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RESEARCH ARTICLE

EVALUATION OF EARLY RECANALIZATION AFTER SONOTHROMBOLYSIS IN ACUTE ISCHEMIC STROKE

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Abstract

Background: Stroke is considered the second most common cause of death and the major cause of disability worldwide. Sonothrombolysis via improving the effectiveness of intravenous thrombolysis may be an effective treatment through enhancing early arterial recanalization.

Objectives: To evaluate the efficacy and safety of sonothrombolysis in treatment of acute ischemic stroke.

Patients and Methods: Patients with acute first ever ischemic stroke affecting the main stem of middle cerebral artery (MCA), within 4.5 hours following stroke onset were classified into 3 groups: 20 patients treated with both sonothrombolysis and tPA, 20 patients with tPA alone and 20 patients with sonolysis alone when tPA is contra-indicated or can't be achieved. Patients with indefinite time of onset of stroke, Poor temporal window, or stroke due to occlusion of intracerebral arteries rather than MCA were excluded.

Results: A considerable improvement of the degree of recanalization of MCA is observed for group (I), with (55 %) of patients had a complete recanalization after 1 hour compared to (35 %) for group II and (15 %) for group III. After 24 hours, full recanalization had been increased to involve (75%) of patients in group I. There was also a considerable clinical improvement as compared to the baseline evaluation scores with significant statistical difference after one hour for sonothrombolysis group and this improvement was maintained after 24 hours with statistically significant difference. After 1 hour, (25%) of patients in group I had a full clinical recovery compared to (10%) in group II and no patients in group III with a statistically significant difference for group I. After 24 hours, more patients had a full clinical recovery in group I (45%). Hemorrhagic transformation occurred in (10%) of patients in group I versus (5%) in group II without statistically significant difference.

Conclusion: Sonothrombolysis can be used for patients with acute ischemic stroke safely without any further delay with a substantial improvement of the degree of recanalization of MCA and considerable clinical improvement.

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Introduction:-

Stroke is considered the second most common cause of death and the major cause of disability worldwide. The proportion of deaths caused by stroke is 10% to 12% in western countries. ⁽¹⁾ The World Health Organization (WHO) estimates that 85% of stroke deaths occur in low and middle-income countries including Egypt. The overall prevalence rate of stroke in Egypt is 963/100,000 with new strokes per year estimated around 150,000 to 210,000 events. ⁽²⁾

Many advances have occurred in the prevention and treatment of stroke during the past few years. Intravenous thrombolysis with tissue plasminogen activator (tPA) has been shown to be effective in selected patients with acute ischemic stroke within 3 – 4.5 hours following stroke onset according to different studies. ⁽³⁾

Intravenous thrombolysis alone might not be adequate to achieve early recanalization, which explains why interventional therapy, either intra-arterial thrombolysis or thrombus extraction, is often regarded as an alternative. But because of the time delay to the start and the lack of availability of these types of interventional treatment, Sonothrombolysis via improving the effectiveness of intravenous thrombolysis may be a promising alternative option. However, not all patients are suitable for receiving intravenous thrombolysis either due to many contraindications or high expenses. So, new treatment modalities are still needed. ⁽⁴⁾

Ultrasound is used routinely for diagnosing and monitoring acute ischemic stroke patients. Experimental studies suggest that ultrasound can help the effect of clot dissolving treatment (thrombolysis) in acute stroke. ⁽⁵⁾

Sonothrombolysis is usually performed in patients with documented arterial occlusion by insonation of major intracranial vessels, including the middle cerebral artery and intracranial internal carotid artery. ⁽⁶⁾

Patients and Methods:-

In this prospective randomized controlled monocenter study, **60** patients with acute first-ever ischemic stroke were recruited from the Department of Neuropsychiatry, and Psychiatry and Neurology Center, Tanta University Hospital, Egypt. They were presented with MCA main stem infarction as evidenced clinically and ascertained by investigational tools as CT brain, MRI brain with diffusion “when needed”, and Transcranial color-coded sonography (TCCS).

Patients were classified into 3 groups:

Group I: including 20 patients who were treated with both sonothrombolysis and rtPA.

Group II: including 20 patients who were treated with rtPA alone

Group III: including 20 patients who were treated with sonothrombolysis alone when rtPA is contra-indicated or cannot be achieved.

