Egyptian Journal of Chest Diseases and Tuberculosis (2015) **64**, 587–591

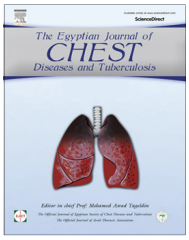
HOSTED BY

ELSEVIER

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

Efficacy of tranexamic acid as pleurodesis agent in malignant pleural effusion

Eman A. Mohammed, Sherif A. Eisa, Nabil A. Abdelghaffar Hibah *

Chest Department, Faculty of Medicine, Benha University, Egypt

Received 5 January 2015; accepted 15 February 2015
Available online 21 March 2015

KEYWORDS

Tranexamic acid;
Pleurodesis;
Malignant;
Effusion

Abstract *Design:* A prospective case series.

Aim: On a search for an effective, safe, cheap, and available sclerosing agent, the present study aimed to evaluate the effectiveness and the safety of tranexamic acid as a chemical agent for pleurodesis in malignant pleural effusion (MPE).

Methods: Tube thoracostomy was done for drainage of pleural fluid. Once the tube in the pleural space drains 150 ml per day or less with fully expanded lung, infusion of pleurodesis solution containing 2000 mg of tranexamic acid [four ampoules of tranexamic acid each is 5 ml (100 mg/ml), mixed with 50 ml of normal saline] was done through the intercostal tube. The tube was then clamped immediately and left in the pleural cavity for 2 h. Follow up chest radiographs were done every 24 h till removal of the tube which was done when daily drainage is 100 ml or less. Chest X ray (CXR) was done after three months to judge success (no fluid re-accumulation). The results were statistically analyzed and tabulated.

Results: Sixteen patients with MPE were included in this study, 9 (56%) males and 7 (44%) females with age ranging from 45 to 70 with mean age ± SD = 57.5 ± 8.3 years. The follow up after 3 months showed a complete response rate (no fluid re-accumulation on CXR) of 75% (12 \ 16), a partial response rate (asymptomatic fluid re-accumulation on CXR) of 12.5% (2 \ 16) and a no response rate (symptomatic fluid re-accumulation on CXR that required pleural drainage) of 12.5% (2 \ 16).

Abbreviations: MPE, malignant pleural effusion; CXR, chest X ray.

* Corresponding author at: Benha University Hospitals, Chest Department, Benha City 13512, Egypt. Tel./fax: +20 013 3227518, mobile: +20 1016940428.
E-mail address: nabil.hibah@yahoo.com (N.A. Abdelghaffar Hibah).

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.
This work was primarily carried out in: Chest Department, Benha University Hospital, Benha, Egypt.

http://dx.doi.org/10.1016/j.ejcdt.2015.02.011

Conclusion: Tranexamic acid was found to be an effective, safe, cheap, and available sclerosing agent for pleurodesis in recurrent malignant pleural effusion.

Introduction and aim of the work

Pleurodesis is a palliative therapy for symptomatic, recurrent malignant pleural effusions (MPE). The success of pleurodesis depends on the tumor burden, pleural fluid pH, and the efficacy of the selected sclerosing agent [1].

On a search for an effective, safe, cheap, and available sclerosing agent, the present study aimed to evaluate the effectiveness and the safety of tranexamic acid as a chemical agent for pleurodesis.

Methods

This study was a prospective case series, conducted on twenty patients with recurrent pleural effusion admitted at Chest Department, Benha University (Benha city, Egypt) from February 2011 to February 2012.

Patients with recurrent pleural effusion and completely expanded lung were included in this work. Patients with unsuccessful lung re-expansion after tube thoracostomy, Bleeding tendency or terminal disease were excluded.

All patients were subjected to full history taking with general and local examination, chest radiograph (postero-anterior and lateral views), chest C.T scan (was done to detect pleural thickening, loculations or underlying lesion as masses), pelvi-abdominal sonography (to detect abdominal causes of effusion or associated ascites), laboratory investigations (including liver function tests, kidney function tests and coagulation profile), pleural biopsy (with Abram's needle or thoracoscopic pleural biopsy for histopathological examination).

