one setting of RFA using RF needle with that expand on deployment up to 5 cm in diameter plus 2-3 sessions PAI 2 weeks apart.

Group2b:- included7 patients (6.6-8 cm) treated by one setting of RFA using RF needle with that expand on deployment up to 5 cm in diameter plus 2-3 sessions PAI 2 weeks apart.

N.B We didn't consider a group for RFA alone because we believed that it would be non ethical since we know for sure that the expansion of the RFA needle arrays is limited to 5 cm only leaving upto 3 cm without ablation since we have lesions upto 8 cm

in diameter. In case of Acetic Acid we thought that it may diffuse to distant tissues covering the whole lesion if not the most of it.For this reason we used a group of PAI and for RFA.

All patients had given their informed consent to the study and were evaluated as follows.**1) Full history:** with special stress on recent abdominal swelling, abdominal pain, and loss of weight or marked deterioration of the general condition.

2) Clinical examination with special stress on ascites, palpable hepatic masses, manifestation of liver cell failure, lower limb edema, chest and heart examination.

3) Investigations:

A) Laboratory investigation including:

- CBC, ESR
- Fasting and post prandial blood sugar.
- **Liver function tests**: ALT, AST, GGT, ALP, Serum albumin, prothrombin time and concentration.
- **Tumor markers:** AFP was done before therapy then 1&3 months after on this study and on follow up of the patients after one month and three months.

B) Radiological investigations:

- Plain X-ray of the chest.
- Abdominal U/S.
- Triphasic spiral CT.
- The informations collected were evaluated using the previous imaging techniques; size, site and the vascularity of focal lesions.

C) Histopathological examination: in one doubtful case an US guided biopsy from the hepatic focal lesion was used to confirm the diagnosis.

The needles used for PAI were either 22-gauge non cutting needles (spinal needle; Becton-Dickinson, Rutherford, NJ) or 21-gauge needles with a closed conical tip and multiple terminal side holes (Pflugbeil, Ottobrunn, Germany; and Ethanoject, TSK, Tokyo, Japan).

After each session, the patient was hospitalized for 72 hrs, if no complications occurred the patient was then discharged. During such a period, patients were closely observed with stress on vital signs, abdominal tenderness or rigidity. They also received prophylactic antibiotics, paracetamol tablets, and cold foments whenever the patients were feverish together with plenty of fluids intake.

Post Treatment Assessment:

All patients were subjected to the following measures, 1 & 3 months after treatment:

A- Full clinical examination.

B- Laboratory investigations:

1- Liver function tests (bilirubin, AST, ALT, alkaline phosphates, albumin and GGT)

2- Renal function tests. 3- Alpha fetoprotein and CEA.

C- Abdominal U/S.

D-Triphasic spiral CT.

Analysis of data was done by IBM computer using **SPSS** (statistical program for social science version -12)

3. Results

Table (1) Symptoms of the studied patients:

ITEM	PAI group (n=15)	RFA+PAI group (n=15)	X^2 test	*P*- value
	No	No		
Accidentally discovered	6(40.0%)	7 (46.7%)	0.136	0.713 (NS)
Pain	6 (40.0%)	7 (46.7%)	0.136	0.713 (NS)
Easy fatigability	4 (26.7%)	6 (40.0%)	2.22	0.136(NS)
Anorexia	2 (13.3%)	4 (26.7%)	0.833	0.361(NS)
Weight loss	5(33.3%)	4 (26.7%)	1.29	0.265(NS)
Fever	1(6.7%)	1 (6.7%)	0.000	1.000(NS)
Bleeding tendency	2 (13.3%)	0 (0%)	2.14	0.143(NS)
Abdominal distension	2(13.3%)	1 (6.7%)	1.03	0.309(NS)

No significant difference was detected between the 2 groups

Table (2) Clinical Examination of the patients:

ITEM	PAI group (n=15)	RFA+PAIgroup (n=15)	X^2 test	*P*- value
GENERAL EXAMINATION:				
Pallor	7 (46.7%)	6 (40%)	0.136	0.713 (NS)
Jaundice	1 (6.7%)	1 (6.7%)	0.000	1.000 (NS)
Palmar erythema	3 (20.0%)	4 (26.7%)	0.186	0.666(NS)
Spider naevi	1 (6.7%)	1 (6.7%)	0.000	1.000 (NS)
Lower limb edema	1 (6.7%)	1 (6.7%)	0.000	1.000 (NS)
ABDOIMNAL EXAMINATION:				
Liver size: Average size Enlarged Shrunken	 6 (40%) 4 (26.7%) 5 (33.3%)	 6 (40%) 4 (26.7%) 5 (33.3%)	0.000	1.000(NS)
Liver consistency: Firm Hard	 2 (13.3%) 2 (13.3%)	 2 (13.3%) 2 (13.3%)	0.00	1.000(NS)
Spleen size Average size. Enlarged	 4 (26.7%) 11 (73.3%)	 5 (33.3%) 10 (66.7%)	0.000	0.690(NS)

No statistical difference between the studied groups regarding the clinical examination.

