



## ORIGINAL ARTICLE

# Comparison between Pleurodesis Effects with Bleomycin and Tetracycline on the Management of Patients suffering from malignant pleural Effusion in the Rasht Hospitals

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### ABSTRACT

Pleural effusion is developed in %17 of patients with malignancies. Malignant pleural effusions are commonly managed with tube thoracostomy drainage followed by chemical pleurodesis. Both tetracycline and bleomycin have been shown to be safe & effective for intrapleural instillation, although neither agent has definitively proved better than the other. The aim of the present study was to compare the efficacy of these two agents in terms of response rate. A prospective, randomized trial was carried out in Rasht Hospitals. Between July 2011 and January 2013, 118 patients with malignant pleural effusion were allocated to receive either intrapleural tetracycline (1.5 g) or bleomycin (1 U/kg) after drainage by tube thoracostomy. Response was evaluated at 4 and 8 weeks after pleurodesis. Demographic, clinical and fluid parameter findings were comparable in both groups. No statistically significant differences were found in terms of efficacy for two drugs used. Overall, 11 (18.64%) and 15 (25.42%) patients had a recurrence of pleural effusion during follow-up in the tetracycline and bleomycin arms, respectively. Considering the comparable efficacy of both agents used for pleurodesis and no superiority of one over the other in this trial, we suggest that economic costs and drug availability should be considered in selection of a sclerosing agent hence Tetracycline is more acceptable.

**Key words:** Bleomycin, Pleural Disease, Malignant Pleural Effusion, Pleurodesis, Tetracycline

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### INTRODUCTION

Malignant pleural effusion is accumulation of fluid in the pleural space caused by pleural invasion of pulmonary and non-pulmonary cancers. Virtually all cancers can metastasize to the pleura. Lung cancer is the most common to involve the pleura because of its proximity to the pleural surface and, its propensity to invade the pulmonary arteries and embolize to the visceral pleura. Breast cancer also frequently metastasizes to the pleura, causing approximately 25% of malignant pleural effusions [1]. 17% of cancers during progression or management cause malignant pleural effusion [2]. Common cancers that cause malignant pleural effusion in order of decreasing frequency are lung cancer, breast cancer, lymphoma, gastrointestinal cancer, ovarian cancer, and mesothelioma [3].

Pleurodesis is an accepted palliative management for patients with symptomatic or recurrent malignant pleural effusion. Pleurodesis is the most cost-effective and least morbid method for controlling a symptomatic malignant pleural effusion. Several sclerosing agents have been used [4]. Initially, tetracycline, talc, and bleomycin were considered as sclerosing agents [5], talc have proper effect but is associated with many side effects including severe pain, nausea and fever due to systemic and pulmonary inflammation [6,7]. In addition, standardized products of talc are not available in Iran and usage of impurity powders is associated with many problems.

In two past decades, tetracycline hydrochloride was most commonly used because of effectiveness, durable effect and low complication rate. Although widespread studies did not performed, bleomycin is alternative and appropriate agent. Intracavitary instillation of bleomycin cause lower pain but is more expensive than tetracycline. Bleomycin is not used in febrile and leukopenic patients [8]. Also betadin have been used to perform pleurodesis [9].

About performing of pleurodesis for treatment of malignant pleural effusion there is global consensus but regional extensive studies are required about the quality of the above action and the method of implementation and also the type of material to perform pleurodesis and complication of this actions [10]. The aim of this study was to compare pleurodesis with tetracycline and blomycin in terms of response rate of patients to them.

## MATERIALS AND METHODS

This study was a prospective, randomized trial. Between July 2011 and January 2013, 118 patients with malignant pleural effusion were studied in the rasht hospital. desired volume was assigned by using the method of Random block in patients that referred to the rasht hospitals. Patients divided to two groups to receive either intrapleural tetracycline (1.5 g) or bleomycin (1 U/kg) after drainage by tube thoracostomy. Inclusion criteria of our study included having confirmed malignant pleural effusion. Patients were required to have a cytologically positive pleural effusion or a positive pleural biopsy in the presence of an exudative effusion, lung reexpansion following tube thoracostomy. Exclusion criteria of our study included having sensitivity to tetracycline or bleomycin; contraindication of using them including lactation and pregnancy; and unexpandable lung. Pleural space was evacuated through a thoracostomy tube. Reexpansion of the affected lung was confirmed with CXR. This CXR was to serve as the baseline for follow-up evaluation of recurrence. patients with malignant pleural effusions were randomly assigned to receive either bleomycin (1unit/kg in 100ml normal saline) or tetracycline (1.5 gram in 100ml normal saline). Following instillation of the assigned agent, the tube was clamped for 4 hours and then the tube was connected to chest bottle. When the chest tube drainage had slowed to less than 100 ml in a 24-hour period, the tube was removed and patient was discharged. We recommended to patients that if warning signs including dyspnea and chest pain, were occurred, patients referred to researcher physician. After discharge, 2 visits were performed for all patients (fourth week, eighth week). In fourth week, physical examination of patients were performed and CXR was performed If the patient was symptomatic. In eighth week, CXR and physical examination of patients were performed. Patients were classified as having recurrences if they had pleural fluid accumulation greater than baseline within follow-up period. Data was analyzed by SPSS19 software. The two groups were compared with respect to demographic characteristics, recurrence rate and length of hospital stay, using the t-test and chi square test for independent samples and Mann-Whitney U. Name and personal details will remain confidential subjects and If patients did not consent, were excluded. All patients after explaining the project and informed consent were enrolled.

## RESULTS

In this study, 118 patients were randomized to bleomycin-treated (59 patients) or tetracycline-treated group (59 patients). In the tetracycline group, 44 patients were male and 15 patients were female; and the mean age was 58.8 years. In the bleomycin group, 36 patients were male and 23 patients were female; and the mean age was 58.53 years. The t-test and chi square test did not show significant statistical difference in terms of demographic and personal variables except gender between tetracycline-treated and bleomycin-treated groups ( $P>0.05$ ).