Patients with indefinite time of onset of stroke or those with poor acoustic temporal window are excluded together with stroke due to occlusion of intracerebral arteries rather than middle cerebral artery, or branch middle cerebral artery occlusion.

Thorough history taking, general medical and neurological assessment were done for each patient. Early brain CT and/or MRI was done to confirm the diagnosis and assess the degree of MCA stenosis according to Alberta Stroke Program Early CT Score (ASPECTS). ⁽⁷⁾

Routine laboratory investigations were done. Cerebral ischemic stroke was managed according to the (American Heart Association/ American Stroke Association) AHA/ASA stroke management guidelines. ^(8,9)

Transcranial Ultrasound:

Transcranial color-coded sonography (TCCS) was done for evaluation of MCA occlusion for all groups immediately, and after 60 minutes to ascertain occlusion and to evaluate recanalization according to Thrombolysis in Brain Ischemia (TIBI) score. ⁽¹⁰⁾

A session of sonothrombolysis was performed using TCCS and adjusted on 2 MHz frequency continuously for one-hour insonating the MCA with manually handled probe via trans-temporal approach, horizontal plane.

Follow up of the patients:

Patients were followed up clinically and radiologically by CT scan done after 24 hours from stroke onset to detect any neurological complication appears during the study like hemorrhagic transformation.

Follow up ultrasound was done for all groups after 24 hours from stroke onset to assess recanalization using the same parameters.

Patients were followed clinically after one hour, 24 hours and one week to assess the early functional outcome of each intervention.

Statistical analysis:

Analysis was performed using Statistical Package for Social Science (SPSS 17, Chicago, IL). Mean and standard deviation (\pm SD) were used for parametric numerical data, while median non-parametric numerical data. Student t-test was used to assess the statistical significance of the difference between two group means, and Paired t-test to assess the statistical difference between two means measured twice for the same study group.

Chi-square test proposed the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Correlation analysis was done using Pearson's correlation coefficient (r) method. ANOVA test was used for comparison among different times in the same group in quantitative data. $P < 0.05$ was considered to be statistically significant for all tests.

Results:-

During the study, 2 patients were died, the first one died after failure of thrombolytic therapy (group II) with progressing malignant MCA infarction, occurred at the second day and the patient died two days later. The second one (group III) died because of aspiration pneumonia after 6 days from stroke onset.

Primary end points of the study were assessed after one hour of different interventions done for each group, aimed at evaluation of MCA recanalization as evidenced by TCCS and graded according to TIBI score. Secondary end points of the study were assessed after 24 hours of stroke intervention regarding maintained and late recanalization of MCA, clinical outcome by NIHSS score which was then re-evaluated after 1week as a short clinical follow up. Evaluation of safety of these interventions were evaluated after 24 hours regarding spontaneous intracranial hemorrhage while other possible complications had not occurred.

Table 1:- Demographic data of the studied groups.

		Group subtype									ANOVA (age) / Chi-Square (sex)	
		Group I			Group II			Group III			F or X^2	P-value
Age	Range	42	-	82	32	-	72	53	-	77	0.694	0.504
	Mean	58.50	\pm	11.43	60.55	\pm	11.30	62.35	\pm	7.90		
	\pm SD	0		2	0		2	0		3		
Sex	Male	12		60.00	13		65.00	12		60.00	0.141	0.932
	Female	8		40.00	7		35.00	8		40.00		

Table 2:- Risk factors among the studied groups.

	Group subtype								Chi-Square	
	Group I		Group II		Group III		Total			
	N	%	N	%	N	%	N	%	X ²	P-value
Diabetes	14	70.00	13	65.00	16	80.00	43	71.67	1.149	0.563
Hypertension	12	60.00	17	85.00	15	75.00	44	73.33	3.239	0.198
Obesity	6	30.00	11	55.00	18	90.00	35	58.33	14.949	0.001*
Smoking	2	10.00	6	30.00	5	25.00	13	21.67	2.553	0.279
Hyperlipidemia	4	20.00	8	40.00	8	40.00	20	33.33	2.400	0.301
Cardiac diseases	14	70.00	7	35.00	11	55.00	32	53.33	4.955	0.084

AF	5	35.71	2	28.57	7	63.64	14	43.75	8.158	0.227
IHD	7	50.00	4	57.14	4	36.36	15	46.88		
PFO	0	0.00	1	14.29	0	0.00	1	3.13		
Prosthetic valve	2	14.29	0	0.00	0	0.00	2	6.25		

Table 3:- General characters of the studied groups.