Table (3) Child's classification among studied groups:

Child classification	Group		Total	X^2 test	*P*-value
	PAI	RFA+PAI			
Child A	11(73.3%)	12 (57.1%)	23(100%)		
Child B	4 (26.7%)	3 (33.3%)	7(100%)		
Child C	0	0	0 (0%)	0.186	0.666(NS)
Total	15 (50%)	15 (50%)	30 100%)		

There was no statistical significant difference in the Child`s classification between the studied groups and our study not included Child`s C classification (one of exclusion criteria).

Table (4) Comparison between the studied groups as regard liver profile before therapy:

Variables	PAI group(n=15)	RFA+PAI group(n=15)	t test	*p*-value
ALT (IU)	75.10±10.63	78.8±18.5	0.112	0.987(NS)
AST (IU)	91.5±22	80.25± 19.5	1.23	0.175(NS)
Bilirubin (mg/dl)	1.6±0.58	2.12± 0.36	1.8	0.162(NS)
Alkaline Phosphtase	120±12	121±17	1.1	0.286(NS)
Prothrombin conc.	78.8±8.5	70±4.5	1.6	0.113(NS)

There was no statistically significant difference in liver profile before therapy between the studied groups.

Table (5 Comparison between the studied groups as regard tumour markers before therapy:

Variable	PAI group (n=15)	RFA+PAI group (n=15)	t test	*p*-value
AFP (ng/ml)	552.1±235.8	566.4±201.5	0.886	0.383 (NS)

No statistically significant difference between the studied groups as regard AFP before therapy (*p*-value > 0.05).

Table (6) Focal lesions as detected by US in the patient groups:

Focal lesions	PAI group (n=15)	RFA+PAI group (n=15)	X^2 test	*P*-Value
Site: Right lobe Left lobe	 13 (86.7%) 2 (13.3%)	 13 (86.7%) 2 (13.3.%)	0.000	1.000(NS)
Echogenicity: Hypoechoic Hyperechoic Heterogeneous	 12(80%) 2 (13.3%) 1 (6.7%)	 12 (80%) 2 (13.3%) 1 (6.7%)	0.000	1.000(NS)
FHL diameter: 5-6.5 cm 6.6-8 cm	 7 (46.7%)= G 1a 8 (53.3%)= G 1b	 8 (53.3%) = G 2a 7 (46.7%) =G 2b	0.202	0.904(NS)

Each patient had only one focal lesion; most of them were hypoechoic in the Rt. Lobe of the liver. No statistical significant difference between the studied groups.

Table (7) Liver profile before and after treatment in group1:

Variables	*Before TTT*	After 1month	t-test	P-value	After 3 month	t-test	*P*-value
ALT	75.2±11.03	84.5±8.61	3.8	0.002(S)	75.2±10.2	0.59	0.565(NS)
AST	67.0±19.0	82.4±19.05	5.07	0.000(S)	72.2±14.7	1.10	0.286 (NS)
Bilirubin (mg/dl)	1.6±0.58	1.51±0.443	2.01	0.063(S)	1.45±.373	2.1	0.053(S)
ALP	118.8±17.3	0.053±13.7	1.45	0.16(NS)	124.3±19.6	0.548	0.59(NS)
Albumin gm/dl	3.28±.307	3.47±.363	2.23	0.041(S)	3.58±.322	0.042	0.001(S)
Proth Conc.	70.1±6.03	2.40±6.12	3.5	0.003(S)	8.07±7.93	4.49	0.001(S)

This table shows statistical significant change in liver enzymes, prothrombin and bilirubin levels before and after 1 &3 months of treatment (p-value less than 0.05).