Tube thoracostomy was done for drainage of pleural fluid. Once the tube in the pleural space drains 150 ml per day or less with fully expanded lung which is confirmed on chest X ray [2], infusion of pleurodesis solution containing 2000 mg of tranexamic acid [four ampoules of tranexamic acid each is 5 ml)100 mg/ml), mixed with 50 ml of normal saline] was done through the intercostal tube. The tube was then clamped immediately and left in the pleural cavity for 2 h during which the patient was turned to the supine, prone, right and left lateral decubitus and sitting position so that pleurodesis solution came in contact with all pleural surfaces. The patient was kept in each position for 30 min. After 2 h, the chest tube was unclamped. Follow up chest radiographs were done every 24 h till removal of the tube which was done when daily drainage is 100 ml or less.

The patients were discharged and followed up after three months using plain CXR to judge success of the procedure (no fluid re-accumulation):

1. Complete response (success) means no radiographic evidence of fluid re-accumulation was noted on follow up.
2. Partial response means re-accumulation of fluid that did not produce symptoms and did not require repeat pleural drainage of any sort on follow up.
3. No response means fluid re-accumulation that produced symptoms and required pleural drainage on follow up.

The results were statistically analyzed and tabulated using SPSS program statistical program (version 14, SPSS Inc., USA: Chicago, IL).

Results

Sixteen patients with malignant pleural effusion were included in this study. There were 12 (60%) males and 8 (40%) females. Their age ranged from 45 to 70 with mean age ± SD = 57.5 ± 8.3 years (Tables 1 and 2).

As regards the side of effusion 9 (56%) cases were left sided pleural effusion and 7 (44%) cases were right sided. The main presenting symptom was dyspnea in 8 (50%) cases and chest pain in 8 (50%) cases (all 8 cases had Mesothelioma).

As regards methods of diagnosis, 8 \ 16 (50%) were diagnosed by thoracoscopic pleural biopsy, 4 \ 16 (25%) were diagnosed by closed pleural biopsy (using Abram's needle) and 4 \ 16 (25%) were diagnosed by positive cytological examination for malignant cells in pleural fluid. The histopathological types of these malignant effusions were Mesothelioma in 8 \ 16 (50%) and Metastatic Adenocarcinoma in 8 \ 16 (50%) cases (Tables 1 and 2).

Regarding the outcome and the response to tranexamic acid pleurodesis 12 (75%) showed complete response, 2 (12.5%) showed partial response and other 2 (12.5%) cases showed no response (Tables 1 and 2). The time for removal of the chest tube after injecting tranexamic acid ranged from 3 to 7 days (mean ± SD = 4.6 ± 1.25 days).

The failed pleurodesis (no response) in the 2 cases who had malignant mesothelioma was caused by thickening of the pleura seen by Thoracoscopy (Fig. 1 shows one of them) and failure of the lung to expand.

As regards complications, no significant complications were detected after tranexamic acid pleurodesis.

The cost of tranexamic acid in Egypt is about 21 LE (less than 3 US dollars) per pack of six 5 ml ampoules (100 mg per 1 ml).

Discussion

On a search for an effective, safe, cheap, and available sclerosing agent with least side effects, the present study aimed to evaluate the effectiveness and the safety of tranexamic acid as a chemical agent for pleurodesis.

Sixteen patients with MPE were included in this study, 9 (56%) males and 7 (44%) females. Their age ranged from 45

Table 1 Data of cases studied regarding age, sex, clinical findings and outcome after tranexamic acid pleurodesis.

Case no	Age**	Sex	Main presenting symptom	Pathology	Diagnosis method	Outcome
1	64	Male	Chest pain	Mesothelioma	Pleural biopsy	Partial response
2	57	Male	Dyspnea	Adenocarcinoma*	Pleural biopsy	Complete response
3	68	Female	Dyspnea	Adenocarcinoma*	Cytology	Complete response
4	53	Female	Chest pain	Mesothelioma	Pleural biopsy	Complete response
5	59	Female	Dyspnea	Adenocarcinoma*	Pleural biopsy	Complete response
6	63	Male	Dyspnea	Adenocarcinoma*	Pleural biopsy	Complete response
7	46	Male	Dyspnea	Adenocarcinoma*	Cytology	Complete response
8	57	Female	Chest pain	Mesothelioma	Pleural biopsy	Complete response
9	48	Male	Dyspnea	Adenocarcinoma*	Pleural biopsy	Complete response
10	68	Female	Chest pain	Mesothelioma	Pleural biopsy	Complete response
11	49	Male	Dyspnea	Adenocarcinoma*	Cytology	Complete response
12	63	Female	Chest pain	Mesothelioma	Pleural biopsy	Complete response
13	49	Male	Chest pain	Mesothelioma	Pleural biopsy	No response
14	45	Female	Dyspnea	Adenocarcinoma*	Cytology	Complete response
15	70	Male	Chest pain	Mesothelioma	Pleural biopsy	Partial response
16	62	Male	Chest pain	Mesothelioma	Pleural biopsy	Partial response

* Metastatic Adenocarcinoma.
** Mean age ± SD = 57.5 ± 8.3 years.

