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Comparison between Tranexamic acid and Doxycycline Pleurodesis in Malignant Pleural effusion by Medical Thoracoscopy

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ABSTRACT
Background: Malignant pleural effusion (MPE) is a morbid disability that places a major strain on the healthcare system. For MPE, pleurodesis and indwelling pleural catheters continue to be standard treatments.
Objective: The aim of the current study was to compare thoracoscopic pleurodesis with tranexamic acid and doxycycline powder as palliative preventative therapies for recurring malignant pleural effusions in terms of effectiveness, safety, and prognosis. **Patients and methods:** A randomized controlled clinical trial included 100 patients with MPE who were divided into 2 groups: Group (I) included 50 patients with thoracoscopic pleurodesis of tranexamic acid and Group (II) included 50 patients with thoracoscopic pleurodesis of doxycycline powder. All patients had their history checked, clinical assessment, pleural fluid laboratory investigations (total proteins, LDH, Differential cell count, cytology for malignant cells, PH, Glucose level, culture and sensitivity, and Adenosine Deaminase (ADA)), chest radiograph, chest ultrasound, computed tomography (CT) scan of the chest, and thoracoscopic pleurodesis.
Results: There was no significant difference between the groups in terms of Light's criteria and lymphocytes (%) in the pleural fluid. However, there was a significant difference between groups regarding Chest x ray at 3rd month and Chest ultrasound at 3rd month. Success of pleurodesis was higher in the Tranexamic acid group (95.5%) compared to the Doxycycline group (81%) with statistically significant difference (P=0.047). **Conclusion:** Medical thoracoscopy is a safe, easy and efficient way to diagnose the malignant pleural effusion as well as performing pleurodesis. Tranexamic acid has a great benefit in pleurodesis with no chest pain during and after pleurodesis and has a higher success rate than doxycycline for pleurodesis.
Keywords: Malignant pleural effusion, Thoracoscopy, Pleurodesis, Tranexamic acid, Doxycycline.

INTRODUCTION

Malignant pleural effusion (MPE) renders people morbidly disabled and places major strain on the healthcare system. More than 500,000 new instances of malignant pleural effusion are anticipated to occur each year in affluent nations [1]. Approximately 44–77% of all exudative pleural effusions are malignant. Nearly half of individuals with disseminated malignancies develop it [2]. The presence of MPE indicates a 4 to 6 months average overall survival rate [3].

All available treatments for MPE are palliative, as there is no cure. The standard treatments for MPE continue to be pleurodesis and indwelling pleural catheters, both of which have recently been demonstrated to be equally successful [4].

If the pleura seem aberrant upon visual observation, pleurodesis using thoracoscopy may be performed, providing both diagnostic and therapeutic treatments in a single sitting [5].

When it comes to causing pleurodesis, the oral forms of doxycycline are just as accessible, affordable, and effective as the parenteral forms [6].

Meanwhile tranexamic acid is an effective, safe, cheap and available sclerosing agent as a chemical agent for pleurodesis [7].

The aim of the current study was to compare thoracoscopic pleurodesis with tranexamic acid and doxycycline powder as palliative preventative therapies for recurring MPE in terms of effectiveness, safety, and prognosis.

PATIENTS AND METHODS

A randomized controlled clinical trial was conducted at Al-Hussein University Hospital, Sayed Galal University Hospital, and Kafr El-Sheikh Chest Hospital between August 2017 and August 2019.

The study enrolled 100 patients known to have MPE either primary or secondary and diagnosed by pleural fluid cytology, via pleural biopsy taken through Abram's needle or medical thoracoscopy. Patients were divided into 2 groups; Group (I) had 50 patients with thoracoscopic pleurodesis of tranexamic acid, while Group (II) had 50 patients with thoracoscopic pleurodesis of doxycycline powder.

We excluded patients without MPE, encysted, multiloculated malignant pleural effusion or those with extensive pleural adhesions, central obstruction causing total lung collapse trapped in the lung, uncorrectable bleeding tendency disorder, previous failed trial of pleurodesis, inability to lie in the lateral decubitus position, known subjective hypersensitivity to constituents, respiratory insufficiency requiring ventilatory support, very poor general condition, or those with uncontrolled cardiac disease.