Table (8) Liver profile before and after treatment in group 2:

Variables	Before TTT	After 1month	t-test	P- value	After 3 month	t-test	*P*-vlaue
ALT	78.1±15.8	86.7±9.2	5.85	0.001(S)	78.1±11.5	1.22	0.267(NS)
AST	83.2±29.5	89.3 ±31.6	3.43	0.003(S)	72.6±12.5	1.21	0.285(NS)
S. bilirubin (mg/dl)	2.12± 0.36	1.8±0.50	1.25	0.29(NS)	1.35±0.29	1.24	0.147(NS)
ALP	130.8±36.2	150.2±45.6	2.58	0.02 (S)	142.6±44.58	1.48	0.160(NS)
S.albumin (gm/dl)	3.1±1.45	3.7±0.36	2.84	00.01 (S)	3.86±0.36	4.38	0.001(S)
Prothrombin Conc.	73.5±6.9	78.5±9.2	2.82	0.027(S)	79.2±5.26	5.01	0.002(S)

Liver enzymes, prothrombin concentration and albumin have significantly improved 1 &3 months after treatment (*p*-value less than 0.05).

Table (9) AFP (ng/ml) before and after treatment in group 1:

Variables	Before TTT	After 1 month	t test	*P*-value	After 3 months	t test	*P*-value
AFP	552.1±235.8	311.2±163	2.41	0.02(S)	214.8±234.1	5.11	0.001(HS)

This table shows a highly significant decrease in AFP in group 1 after 1 & 3 months of treatment

Table (10) AFP (ng/ml) before and after treatment in group 2:

Variables	BeforeTTT	After 1 month	t-test	*P*-value	After3 months	t-test	*P*-value
AFP	566.4±201.5	226.11±154.3	3.91	0.001(HS)	137.3±88.11	0.67	0.001(HS)

This table shows a highly significant decrease in AFP in group 2 after 1 & 3 months of treatment.

Table (11) AFP (ng/ml) after 1 month of follow up:

Variables	PAI group (N =15)	RFA+PAI group(N=15)	t test	*P*-value
AFP	311.2±163	226.11±154.3	3.62	0.03(S)

This table shows that AFP has decreased significantly to lower levels in group 2 after 1 month.

Table (12) AFP (ng/ml) after 3 month of follow up:

Variables	PAI group(N=15)	RFA+PAI group(N=15)	t test	*P*-value
AFP	214.8±234.1	137.3±88.11	3.30	0.02(S)

This table shows that AFP has decreased significantly to lower levels in group 2 after 3 month (*p*-value less than 0.05).

Table (13) Changes in US after procedure in both groups (one week after procedure):

ITEM	PAI group (NO of FL=15)	RFA+PAI group (NO of FL=15)	X^2 test	*P*- VALUE
Number of FL: Same number Change of number	 15 (100%) 0 (0%)	 15 (100%) 0 (0%)	0.000	1.000(NS)
Diameter of FL: • Increased • Same • Decreased	 13 (86.6%) 2 (13.3) 0 (0%)	 14(93.3%) 1(6.66%) 0 (0%)	0.690	0.449 (NS)
Echogenicity of FL: Changed Same	 12 (80%) 3 (20%)	 13 (86.6%) 2 (13.3%)	0.238	0.259 (NS)

There was no statistical significant difference in the US findings after 1 week of the procedure in both groups.

Table (14) results of ablation in both groups:

ITEM	PAI group (NO of) FL=15	RFA+PAI group (NO of FL=15)	X^2test	*P* –VALUE
Diameter of FL: -Complete -Partial	 3(20%) 12(80%)	 7(46.6%) 8(53.3%)	7.062	*0.001 (HS)*

Complete ablation was achieved in 20 % & in 46.6 % of group1 & group2 respectively. The difference was highly significant.

Table (15): Results of ablation in the subgroups(a =5-6.5 cm & b = 6.6-8 cm):

ITEM	PAI group (NO of FL=15)			RFA+PAI group (NO of FL=15)			X^2test	*P* –VALUE
	G 1a=7	G 1b=8	Total	G 2a=8	G 2b=7	Total		
Ablation of FL: complete Partial	2(28.5%) 5(71.4%)	1(12.5%) 7(87.5%)	3(20%) 12(80%)	5(62.5%) 3(37.5%)	2(28.5%) 5(71.4%)	7(46.6%) 8(53.3%)	6.5	*0.01 (S)*

Complete ablation was achieved in 28.5% VS 62.5% of subgroups a, 12.5% VS 28.8% subgroups b with significant difference between the 2 groups.