	Group subtype								Chi-Square	
	Group I		Group II		Group III		Total		X ²	P-value
	N	%	N	%	N	%	N	%		
Right hemispheric	14	70.00	14	70.00	7	35.00	35	58.33	6.720	0.035*
Left hemispheric	6	30.00	6	30.00	13	65.00	25	41.67		

TACI	12	60.00	12	60.00	11	55.00	35	58.33	0.137	0.934
PACI	8	40.00	8	40.00	9	45.00	25	41.67		

*according to Oxfordshire classification

TACI total anterior circulation infarction, PACI partial anterior circulation infarction.

Atherosclerotic	10	50.00	11	55.00	14	70.00	35	58.33	10.312	0.112
Cardio-embolic	8	40.00	3	15.00	2	10.00	13	21.67		
Undetermined	2	10.00	4	20.00	4	20.00	10	16.67		
Cryptogenic	0	0.00	2	10.00	0	0.00	2	3.33		

According to TOAST classification

Group I: patients treated with both sonothrombolysis and rtPA.

Group II: patients treated with rtPA alone

Group III: patients treated with sonothrombolysis alone

The study results showed no significant statistical difference concerning stroke onset to treatment initiation time. However, this long time (207.27 ± 24.04 min - 208.1 ± 25.84 min - 212.7 ± 18.16 min) for group I, II and III respectively might be considered one of the drawbacks of this study reflecting a major health problem for early stroke management. It is well known that early initiation of rtPA therapy following stroke onset is directly proportionate to better outcome⁽¹¹⁾. This in turn might have a negative impact on the study end results.

Table 4:- Median TIBI score among the studied groups.

TIBI Score		Group subtype									ANOVA		TUKEY'S Test		
		Group I			Group II			Group III			F	P-value	I&I I	I&I II	II&I II
At first presentation	Range	0	-	4	1	-	4	2	-	4	8.75	<0.00	0.28	0.02	<0.0
	Mean ±SD	2.54 5	±	1.4 71	2.00 0	±	1.1 55	3.55 6	±	0.7 05	1	1*	2	4*	01*
After 30 Minutes	Range	1	-	5	1	-	5	3	-	5	6.37	0.003	0.03	0.57	0.003
	Mean ±SD	3.54 5	±	1.1 01	2.72 7	±	1.3 16	3.88 9	±	0.5 83	1	*	7*	4	*
After 60 Minutes	Range	1	-	5	1	-	5	4	-	5	3.45	0.038	0.05	0.98	0.095
	Mean ±SD	4.27 3	±	1.1 62	3.45 5	±	1.4 71	4.22 2	±	0.4 28	4	*	3*	9	
After 24 Hours	Range	2	-	5	1	-	5	4	-	5	5.45	0.007	0.03	0.80	0.009
	Mean ±SD	4.45 5	±	0.9 12	3.63 6	±	1.4 65	4.66 7	±	0.4 85	0	*	5*	5	*
At F-A30M	Differences	- 1.00 0	±	1.0 69	- 0.72 7	±	0.9 85	- 0.33 3	±	0.4 85	2.69 0	0.076			
	Paired Test	<0.001*			0.002*			0.010*							

At F-A60M	Differences	-1.727	±	1.453	-1.455	±	1.535	-0.667	±	0.686	3.399	0.040*	0.771	0.036*	0.151
	Paired Test	<0.001*			<0.001*			0.001							
At F-A24H	Differences	-1.909	±	1.269	-1.636	±	1.649	-1.111	±	0.758	1.878	0.162			
	Paired Test	<0.001*			<0.001*			<0.001*							