All patients were subjected to history taking, clinical assessment, serum laboratory investigation (Complete Blood Count, Liver functions, kidney functions, and INR), pleural fluid laboratory investigations (total proteins, LDH, Differential cell count, cytology for malignant cells, PH, Glucose level, culture and sensitivity, and Adenosine Deaminase

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(ADA)), chest radiograph, chest computed tomography (CT), and thoracoscopic pleurodesis.

Thoracoscopic pleurodesis: The damaged hemithorax was raised while the patient was positioned in the lateral decubitus position. Throughout the surgery, opiates were intravenously administered to produce drowsiness and analgesia. We created a 1.5–2 cm incision in the skin, just above the superior rib. The parietal pleura was accessible thanks to blunt dissection. A 10 mm trocar was placed after needle aspiration confirmation of fluid in the pleural area. The pleural space was entered using the thoracoscope. Under direct observation, all remaining pleural fluid was aspirated, and the whole pleural surface was examined.

We injected 0.5 ml atropine sulfate intramuscular intramuscularly 30 minutes before the procedure. One gm of doxycycline packed into sterile sachets ready to be used when needed. On other hand tranexamic acid solution two gm present in four ampules (each ampule 500mg)

To ensure complete coverage of the pleural cavity by powder or liquid (insufflation), the thoracoscope was maneuvered and directed to all areas of the cavity through the working channel of the thoracoscope. A small bottle containing the powder or liquid (each separated) was connected to a pneumatic atomizer.

A 28 F or 32 F chest tube was introduced after pleurodesis to aid in lung re-expansion. The chest tube was left in place until the fluid outflow reached 50 ml to 100 ml per day, at which point it was withdrawn.

During the period following thoracoscopic pleurodesis the patient was followed for any complications of the maneuver e.g. bleeding, subcutaneous emphysema, etc., or any side effects of the sclerosing agent used for pleurodesis e.g. fever, pain, ARDS and etc.

The patients were discharged and followed up for 3 months by chest radiograph and chest US to evaluate success of pleurodesis.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board [IRB] of the Faculty of Medicine, Al-Azhar University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

The software used for it was SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were used for quantitative variables in descriptive statistics, whereas the number and percentage were employed for qualitative variables. Chi-square test was used in analytical statistics to evaluate the variances in frequency of qualitative variables. Independent samples t-test was used to evaluate any variations in the means of the quantitative variables between the two groups. Assuming a significant level of $P<0.05$ and a very significant level of $p< 0.001$, the statistical procedures were validated.

RESULTS

There was a statistically non-significant difference between both groups regarding marital status, residence, occupation and smoking habits ($P>0.05$) (**Table 1**).

Table (1): Sociodemographic characteristics of both groups.

Variables		Tranexamic acid group n=50 (%)	Doxycycline group n=50 (%)	Total n=100 (%)	P-value
Age (years)	Mean ± SD Min – Max	56.48 ± 10.63 40 – 77	58.28 ± 7.96 42 – 75	57.38 ± 9.33 40 – 77	0.335
Sex	Male	26 (52)	30 (60)	56 (56)	0.546
	Female	24 (48)	20 (40)	44 (44)	
Marital status	Married	50 (100)	48 (96)	98 (98)	0.495
	Widow	0 (0.0)	2 (4)	2 (2)	
Residence	Greater Cairo	39 (78)	30 (60)	69 (69)	0.083
	Other Governorates[1]	11 (22)	20 (40)	31 (31)	
Occupation	Farmer	6 (12)	6 (12)	12 (12)	0.086
	Employee	2 (4)	6 (12)	8 (8)	
	Free work	12 (24)	14 (28)	26 (26)	
	Housewife	30 (60)	20 (40)	50 (50)	
	No work	0 (0.0)	4 (8)	4 (4)	
Smoking habits	Smoker	6 (12)	5 (10)	11 (11)	0.928
	Ex-smoker[2]	8 (16)	9 (18)	17 (17)	
	Non-smoker	36 (72)	36 (72)	72 (72)	

[1]: Include Dakahlia, Bani sewif, Gizza and Kafr Elsheikh. [2]: Range from 2 – 8 years.

Regarding clinical findings, our study showed that dyspnea grade III was insignificantly higher in Group I (P=0.069), cough was insignificantly higher in Group II (P=0.088), and the right sided pleural effusion was insignificantly higher in Group II (P=0.097). There was a statistically non-significant difference between both groups regarding chest pain, expectoration and toxic manifestations (P values 0.795, 0.521 and 0.810, respectively) (**Table 2**).