Table (16) comparison between the different subgroups after ablation:

	Subgroups a				Subgroups b			
	G 1a=7	G 2a=8	X^2test	*P* -VALUE	G 1b=8	G 2b=7	X^2test	*P*-VALUE
Ablation of FL: -Complete -Partial	2(28.5%) 5(71.4%)	(62.5%) 3(37.5%)	7.1	*0.001(HS)*	1(12.5%) 7(87.5%)	(28.5%) 5(71.4%)	6.5	*0.02(S)*

Comparing subgroups 1a Vs 2a & 1b Vs 2b complete ablation was better in 1a & 2a due to the smaller sizes of the lesions.

Table (17) Changes in sizes of the tumours after 3 months of procedure in both groups:

ITEM	PAI group (NO of FL=15)			RFA+PAI group (NO of FL=15)			X^2test	*P* –VALUE
	G 1a=7	G 1b=8	Total	G 2a=8	G 2b=7	Total		
Diameter of FL: Same Increased	4(57.1%) 3(42.8%)	8(100%) 0(0%)	12(80%) 3(20%)	4(50%) 4(50%)	7(100%) 0(0%)	11(73.3%) 4(26.6%)	0.202	0.894(NS)

The diameter remained the same in 12(80%) of group 1 and 11(73.3%) of group 2 and increased in 3(20%) patients in group 1 and in 4(26.6%) of group 2. No significant difference between the 2 groups.

Table (19 Procedure related complications in both groups:

ITEM	PAI group (N=15)	RFA+PAI group (N=15)	X^2 test	*P* –VALUE
Transient pain	13 (86.7%)	11 (73.3%)	1.766	0.189(NS)
Fever	2 (13.3%)	2(13.3%)	0.000	1.000(NS)
PV thrombosis	0 (0%)	1 (6.7%)	1.034	0.320(NS)
Ascites	0 (0%)	0 (0%)	0.000	1.000(NS)

The transient pain and fever were more common complications

4. Disscution

Hepatocellular carcinoma is a global dilemma **(Di Bisceglie, 2002).** Its incidence is rising in Egypt. Screening for HCC, particularly in cirrhotic patients or those with chronic HBV, is very important to discover it early. Surgical resection could be successful if the lesion is small, confined to one lobe in patients with extremely well preserved liver function **(Llovet & Beaugrand, 2003)**

Radio Frequency Thermal Ablation (RFA) is a local ablation technique designed to destroy the tumor by heating, in patients with unresectable liver tumors. The technique is save and effective **(Azab *et al.*, 2007 & 2008).** Most of the Egyptian studies dealt with lesions ≤ 7 cm in diameter **(Tabashy, 2004, Darweesh , 2005, El Shahawy , 2005 and Mohey , 2007)**

Percutaneous acetic acid injection (PAI) may have good penetration into cancer cells in the tumor capsule or intratumoral septa. **(Okada, 1999)** and it is better than ethanol in this respect **(Azab *et al.*, 2009)**

The aim of the current study is to evaluate the efficacy of PAI if used alone or combined with RFA for the management of large tumours ranging from 5-8 cm in diameter. The study included 30 patients with liver cirrhosis and documented HCC by Ultrasound and Triphasic CT scanning ± AFP levels ≥ 200ng/ml. They were randomly assigned to 2 groups, each group was subdivided into 2 subgroups according to the size of the tumor, Group 1a:-included 7 patients (5-6.5 cm in diameter) managed by 2-3 sessions of PAI only, 1 weeks apart. Group 1b:-

included 8 patients (6.6-8 cm) managed by 2-3 sessions of PAI only, 1weeks apart. Group 2a:- included 8 patients (5-5.6 cm) treated by one setting of RFA using RF needle with that expand on deployment up to 5 cm in diameter plus 2-3 sessions PAI 2 weeks apart.Group2b:- included7 patients (6.6-8 cm) treated by one setting of RFA using RF needle with that expand on deployment up to 5 cm in diameter plus 2-3 sessions PAI 2 weeks apart. We didn't use a group for RFA only because we used the needle with arrays that could expand to 5 cm in diameter only leaving the rest of the lesion without ablation.

In our study the most presenting complaint in both groups was right hypochondrial pain, being present in 40% of group 1 and 46.7% of group 2. This is consistent with what had been reported by **Sherlock and Dooley (2002),** to be suspected if a patient with liver cirrhosis develops right upper quadrant pain.