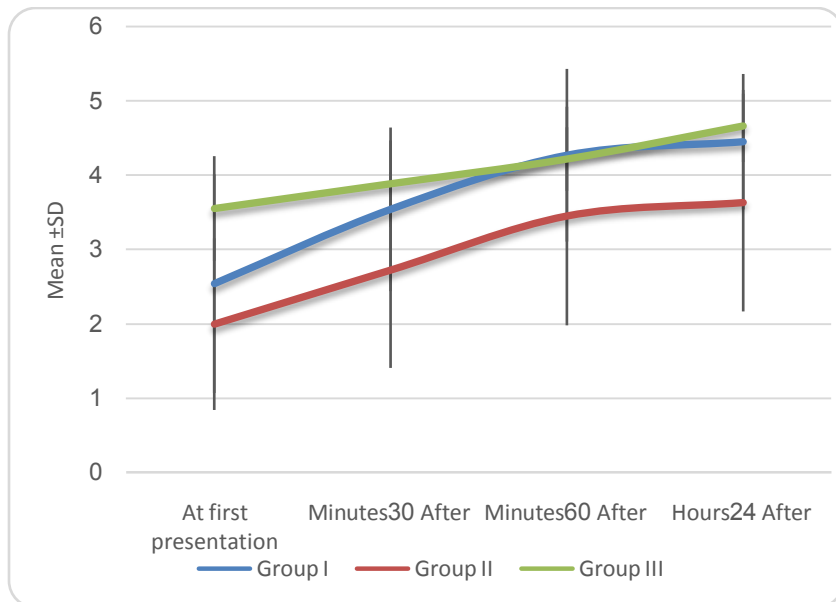


Figure 1:- Median TIBI score among the studied groups.

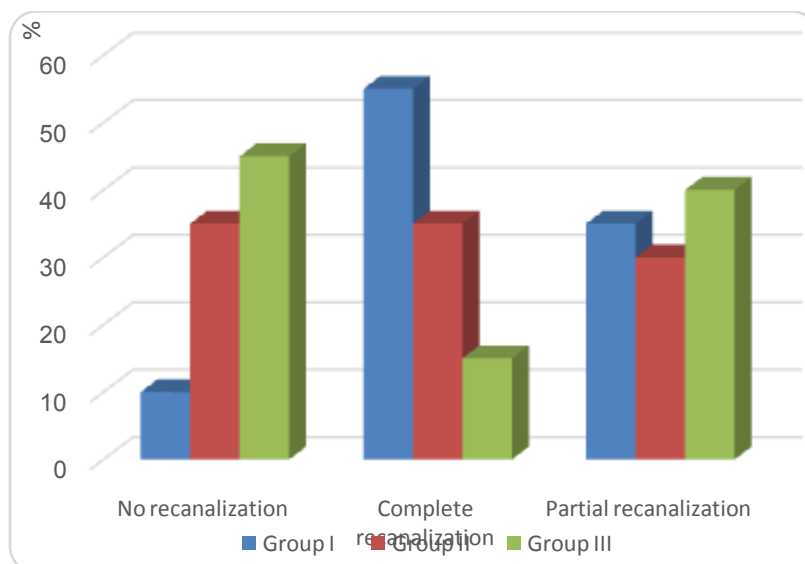


Figure 2:- Degree of early recanalization of affected MCA after one hour of intervention among the studied groups.

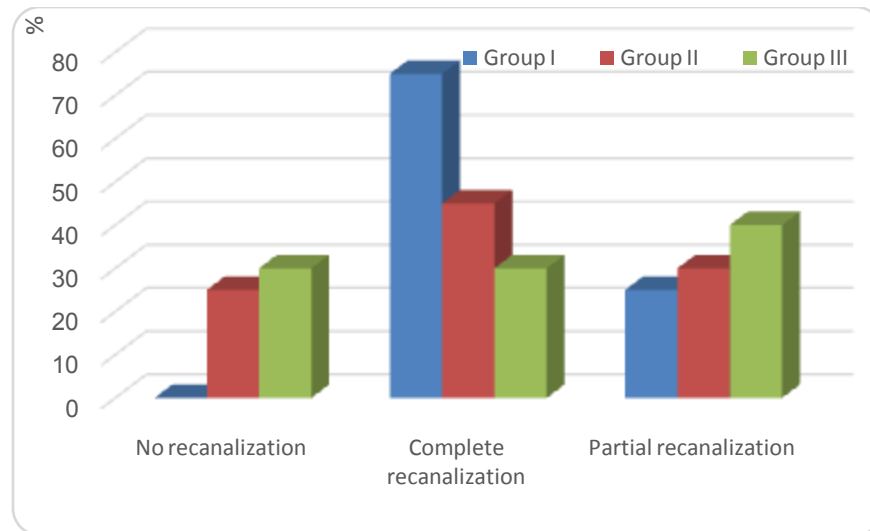


Figure 3:- Degree of recanalization of affected MCA after 24 hours of intervention among the studied groups.