Table 2 Data of cases studied regarding age, sex, clinical findings and outcome after tranexamic acid pleurodesis in number and percent.

	No. of patients	%
Sex		
Male	9	56
Female	7	44
Effusion side		
Left	9	56
Right	7	44
Main presenting symptom		
Dyspnea	8	50
Chest pain	8	50
Method of diagnosis		
Thoracoscopic biopsy	8	50
Closed pleural biopsy	4	25
Cytology	4	25
Pathology of malignant effusions		
Mesothelioma	8	50
Metastatic Adenocarcinoma	8	50
Response to tranexamic acid pleurodesis		
Complete response	12	75
Partial response	2	12.5
No response	2	12.5

to 70 with mean age ± SD = 57.5 ± 8.3 years (Tables 1 and 2).

As regards the side of effusion 9 (56%) cases were left sided pleural effusion and 7 (44%) cases were right. In a study by Shalabi [3], 8 (40%) cases were left sided, 11 (55%) cases were right sided pleural effusion and one case (5%) presented with bilateral pleural effusion, massive on the left and mild on the right side. In EL-Bouhi et al. [4] study 4 (20%) cases were left sided pleural effusion and 16 (80%) cases were right side.

The main presenting symptom in this study was dyspnea in the 8 Adenocarcinoma cases (50%) and chest pain in the 8 Mesothelioma cases. Shalabi [3] reported that 15 (75%) cases presented with dyspnea and 5 (25%) cases presented with chest pain (all cases with chest pain had Mesothelioma). Antman [5] stated that the main presenting symptom in malignant mesothelioma is chest pain in 60% to 70% and dyspnea and cough in 25% and 20% respectively.

Regarding the method by which diagnosis was made in this study, thoracoscopic pleural biopsy made the diagnosis in 8 \ 16 (50%) cases, closed pleural biopsy (using Abram's needle) in 4 \ 16 (25%) cases and positive cytological examination for malignant cells in other 4 \ 16 (25%) cases. The histopathological types of the malignant effusions were Mesothelioma in 8 \ 16 (50%) and Metastatic Adenocarcinoma in 8 \ 16 (50%) cases. In another study [3] the histopathological types of these malignant effusions were Mesothelioma in 3 \ 15 (20%) and Adenocarcinoma in 12 \ 15 (80%) cases. In a study by EL-Bouhi et al. [4] 12 (60%) patients had malignant pleural effusion, 4 (20%) had hepatic hydrothorax and other 4 (20%) cases had renal failure.

All patients were subjected to injection of pleurodesis solution of 50 ml of normal saline with four ampoules of tranexamic acid each is 5 ml)100 mg/ml(infused through intercostal tube. This coincided with the study of Badawy and Eisa [6]

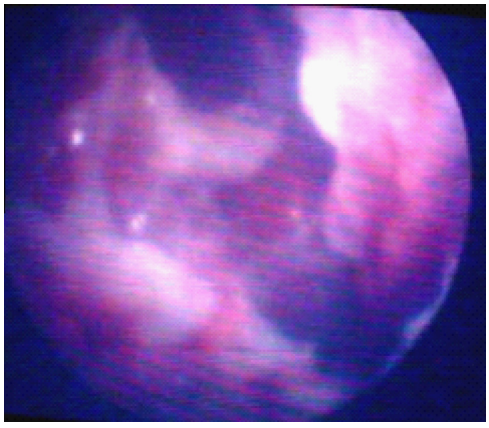


Figure 1 Marked pleural thickening and infiltration in a case of malignant pleural mesothelioma.

in which he used 50 ml of normal saline solution with four ampoules of tranexamic acid each is 5 ml)100 mg/ml(was infused through intercostal tube. This differs from the study of Shalabi [3] in which Pleurodesis was done after thoracocentesis (without intercostal tube placement) by an injection of 25 ml of tranexamic acid (containing 2500 mg), and from EL-Bouhi et al.'s [4] study who used a high dose of tranexamic acid which is 10 ampoules of tranexamic acid each 5 ml)100 mg/ml) infused through intercostal tube.