Table (2): Clinical findings of both groups before pleurodesis.

Variables		Tranexamic acid group n=50 (%)	Doxycycline group n=50 (%)	Total n=100 (%)	P-value
Dyspnea grade	Grade I	0 (0.0)	2 (4.0)	2 (2.0)	0.069
	Grade II	20 (40.0)	28 (56.0)	48 (48.0)	
	Grade III	30 (60.0)	20 (40.0)	50 (50.0)	
Cough	Yes	29 (58.0)	38 (76.0)	67 (67.0)	0.088
	No	21 (42.0)	12 (24.0)	33 (33.0)	
Chest pain	Yes	42 (84.0)	40 (80.0)	82 (82.0)	0.795
	No	8 (16.0)	10 (20.0)	18 (18.0)	
Expectoration	Yes	14 (28.0)	18 (36.0)	32 (32.0)	0.521
	No	36 (72.0)	32 (64.0)	68 (68.0)	
Toxic manifestations	Yes	40 (80.0)	38 (76.0)	78 (78.0)	0.810
	No	10 (20.0)	12 (24.0)	22 (22.0)	
Side of pleural effusion	Rt side	27 (54.0)	36 (72.0)	63 (63.0)	0.097
	Lt side	23 (46.0)	14 (28.0)	37 (37.0)	

As regarding Light's criteria and lymphocytes % in pleural fluid between both groups there was a non-significant difference between the two groups. lactate dehydrogenase (LDH) had insignificantly higher mean in Group I than in Group II (**Table 3**).

Table (3): The mean values of parameters of Light's criteria and lymphocytes (%) in pleural fluid of both groups.

Variables		Tranexamic acid group n=50 (%)	Doxycycline group n=50 (%)	Total n=100 (%)	P-value
Total proteins (g/dl)	Mean ± SD	4.74 ± 0.72	4.62 ± 0.6	4.68 ± 0.66	0.367
LDH (units/L)	Mean ± SD	960.84 ± 238.51	685.92 ± 170.11	818.38 ± 202.13	0.064
Lymphocyte (%)	Mean ± SD	76.52 ± 10.88	78.24 ± 8.77	77.38 ± 9.82	0.381

Our study showed that diffuse epithelial mesothelioma was higher in Group I than Group II, with no significant difference (**Table 4**). The mortality in tranexamic acid group was 12% during follow up period while in doxycycline group was 16 % with a statistically non-significant difference between both groups (P=0.774).

Table (4): Type of malignancy in the 2 studied groups.

Type of malignancy (biopsy results)	Tranexamic acid group n=50 (%)	Doxycycline group n=50 (%)	P-value
Diffuse epithelial mesothelioma	40 (80)	34 (68)	0.082
Adenocarcinoma	7 (14)	4 (8)	
Metastatic adenocarcinoma	2 (4)	8 (16)	
Positive malignant cell	1 (2)	4 (8)	

During the 1st month, 4 cases of the Doxycycline group were died out of 50 and among the remaining 46 cases, 3 patients (6.5%) developed effusion while in the Tranexamic acid group, no effusion detected with no significant difference between both groups (P=0.106). During the 2nd month, 6 cases of the Tranexamic acid group were died out of 50 and among the remaining 44 cases, 2 patients (4.5%) developed effusion while in the Doxycycline group, 2 cases were also died and among the remaining 43 cases, a total of 6 patients (13.6%) developed effusion with no significant difference between both groups (p=0.266). During the 3rd month, 2 cases of the Doxycycline group were also developing effusion and among the remaining 39 cases, a total of 8 patients (19%) developed effusion compared to no case in Tranexamic acid group with statistically significant difference (P=0.047) (**Table 5**).