Secondary to randomization of cases, it was noticed that there were some clinical differences in the clinical severity and degree of stenosis of MCA among the groups as described in tables (4,5). However, these differences are not statistically significant when compared among each other. In addition, follow up of clinical improvement and arterial recanalization is mainly evaluated in comparison to the baseline levels of the same group and such rate of change is then compared to other groups.

Thrombolysis in brain ischemia (TIBI) score was used to assess the occlusion and recanalization of MCA. This variability in the median scores among the groups is partly related to alternating randomization in a relatively small sample size (Randomization bias) and partly to disruption of randomization for group III where we were obligated to start just sonolysis for a non-blinded selected group (Selection bias). To avoid these bias, patients were longitudinally assessed and compared to their baseline median score and then compared in relation to the rate recanalization and clinical improvement.

The study results showed a substantial improvement of the degree of recanalization of MCA for group (I). The rate of recanalization was much higher for group I compared to other groups after the follow up timing intervals particularly after 60 minutes ($p=0.040$) and on a longitudinal comparison in the same group from the first baseline TIBI score and after 30 minutes, 60 minutes and 24 hours ($p<0.001^*$).

The recanalization state was further analyzed. It was found that, in group I (sonothrombolysis group), (55 %) of patients had a complete recanalization of MCA (TIBI score equals to 5) after 1 hour. While in group II (rtPA alone), (35 %) of patients had a complete recanalization. It is to be noted that two patients in this group had a re-occlusion during the one-hour infusion period and obtained slight partial recanalization after 24 hours scan. For group III, only (15 %) of patients had a complete recanalization. There was a marked difference in favor of the sonothrombolysis group concerning early recanalization after 1 hour ($p=0.030$).

Percentage of patients in group I with full recanalization had been increased to become (75%) after 24 hours which is markedly higher than other groups (45% for group II, 30% for group III).

Table 5:- Median NIHSS score among the studied groups.

NIHSS		Group subtype									ANOVA		TUKEY'S Test		
		Group I			Group II			Group III			F	P-value	I&II	I&III	II&I II
At first presentation	Range	8	-	18	10	-	20	8	-	18	1.78	0.177			
	Mean \pm SD	12.7 \pm 2.9		95	14.3 \pm 3.5		80	12.6 \pm 3.3		61	6				
After 60	Range	4	-	12	2	-	20	6	-	15	4.21	0.020	0.021	0.100	0.85

Minutes	Mean ±SD	8.09 1	±	2.9 75	11.4 55	±	5.2 44	10.7 78	±	3.4 22	0	*	*		8
After 24 Hours	Range	2	-	10	2	-	20	4	-	15	8.49 1	0.001 *	0.001 *	0.018 *	0.59 5
	Mean ±SD	6.09 1	±	2.7 76	10.9 09	±	5.1 17	9.66 7	±	3.7 26					
After 1 Week	Range	2	-	8	2	-	18	3	-	14	9.70 7	<0.00 1*	<0.00 1*	0.006 *	0.70 8
	Mean ±SD	4.27 3	±	2.1 42	8.80 0	±	4.5 14	7.88 9	±	3.6 44					
At F- A60M	Difference	4.63 6	±	3.4 99	2.90 9	±	2.3 69	1.88 9	±	0.7 58	5.99 3	0.004 *	0.072	0.004 *	0.42 5
	Paired Test	<0.001*			<0.001*			<0.001*							
At F- A24H	Difference	6.63 6	±	3.3 88	3.45 5	±	2.3 24	3.00 0	±	1.3 72	12.5 78	<0.00 1*	<0.00 1*	<0.00 1*	0.84 2
	Paired Test	<0.001*			<0.001*			<0.001*							
At F- A1W	Difference	8.45 5	±	3.5 55	5.20 0	±	1.8 81	4.77 8	±	1.6 65	12.6 05	<0.00 1*	<0.00 1*	<0.00 1*	0.87 0
	Paired Test	<0.001*			<0.001*			<0.001*							