Ahmed *et al.* (2001) and Azab *et al.* (2009) reported right hypochondrial pain in 40-47% of cases and **Haseeb,(2000)** reported it in 68% of their patients.

On general examination, hepatomegaly was detected in 4(26.7%) in both groups. Splenomegaly was detected in 11(73.3%) of group 1 and in 10(66.7%) of group2. Our results were in agreement with the results of the studies done by **El-Kady *et al.* (2001), Darweesh, (2005), and Azab *et al.* (2007 & 2009) .**

According to the ultrasonographic assessment of the studied groups before treatment, cirrhotic picture was seen in 100% in both groups. This high association between cirrhosis and HCC is agreed upon by **Haseeb (2000) Ahmed *et al.* (2001) and Azab *et al.* (2009)** found that 23 out of 25 patients (92%) had liver cirrhosis. **Rosen and Nagorney (1997)** found that more than 75% of their patients with HCC have underlying cirrhosis.. A study done by **Mabrouk (1997)** on 34 Egyptian patients with HCC revealed that all had liver cirrhosis.

The size of the liver was average in 6(40%) patients of group 1 and in 5(33.3%) patients of group 2, enlarged in 5(33.3%) of group 1 and in 4(26.7%) of group 2, and shrunken in 5(33.3%) patients in each group. Splenomegaly was detected in 11(73.3%) patients of each group. No ascites was detected. Our results were in agreement with **El-Kady *et al.* (2001)** and **Darweesh (2005)** studies.

In these study 13 (86.6%) patients of group 1 and 12(80%) patients of group 2 had their focal lesions in the right lobe. This is in agreement with **Haseeb (2000**) who found 32 out of 42 lesions (76%) in the right lobe while a higher percent (95%) were reported by **Ahmed *et al.* (2001).** The fact that focal lesions are more frequent in the right lobe is supported by **Rosen & Nagorney (1997**). The focal lesions were hypoechoic in 13(86.7%) of group 1 and 12(80 %) of group2. Our results are in agreement with **Salama *et al.* (2003)** and **Lencioni & Menu (1999**) who found that HCC is hypoechoic in more than 80% of their patients.

The CBC, transaminases, Serum bilirubin, alkaline phosphatase, albumin and prothrombin time &concentration were performed before treatment to all patients in both groups and they were repeated after the procedure. Billirubin, albumin and prthrombin concentration have significantly improved when evaluated 1&3 month after the procedure. This is in agreement with **Huang *et al.* (2001), Salama *et al.* (2003) and Darweesh *et al.* (2005**).

Alpha feto-protein (AFP) was elevated in 7(46.6%) & 8(53.3%) of group 1 & 2 respectively, ranging from 200-4500 ng/ml. The mean values for the 2 groups were 552.1±235.8 & 566.4±201.5 respectively. It decreased significantly 1 & 3 months after the procedure. Previous studies by **Azab *et al.* (2009)** showed similar figures. **Mohamed *et al.* (2000)** found elevated AFP in 45.1% of his HCC patients. **Abdl Ghafar et al., (2002)** found that most cases (73.3%) presented with high levels (>100 ng/ml). The cut off value of AFP is debated and ranges between 200 and 1000 ng/ ml with increasing specificity by increasing the cut off level **(Abdel–Hameid, 1998).**

There was change in tumour echogenicity from hypo- or isoechoic to hyperechoic in 12(80%) of group 1 and 13(86.6%) of group 2 after 1 week of the procedure. This goes with **Rossi *et al.* (2000)** who confirmed that US appearance of HCC is modified after ablation. Usually hypoechoic & isoechoic HCC lesions become hyperechoic **(Azab *et al.*, 2009).**

At the end of treatment the US outcome is not entirely reliable. For this reason we did not depend on US picture alone but sequential AFP measurement and triphasic spiral CT were done to evaluate the therapeutic effect. AFP was measured in patients with elevated levels 1&3 months after the procedure. AFP has a plasma half-life of 5 days and therefore reflects production of tumour cell mass **(Brumm *et al.*, 1989)** and decreased significantly during the follow up period**.**

The diameter of the lesions after the procedure increased in **13 (86.6%)**patients of group 1 in comparison to **14(93.3%)** patients of group 2, remained the same in 5 (33.3%) of group 1 and 3 (20%) of group 2. The increased diameter is due to the penetration of the surrounding tissues by acetic acid. This gives a safety margin for HCC **(Azab *et al.*, 2009)** allowing necrosis of malignant cells that may be found in the capsule of the tumor**.**

The spiral CT done before the procedure showed early enhancement of the lesions in the arterial phase & wash out in the delayed & venous phases in 100% of cases. Our results are in agreement with **Darweesh. (2005)** as he concluded that contrast enhanced spiral CT is currently the most sensitive test for managing thermal ablation for patients with HCC.