Table (5): Imaging Chest XR follow up for the studied patients 1, 2- and 3-months post pleurodesis

Variables		Tranexamic acid group n = 50 (%)	Doxycycline group n = 50 (%)	P-value
Chest XR (1st month)	Effusion	0 (0.0)	3 (6.5)	0.106
	No effusion	50 (100.0)	43 (93.5)	
Total after 1 month follow up		**50/50 (100.0)**	**43/50 (92.0) [1]**	
Chest XR (2nd month)	Effusion	2 (4.5)	2die	0.266
	No effusion	42 (95.5)	41	
Total after 2 months follow up		**42/50 (88.0) [2]**	**41/50 (88.0) [3]**	
Chest XR (3rd month)	Effusion	0	2effsion	0.047*
	No effusion	42 (95.5)	39 (81.0)	
Total after 3 months follow up		**42/50 (88.0)**	**39/50 (84.0) [4]**	

[1]: Four cases died after 3 weeks. **[2]**: Four cases died after 6 weeks and two cases died after 8 weeks. **[3]**: Two cases died after 5 weeks. **[4]**: Two cases died after 10 weeks. *: Significant.

We evaluated all patients by Chest US at 1st, 2nd and 3rd months post pleurodesis. During the 1st month, 4 cases of the Doxycycline group were died out of 50 and among the remaining 46 cases, 3 patients (6.5%) developed effusion (moderate effusion) while in the Tranexamic acid group no effusion with no significant difference between both groups (P=0.106). During the 2nd month, 6 cases of the Tranexamic acid group were died out of 50 and among the remaining 44 cases, 2 patients (4.5%) developed moderate effusion while in the Doxycycline group, 2 cases were also died and among the remaining 43 cases, a total of 6 patients (13.6%) developed moderate effusion with no significant difference between both groups (P=0.266). During the 3rd month, 2 cases of the Doxycycline group were also developing moderate effusion and among the remaining 39 cases, a total of 8 patients (19%) developed moderate effusion compared to no cases in the Tranexamic acid group with statistically significant difference (P=0.047) (**Table** 6).

Table (6): Imaging Chest US follow up for the studied patients 1, 2- and 3-months post pleurodesis.

Variables		Tranexamic acid group n = 50 (%)	Doxycycline group n = 50 (%)	P-value
Chest US (1st month)	Effusion	0 (0.0)	3 (6.5)	0.106
	No effusion	50 (100.0)	43 (93.5)	
Total after 1 month follow up		**50/50 (100.0)**	**43/50 (92.0) [1]**	
Chest US (2nd month)	Effusion	2 (4.5)	2	0.266
	No effusion	42 (95.5)	41	
Total after 2 months follow up		**44/50 (88.0) [2]**	**41/50 (88.0) [3]**	
Chest US (3rd month)	Effusion	2 (4.5)	2	0.047*
	No effusion	42 (95.5)	39 (81.0)	
Total after 3 months follow up		**42/50 (88.0)**	**39/50 (84.0) [4]**	

[1]: Four cases died after 3 weeks. **[2]**: Four cases died after 6 weeks and two cases died after 8 weeks. **[3]**: Two cases died after 5 weeks. **[4]**: Two cases died after 10 weeks. *: Significant.

Success of pleurodesis was higher in the Tranexamic acid group (95.5%) compared to the Doxycycline group (81%) with statistically significant difference (P=0.047) (**Figure 1**).