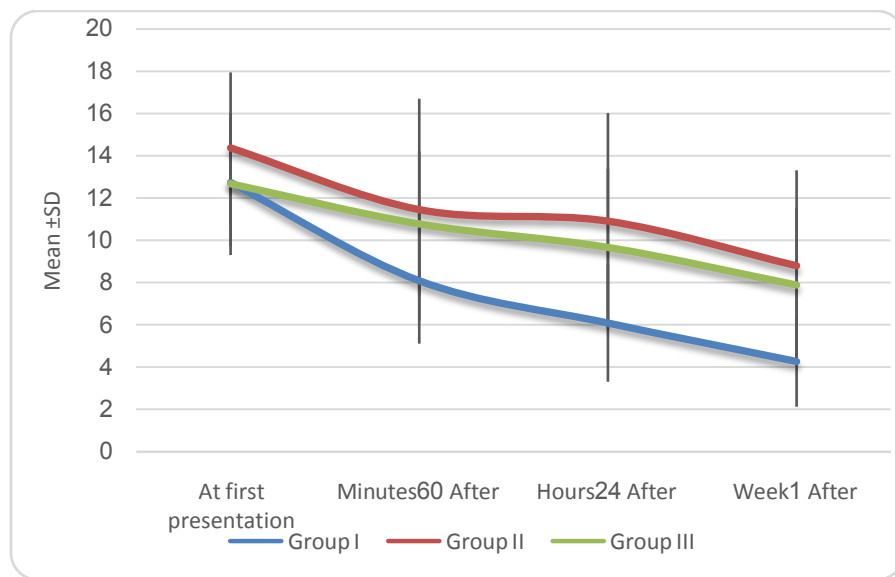


Figure 4:- Median NIHSS score among the studied groups.

Clinical severity was assessed and followed up by the National Institute of Health Stroke Scale (NIHSS) scoring system, with slightly different variation for group II without statistical difference as detailed in table (5).

Immediately after one hour of medical intervention for all groups, NIHSS score was re-evaluated to determine the effect on the clinical recovery. There was a considerable improvement as compared to the baseline evaluation scores for each group with significant statistical difference for group I compared to other groups. This clinical improvement is maintained after 24 hours in favor of group I with statistically significant difference compared to the median baseline scores of each group ($p = 0.001^*$). After 1 week of clinical follow up, patients in group (I) had a marked clinical improvement with residual mild deficit and statistically significant difference compared to other groups ($p = 0.001^*$).

It was noted that (25%) of patients in group I had full clinical recovery as defined by improving NIHSS score for 10 or more points or total NIHSS score is less than 4 (12), compared to (10%) of patients in group II while no patients in group III had a full clinical recovery with also a statistically significant difference for group I ($p = 0.046^*$). More

patients had a full clinical recovery after 24 hours in group I (45%) while there were no more cases with full clinical recovery in group II (10%) and improvement was just for the median score for the range of recovery. Noticeably, 3 out of 20 patients (15%) in group III had a full clinical recovery denoting the late ameliorating effect of sonolysis on the functional outcome.

Table 6:- Correlation between sonographic MCA recanalization and clinical outcome by NIHSS score after 24 hours.

NIHSS After 24 Hours	TIBI Score After 24 Hours	
	R	P-value
Group I	-0.614	0.002*
Group II	-0.414	0.022*
Group III	-0.195	0.437

There was also a significant correlation between improving recanalization (measured by increasing TIBI values) and clinical recovery (measured by decreasing NIHSS values) after 24 hours suggesting a better outcome for each maneuver done in group (I and II) with significant statistical values for both groups ($p= 0.002$ and 0.022 respectively).

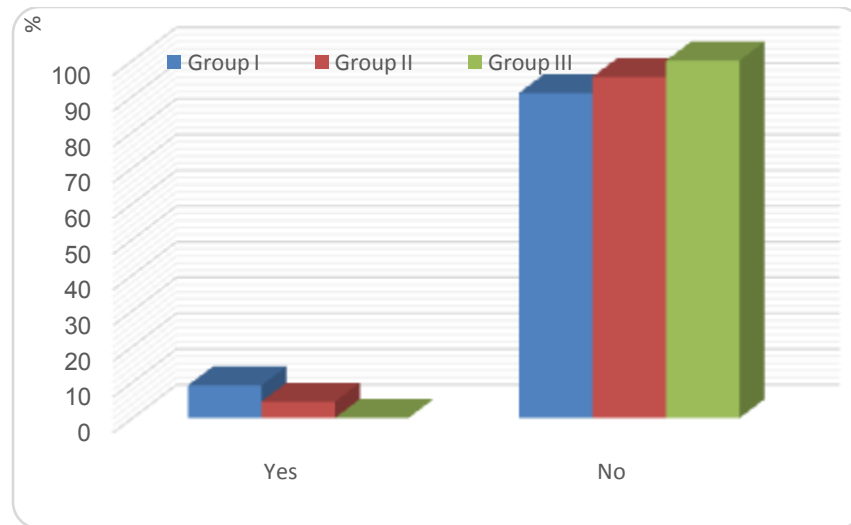


Figure 5:- Hemorrhagic transformation among the studied groups.