Regarding outcome and the response to tranexamic acid pleurodesis in this study, 12 (75%) showed complete response, 2 (12.5%) showed partial response and other 2 (12.5%) cases showed no response. The time for removal of the chest tube after injecting tranexamic acid ranged from 3 to 7 days (mean ± SD4.5 ± 1.25 days). The failed pleurodesis in the 2 cases who had malignant mesothelioma resulted from thickening of the pleura seen by Thoracoscopy (Fig. 1 shows one of the cases) and failure of the lung to expand.

So the complete success rate in this study, using tranexamic acid pleurodesis in malignant effusions was 75% (12 out of 16 cases) which agrees with that reported by Badawy and Eisa [6] (73.5% success rate), but lower than the results reported by Shalabi [3] (success rate of 84.2%) and EL-Bouhi et al. [4] (success rate 90%). The much higher success rate in El-Bouhi et al. [4] may be due to a higher dose of tranexamic acid used (5000 mg) and the exclusion of partial success cases in this study (2 cases = extra 12.5%).

The results in this study were slightly higher than the results of other studies that used other chemical agents for pleurodesis, for example the results obtained by Zimmer et al [7] using tetracycline for pleurodesis with a success rate of 65%, and are higher than the results achieved by Martínez et al [8] using bleomycin for pleurodesis with a success rate of 60–80%.

In a report by Essam et al. [9] comparing bleomycin or tranexamic acid alone versus a combination of both concluded that the combination of bleomycin (1 Unit/kg, with maximum of 40 Unit) and tranexamic acid (30 mg/kg, with maximum of 2 gm) for pleurodesis was more efficient (65%) than each alone (35% and 27%, respectively).

Ramadan et al. [10] studied different pleurodesis agents in malignant pleural effusion and found that efficacy was 70% for bleomycin, 80% for doxycycline and 80% for povidone iodine, while 5-fluorouracil had the lowest success rate (50%).

Mohammed and Hassan [11] studied the oral form of doxycycline and reported that 72.7% (16 out of 22 patients with malignant pleural effusion) had successful pleurodesis and Chest tube duration averaged 4.2 ± 2.6 days with complications included chest pain in 10 patients (45.5%), fever in 2 (9.1%) patients, and pain and fever in 5 patients (22.7%).

Shouman et al. [12] studied Chemical pleurodesis for malignant pleural effusion in 75 patients and reported that using Tetracycline, talc slurry, iodopovidone and bleomycin, resulted in an insignificantly different success rates of 80%, 80%, 66.6%.73.3%, at 30 days and, 66.6%, 73.3%, 60%, 66.6%, at 60 days respectively. Chest tubes were removed after an average of 7.2 ± 1.4 days for tetracycline, 7 ± 0.8 days for talc slurry, 7.6 ± 0.9 days for iodopovidone and 6.4 ± 1.5 days for bleomycin which did not differ significantly. Chest pain was more common in the tetracycline group, dyspnea was more common in the talc group, and fever was more common in the iodopovidone group.

In a report [13] that reviewed the literature for pleurodesis in the treatment of malignant pleural effusions between 1966 and 1992 concluded that the total success rate was 64%. [Corynebacterium parvum was 76%, Doxycycline was 72%, Tetracycline was 67%, Bleomycin was 54% and Talc was 93% (the highest).]

As regards complications, no significant complications were detected after tranexamic acid pleurodesis. Others [3,4,6] found no complications after using tranexamic acid for pleurodesis.

The complications which were noted with different sclerosant agents are chest pain, fever and cough [14]. Tetracycline was the most common agent used in the past, but it is no longer available now with an average success rate of 65% and reported complication as chest pain, fever and cough [7].

Werebe et al. [15] reported that talc is the most commonly used substance for pleurodesis which is highly effective and widely available with an average success rate of 90% but may cause systemic embolization in animal and ARDS in 9% of patients after talc pleurodesis.

Martínez et al. [8] reported that bleomycin is the most widely administered antineoplastic agent with a success rate of 60–80%, but with complications including chest pain, fever, and nausea and is costly.