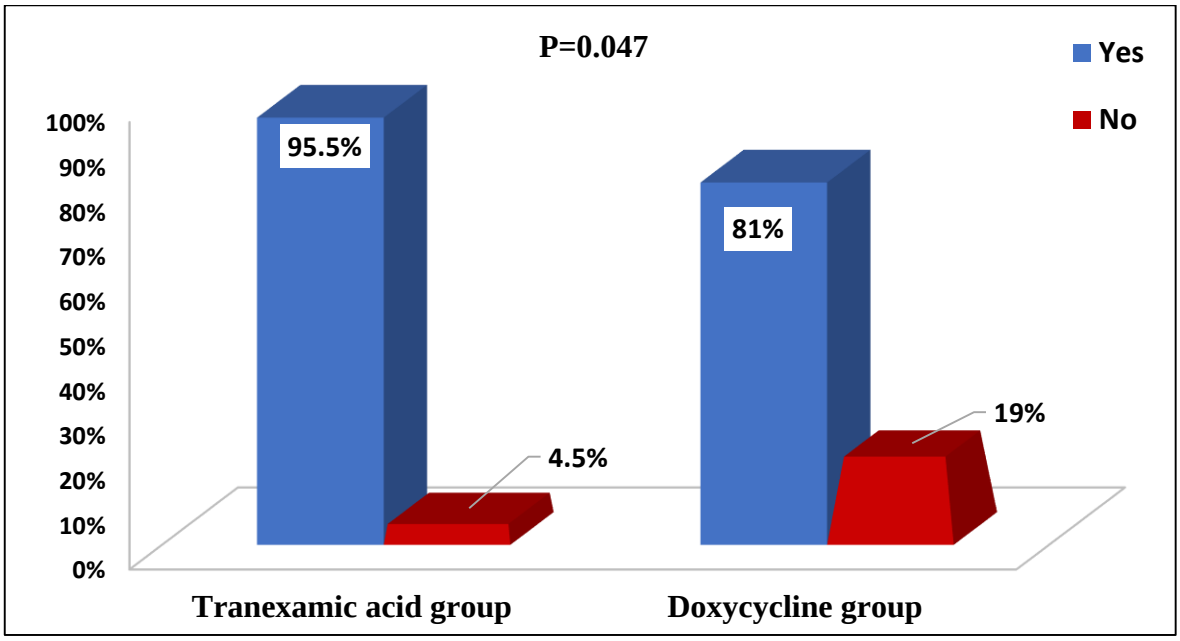

Figure (1): Success of pleurodesis in both groups.

DISCUSSION

With an estimated yearly frequency of 150,000 cases, MPE are one of the main causes of recurrent pleural effusions globally [8].

It is well acknowledged that pleurodesis may effectively treat recurrent MPE. On the optimum approach to accomplish pleurodesis, however, there is no established agreement. Wide disparities in the usage of sclerosing agents and pleurodesis techniques were found in the results of a worldwide study of pulmonologists [9].

Our study showed that a statistically non-significant difference between both groups regarding symptoms as dyspnea, cough, chest pain, expectoration, toxic manifestation and side of pleural effusion. This was in agreement with **Mohsen *et al.*** [10] statistically non-significant difference regarding Clinical findings specially dyspnea. Also, **Mohammed *et al.*** [11] study showed non-significant difference between both groups regarding Side of pleural effusion.

Our study showed that there no chest pain developed during and after pleurodesis in group I patients while all patients in group II developed chest pain during and after pleurodesis. This study is correlated with the study of **Song *et al.*** [12] who reported that the patients with the doxycycline pleurodesis complained of severe chest pain after pleurodesis

We found that malignancy Types in Group I was 80% diffuse epithelial mesothelioma, 14% adenocarcinoma, 4% metastatic adenocarcinoma and 2% positive malignant cell, while Group II contained 68 % diffuse epithelial mesothelioma, 8 % adenocarcinoma, 16 % metastatic adenocarcinoma and 8% positive malignant cell. These results agreement with **Kolschmann *et al.*** [13] and **Das *et al.*** [14] who found bronchogenic carcinoma, breast carcinoma and malignant mesothelioma to be the leading primary sources of malignant pleural effusion while mesothelioma is the least, this deviation may be due to the large number of patients in the current study inhabiting Shobra El-Kheima, where malignant mesothelioma is not a rare tumor due to previous heavy asbestos exposure.

Our study showed the mortality in Group I was 12% during follow up period while in Group II was 16 % with a statistically non-significant difference between both groups (P=1.0). This was in agreement with **Barbetakis *et al.*** [15] who study show mortality may occur during follow up after pleurodesis. However, our results were aganist **Mohsen *et al.*** [10] who do not get any mortality among the patients of both studied groups.

Our study showed that the imaging follow up for the studied patient's 1st, 2nd and 3rd months post pleurodesis show difference between Chest x ray and Chest ultrasound for detection of the amount of pleural effusion. This was in agreement with **Kalokairinou-Motogna *et al.*** [16] show ultrasound is highly sensitive for detection the effusion.

Our study show success of pleurodesis was higher in tranexamic acid group (90.5%) compared to doxycycline group (72%) with statistically significant difference. This was in agreement with **Mohammed *et al.*** [17] who found good outcome and the response to tranexamic acid pleurodesis. Also, **Abd Elzaher and El Dib** [18], found that tranexamic acid is a safe, cheap, and effective agent for pleurodesis and higher success rate.

CONCLUSION

Medical thoracoscopy is safe, easy and efficient way to diagnose the malignant pleural effusion as well as performing pleurodesis especially when it is done by

a well experienced skillful hand. Tranexamic acid has a great benefit in pleurodesis with no chest pain during and after pleurodesis and has a higher success rate than doxycycline for pleurodesis.

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