Complete ablation was achieved in 46.6% of the group treated by combining RFA & PAI compared to 20% of the group treated by PAI alone. This is probably because PAI couldn't spread completely to the periphery of the tumors espically the large ones. When we started by RFA it induced necrosis for the central part of the tumor about 5 cm in diameter or a little bit more according the expansion of the RF needle arrays. We believe that acetic acid when injected after this central necrosis it diffuses more easily to the periphery of the tumors causing necrosis of larger volumes of HCC. This could explain the better results when RFA is conducted before acetic acid.

RFA alone used for large tumors gave less favourable results as that seen the study of **Livraghie *et al.* (2000)** who used RFA for tumors 5.1-9.5 cm in diameter. Complete ablation was achieved in 25% of the tumors presumably of small sized lesions. This percent of ablation is comparable to that of our study when we used acetic acid alone, but starting by RFA complete ablation was achieved in 46.6% compared to the 25% that was achieved by RFA alone in **Livraghie *et al.* (2000)** Study.

Our results indicate that combined therapy could achieve better results in the smaller lesions (5-6.5 cm), since complete ablation was detected in 62.5% of subgroup 2a compared to 28.5% of subgroup 1a with highly significant difference. Previous studies have shown the advantage of early detection of HCC because ablation in this situation will give better results. **Azab *et al.* (2009)** obtained good response in treating relatively small lesions (3-6 cm) by PAI (86.7%). In our study RFA caused necrosis of most of HCC mass around (5-6.5 cm). The periphery of the lesion with thickness less than 2 cm could then be perfused by acetic acid causing necrosis if most if not all the tumor mass, since 2 sitting were done for such small HCC .

The complications of the procedures were minimal in our study. No mortalities related to the technique in both groups. Transient abdominal pain during the sessions was the most encountered problem. The abdominal pain was sometimes associated with shoulder pain in focal lesions of the right lobe near the diaphragm that was relieved by I.V analgesics. Only few patients had transient fever which could be due to tissue necrosis that was relieved by antipyretics .Our results correspond to those recorded by **Livraghi *et al.* (1999) Salama *et al.* (2003) and Azab *et al.* (2007).**

In our study AFP proved to be of great value for the follow up of patients who have had elevated levels before the procedure. It decreased below the diagnostic levels in patients having full ablation, in group 1 from 552.1±235.8 to 311.2±163 & 214.8±234.1, 1 and 3 months later and in group2 from 566.4±201.5 to 226.11±154.3& 137.3±88.11, one and three months later. These results are in line with studies done by **Rossi *et al.* (2000)**. **And Azab *et al.* (2007&2008)**

On follow up of the cases after the procedures, liver enzymes ALT, AST, S.bilirubin and prothrombin concentration showed statistically significant improvement after 1 and 3 months of ablation. This is in line with the studies done by **Azab et al., (2007 & 2008).** This is probably due to the removal of the deleterious effect of the tumour on the surrounding tissues.

At last but not at least it is concluded that the combination therapy of RFA & PAI for large HCC lesions could induce good ablation in a proportion of the patients & partial ablation in the rest which might be useful in ameliorating the symptoms of that ugly disease.

Recommendation

From this study we recommend the following:

1-Screening for HCC by US and AFP periodically in high risk patients like chirrotics and HBV, every 3 months is important to detect small lesions, it could be then surgically resectable or completely ablated.

2-If accidentally discovered and was large (up to 8 cm in diameter), a reasonable percentage of patients could benefit from percutaneous ablation modalities, either single or in combination, like what have been done in our study.

3-The development of RFA with larger diameters (e.g 7 cm) could be a useful tool for large tumors giving better results than the 5 cm used in this study.

4-Combination of different modalities is in need to be evaluated to test which combination gives the best results.

5-The higher the number of patients included in such studies the more precise information about the best modalities could be collected.

6-Larger periods of follow up for such patients to evaluate the recurrence at the site of the tumor or development of lesions at other sites and the effect on survival of patient are needed.

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