Fry et al. [16] reported that non chemical pleurodesis, thoracostomy with pleurectomy and de-cortication are effective but these operations have a mortality of 10% and a high morbidity as prolonged air leaks.

Spiegler et al. [17] reported complete response to pleurodesis in 48%, a partial response in 31%, and 21% did not respond to pleurodesis. Chemical pleurodesis was performed as an outpatient procedure (using talc slurry or bleomycin). The follow up was done after 4 weeks of the procedure and judging success using same criteria we used in our study.

Conclusion

Tranexamic acid was found to be an effective, safe, cheap, and available sclerosing agent for pleurodesis in recurrent malignant pleural effusion.

Disclosure of Financial Support

None to declare.

Conflict of interest

No conflicts of interest to be declared.

References

[1] F. Rodriguez-Panadero, A. Montes-Worboys, Mechanisms of pleurodesis, Respiration 83 (2012) 91–98.
[2] J.E. Heffner, J.S. Klein, Recent advances in the diagnosis and management of malignant pleural effusions, Mayo Clin. Proc. 83 (2) (2008) 235–250.
[3] H.M. Shalabi, Closed Pleurodesis with Tranexamic Acid, Thesis for Master Degree, Ain Shams University, 2001.
[4] M. El-Bouhi, T. El-Naggar, M. Mansour, Pleurodesis with tranexamic acid, Egypt. J. Chest Dis. Tuberculosis 49 (2000) 15–18.

[5] K.H. Antman, Natural history and epidemiology of malignant mesothelioma, Chest 103 (4 suppl.) (1993) 373S–376S.
[6] M. Badawy, K. Eisa, Pleurodesis with tranexamic acid, Thesis for Master Degree, Sohag University. Cardiothoracic Surgery Department, 2008.
[7] P.W. Zimmer, M. Hill, K. Casey, E. Harvey, D.E. Low, Prospective randomized trial of talc slurry versus bleomycin in pleurodesis for symptomatic malignant pleural effusions, Chest 112 (1997) 430–439.
[8] E. Martínez-Moragón, J. Aparicio, M.C. Rogado, J. Sanchis, F. Sanchis, V. Gil-Suay, Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin, Eur. Respir. J. 10 (1997) 2380–2383.
[9] Essam Mohamed, Elsayed Ali, Hamdy Mahmoud, Pleurodesis for malignant pleural effusions: a comparison of bleomycin or tranexamic acid alone versus a combination of both, ERJ 42 (suppl. 57) (2013) P3072.
[10] Ramadan M. Bakr, Ibrahim I. El-Mahalawy, Gehan A. Abdel-Aal, Ali A. Mabrouk, Ahmed A. Ali, Pleurodesis using different agents in malignant pleural effusion, Egypt. J. Chest Dis. Tuberculosis 61 (2012) 399–404.
[11] Khaled H. Mohamed, Osama A. Hassan, A new look at an old agent for pleurodesis, Egypt. J. Chest Dis. Tuberculosis 62 (2013) 617–620.
[12] W. Shouman, A. Elgazzar, R.M. Hussien, M. ElShaaray, R.W. Light, Chemical pleurodesis for malignant pleural effusion, Egypt. J. Chest Dis. Tuberculosis 61 (2012) 115–120.
[13] P.B. Walker-Renard, L.M. Vaughan, S.A. Sahn, Chemical pleurodesis for the treatment of malignant pleural effusions, Ann. Intern. Med. 120 (1994) 56.
[14] J.P. Janssen, G. Collier, P. Astoul, G.F. Tassi, M. Noppen, F. Rodriguez-Panadero, Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study, Lancet 369 (2007) 1535–1539.
[15] E.C. Werebe, R. Pazetti, J.R. Milanez de Campos, P.P. Fernandez, V.L. Capelozzi, F.B. Jatene, F.S. Vargas, Systemic distribution of talc after intrapleural administration in rats, Chest 115 (1999) 190–193.
[16] W.A. Fry, J.D. Khandekar, Parietal pleurectomy for malignant pleural effusion, Ann. Surg. Oncol. 2 (1995) 160–164.
[17] P.A. Spiegler, A.N. Hurewitz, M.L. Groth, Rapid pleurodesis for malignant pleural effusions, Chest 123 (6) (2003) 1895–1898.