No significant change among the studied groups in terms of hemorrhagic transformation with 2 patients in group I and 1 patient in group II only who had such a complication during the study as shown in figure (5). However, all were asymptomatic.

Discussion:-

This study showed that there was no any further delay when ultrasound is added to usual intravenous thrombolytic treatment with a substantial improvement of the degree of recanalization of MCA for sonothrombolysis group after 60 minutes and 24 hours ($p<0.001^*$).

For rtPA applied alone in group II, the study results came in accordance with the usual and well-known recanalization percentage of IV thrombolysis which lies between 30-40%.⁽¹³⁾ But because of this percentage, many patients are left with a substantial brain damage, with high rates of disability and mortality.⁽¹⁴⁾

The earliest trial to combine ultrasound to rtPA was CLOTBUST trial - Combined Lysis of Thrombus in Brain Ischemia Using Transcranial US and Systemic t-PA trial - (2004). It was a multi-center, randomized clinical trial on 126 patients with acute occlusion of the (MCA). All patients were treated with intravenous rt-PA within 3 hours after the onset of symptoms. The target patients received 2-MHz transcranial Doppler (TCD) monitoring for 2 hours

along with rtPA. A complete reperfusion was observed for 49% of the patients in the target group (rtPA+US) and for only 30% of the control group which are closely related to the current study results.⁽¹⁵⁾

However, there were some limitations of the CLOTBUST trial including inhomogenous patient sample (patients with main stem and branch MCA stenosis) which is avoided in the current study as we just include main stem (M1-MCA) and exclude branch arterial occlusion.

The Combined Lysis of Thrombus in Brain Ischemia With Transcranial Ultrasound and Systemic T-PA-Hands-Free study is a multicenter, double-blind, phase 3, randomized controlled trial done at 76 medical centers in 14 countries (CLOTBUST-ER), using of t-PA plus a novel operator-independent US device in patients with ischemic stroke caused by proximal intracranial occlusion.⁽¹⁶⁾ Recently, the trial was stopped after the second interim analysis with results showing that sonothrombolysis was feasible and most likely safe, but no clinical benefit was seen at 90 days.⁽¹⁷⁾

However, in the current study the long term functional outcome is not assessed, and clinical recovery was just assessed after one week showing a significant clinical improvement.

Another monocenter study (Lübeck study) in Germany, in which, 37 Patients with exclusively main stem MCA were randomly selected to receive TCCS instead of TCD allowing better orientation of the arterial thrombus and they were insonated for just one hour. 58% of sonothrombolysis group had a complete recanalization versus 22% of the rtPA group. These results are so close to the current study results.⁽¹⁸⁾

In a smaller study of 18 patients with acute ischemic stroke ineligible to rtPA treatment, divided into two arms. 62% of sonolysis group (first arm) showed MCA recanalization (all of them were partial) versus 0% recanalization for a group with a conservative treatment alone (second arm).⁽¹⁹⁾

This comes in accordance with the current study results for 20 patients treated by sonolysis alone (group III) with 55.55% showed recanalization after 1 hour (15% complete, 40% partial).

The results of Eager and co-workers (2008) showed relatively different results about 24-hours follow up ultrasound scan, with percentage of full recanalization for sonothrombolysis group (88.9%, 16/19 patients) versus rtPA alone (82.4%, 14/18 patients) (18). This could be explained by limited sample sizes for both studies (20 patients in our study and 18 patients for that study) and different in the baseline severity of canalization state.