Primary malignancies in our patients in order of decreasing frequency were as follow: lung cancer 31.4%, breast cancer 28%, unknown origin 12.7%, gastric cancer 7.6%, colorectal cancer 5.9%, thyroid cancer 3.4%, ovarian cancer 2.5%, mesothelioma 1.7%, renal cancer 0.8% and melanoma 0.8% (Table 1). Patients symptoms were dyspnea (115 patients), chest pain (64 patients), cough (67 patients) and hemoptysis (10 patients) (Table 2). The chi square test did not show significant statistical difference in terms of symptom numbers between tetracycline-treated and bleomycin-treated groups ( $P>0.609$ ).

Laboratory examination of pleural fluid including glucose, protein, LDH and PH were normally distributed in both groups. The t-test did not show significant statistical difference in terms of mean laboratory findings of pleural fluid between tetracycline-treated and bleomycin-treated groups ( $P>0.05$ ) (table 3). In summary, our study showed that the distribution of patients in the two study groups in term of clinical finding, laboratory values of pleural fluid and age without statistically significant differences were normal.

Eleven of the 59 tetracycline-treated patients and fifteen of the 59 bleomycin-treated patients had recurrence. The chi square did not show significant statistical difference in terms of recurrence rate between the tetracycline-treated and bleomycin-treated groups ( $P=0.594$ ) (table 4).

Mean length of hospital stay for the tetracycline-treated and bleomycin-treated patients were 4.28 and 4.08 days, respectively and mean length of hospital stay after pleurodesis were 1.88 and 1.69 days, respectively. Mean hospital stay and mean hospital stay after pleurodesis did not have normal distribution in the two groups, and Mann-Whitney U did not show significant statistical difference in terms of mean length of hospital stay and mean length of hospital stay after pleurodesis between tetracycline-treated and bleomycin-treated groups ( $P=0.267$  and  $P=0.874$ , respectively ) (Table 5).

Table 1- Distribution frequency of malignancy types in our study patients		
Malignancy type	Number	Percent
Lung cancer	37	31.4
Breast cancer	33	28
Unknown origin	15	12.7
Gastric cancer	9	7.6
Colorectal cancer	7	5.9
Thyroid cancer	4	3.4
Lymphoma	4	3.4
Ovarian cancer	3	2.5
Mesothelioma	2	1.7
Sarcoma	2	1.7
Renal cancer	1	0.8
Melanoma	1	0.8
Total	118	100

Table 2- Distribution frequency of symptoms in our study patients		
Symptoms	Number	Percent
Dyspnea	115	97.4
Cough	67	56.7
Chest pain	64	54.2
Hemoptysis	10	8.4

Table 3- Comparison of mean laboratory parameters of pleural effusion in our study patient						
Laboratory parameter	Group	Number	Mean	Standard Deviation	t- level	P-value
PH	tetracycline	5	7.22	0.1	1.52	0.148
	bleomycin	12	7.32	0.13		
Glucose	tetracycline	59	116.86	40.86	0.437	0.663
	bleomycin	59	113.88	0.33		
Protein	tetracycline	59	4.66	1.06	0.35	0.727
	bleomycin	59	4.72	0.81		
LDH	tetracycline	59	845.7	551	1.48	0.14
	bleomycin	59	997.3	556		

Table 4-Frequency distribution of the overall treatment and recurrence of our study patients							
Group Treatment Conditions	Tetracycline		Bleomycin		Total		P-value
	Number	Percent	Number	percent	number	Percent	
Complete treatment	48	81.36	44	74.58	92	77.97	0.594
Recurrence	11	18.64	15	25.42	26	22.03	
Total	59	100	59	100	118	100	

Table 5-The mean hospital stay and mean hospital stay after pleurodesis in the tetracycline-treated and bleomycin-treated patients						
Variant	Group	Number	Mean	Standard deviation	Value of Z	P-value
Hospital Stay	Tetracycline	59	4.28	5.03	0.159	0.874
	Bleomycin	59	4.08	3.31		
Hospital stay after pleurodesis	Tetracycline	59	1.88	0.98	1.11	0.267
	Bleomycin	59	1.69	0.89		

## DISCUSSION

Patients with malignant pleural effusion have poor prognosis and pleurodesis is a palliative treatment to stop the accumulation of pleural effusion and improve the quality of life in the remaining life of these patients. In two past decades, tetracycline hydrochloride was most commonly used because of effectiveness, durable effect, low cost and low complication rate and bleomycin is an alternative and appropriate agent but is more expensive than tetracycline and Information on its effectiveness has not been confirmed in all cases [4].

Only four randomized prospective study was performed to compare the effects of these two sclerosing agents. In three studies, despite the low number of patients, no difference in cure rates observed [4,8,11] and In a multicenter study, bleomycin was more effective in reviewing 30 to 90 days [12]. In the present study, the effectiveness of both agents is equivalent. Although the number of complete treatment in the tetracycline-treated group was higher than bleomycin-treated patients, during the two-month follow-up in our study, none of the patients died. Recurrence cases occurred from 12 days to two months. In the Martinez study during 6 months follow-up, most recurrences occurred in the first month [4]). None of the patients showed symptoms of sensitivity to drugs and the side effects of two agents were not reported. These results are comparable and consistent with studies by Martinez and his colleagues and due to the effectiveness of both the sclerosing agent, it seems tetracycline according to less expensive than bleomycin (7 dollars versus 130 dollars) and ease of preparation in the Iranian market, is more appropriate choice for pleurodesis in patients with malignant pleural effusion.

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