In terms of clinical recovery, the current study results came in accordance with that of CLOTBUST trial showed that clinical recovery occurred within 2 hours (Total NIHSS score ≤ 3 or Reduction in NIHSS score by ≥ 10 points) was higher in the ultrasound group (29%) than in the non-ultrasound group (21%). Patients who had both clinical recovery and complete recanalization within 2 hours were 28% in the ultrasound group compared to the non-ultrasound group (8%) with clear trend towards better outcome after 3 months follow up.⁽¹⁵⁾

The study results also come in accordance with that of Eagers and co-workers, 2008 who found that 55.6% of patients received sonothrombolysis had a clinical improvement (NIHSS improvement more than 4) compared to 27.8% of the rtPA group and a similar percentage after 4 days of follow up denoting the positive effect of ultrasound on the functional clinical recovery.⁽¹⁸⁾

They also concluded that compared with baseline, at day 1, the NIHSS values improved more strongly in the US group than in the no-US group (median 10.5, IQR 12.5 versus median 15.5, IQR 7.0). At day 4, the NIHSS values had improved more strongly in the US group compared with the no-US group (median 14, IQR 14.0 versus median 17.5, IQR 9.5).⁽¹⁸⁾

In a study done for patients ineligible to rtPA and had received sonolysis and randomized against another group with conservative treatment, significant improvement of the clinical course after 4 days and functional independence after 3 months were found in 2 out of 8 patients of the sonolysis group compared to none of 7 patients in the control group.⁽¹⁹⁾

Mechanisms of Ultrasound Thrombolysis remain poorly understood. Inertial cavitation (i.e. the formation and violent collapse of gas-filled bubbles in a fluid exposed to US) gives rise to transient microjets that mechanically disintegrate the thrombus.⁽²⁰⁾ Stable cavitation (i.e. sustainable, nonlinear, periodic contraction or expansion of a gas bubble) may be more effective in clot lysis than inertial cavitation.⁽²¹⁾ Ultrasound also facilitates the penetration of fibrinolytic drugs into the thrombus and the binding to fibrin⁽²²⁾ because US promotes the motion of fluids around the clot surface through a process called microstreaming. Moreover, pressure waves may increase the permeation of t-PA into the interior of the fibrin network.⁽²³⁾ Heating is uniformly present in tissue exposed to US but has been deemed too mild to explain the thrombolytic effects.⁽²⁴⁾

In terms of the safety consideration of sonothrombolysis, the percentage of hemorrhagic transformation was partly similar to that in other studies. In the study of CLOTBUST, the results of spontaneous intracranial hemorrhage were the same in each group (4.8%).⁽¹⁵⁾ While in Lubeck study, intracerebral hemorrhage had occurred with 3 patients in the US- group versus 1 patient in the control group (sICH, in US-group 15.8% versus 5.6%, $p=0.604$).⁽¹⁸⁾

In the study of sonolysis done alone for patient ineligible to rtPA, it was found that there was no spontaneous intracerebral hemorrhage occurred in the US-group and control group⁽¹⁹⁾ which is similar to our study results.

A Cochrane study of sonothrombolysis for acute ischaemic stroke has shown that a statistically significant improvement in the primary outcome of clinical outcome at three months after stroke, and a promising increase in the recanalization rate. These results were seen across all intervention comparisons (sonothrombolysis versus control, with or without tPA). Which is closely related to the current study results except for the long term clinical follow up.⁽⁵⁾

Conclusions:-

1. Ultrasound enhanced thrombolysis can be used for patients with acute ischemic stroke without any further delay when added to usual intravenous thrombolytic treatment.
2. A substantial improvement of the degree of recanalization of MCA had been observed for sonothrombolysis group after 60 minutes and maintained after 24 hours.
3. A considerable clinical improvement is observed for the sonothrombolysis group and maintained after 24 hours and one week of follow up.
4. A significant correlation between improving recanalization and clinical recovery was observed for each group.
5. Sonothrombolysis is a safe method with no significant risk of hemorrhagic transformation.

Recommendations:-

1. Ultrasound enhanced thrombolysis can be used as an adjuvant and safe method to enhance the arterial recanalization for patients with acute ischemic stroke.
2. It can be used in combination to usual intra-venous rtPA, helping in arterial monitoring and adding beneficial effects regarding the early recanalization and functional clinical recovery.
3. When rtPA is contra-indicated or can't be achieved in addition to other interventional modalities, ultrasound alone can be used safely, however a little significance is observed in this study.
4. Larger multi-center studies with a larger sample size and longer duration for clinical follow up are still needed to assess the efficacy, safety and the best maneuver for sonothrombolysis.
5. More effort is needed to be done to facilitate the availability of ultrasound machines at different stroke centers all over Egypt, with intended detailed training program of medical personnel.

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Competing interests:

The authors declare that they have no competing interests.

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