Original Article

Long-term results of pleurodesis in malignant pleural effusions: Doxycycline vs Bleomycin

Rahmatollah Rafiei, Behnam Yazdani, Sayed Milad Ranjbar, Zahra Torabi, Sedigheh Asgary[1], Somayeh Najafi[2], Mahtab Keshvari[1]

Islamic Azad University, Najafabad Branch, Najafabad, Isfahan, [1]Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, [2]Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The aim of this study was to compare the response of doxycycline and bleomycin in pleurodesis of malignant pleural effusions.

Materials and Methods: The radiologic and clinical responses of doxycycline and bleomycin in pleurodesis of malignant pleural effusions were compared in this randomized clinical trial. Forty-two patients were randomized to receive either bleomycin 45 mg or doxycycline 600 mg as the sclerotherapy agent. Chest X-rays were taken before and after intervention, 10 days and 2 months later to compare the radiologic response. Dyspnea and other side effects, before and after intervention, 10 days and 2 months later were recorded and compared. Chi-square test was applied to analyze the data.

Results: The prevalence of dyspnea and its different severities, 10 days and 2 months after intervention were significantly different ($P < 0.05$) between the two groups. Analysis of pleural effusions revealed a significant difference ($P < 0.05$) between Doxycycline vs. Bleomycin 2 months after the intervention. Three months after pleurodesis, only one patient in bleomycin group needed pleural fluid drainage.

Conclusion: Pleural effusions did not change with use of doxycycline and bleomycin in short time but long-term results of doxycycline sclerotherapy was better than bleomycin sclerotherapy in malignant pleural effusions that was supported by this study. However, additional studies with larger sample size are necessary to confirm the results.

Key Words: Bleomycin, doxycycline, malignant pleural effusion, sclerotherapy

Address for correspondence:
Dr. Rahmatollah Rafiei, Islamic Azad University Najafabad Branch, Najafabad, Isfahan, Iran. E-mail: rahmatollahrafiei@yahoo.com
Received: 19.02.2013, **Accepted:** 05.05.2013

INTRODUCTION

Malignant pleural effusion is commonly exudative type diagnosed cytologically[1] and is a significant public health problem.[2,3] It deteriorates the quality of life in patients with cancer.[1,4,5] Its management depends on underlying malignancy and the extent of disease.[6] Treatment goals for these patients should focus on relief or elimination of dyspnea, restoration of normal activity and function, minimization or elimination of hospitalization, and efficient use of medical care resources.[2,3] The standard management approach begins with a diagnostic and/or therapeutic thoracentesis. If the effusion recurs, other options include repeated thoracentesis, tube thoracostomy

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.137831

How to cite this article: Rafiei R, Yazdani B, Ranjbar SM, Torabi Z, Asgary S, Najafi S, *et al*. Long-term results of pleurodesis in malignant pleural effusions: Doxycycline vs Bleomycin. Adv Biomed Res 2014;3:149.

with chemical pleurodesis, placement of an indwelling cuffed, tunneled pleural catheter with or without pleurodesis, medical thoracoscopy, or video-assisted thoracoscopic surgery with pleurodesis.[7] Some are treated with systematic chemotherapy whereas most are preterminal event and need palliative therapy to minimize discomfort and cost.[8,9] It is done through tube thoracostomy and sclerotherapy, thoracentesis, or pleural shunts. Sclerosing agent is an important factor in success of sclerotherapy. There is no universal agreement on the most effective and least harmful agent in inducing pleurodesis in malignant pleural effusion.[10] Although doxycycline has been widely used to treat malignant pleural effusions,[11-16] its long-term effects in comparison with bleomycin have been less studied. The aim of this study is to compare the therapeutic effects of two medications on malignant pleural effusions.

MATERIALS AND METHODS

This study was a randomized clinical trial to compare the radiologic and clinical responses of two different sclerotherapy agents, doxycycline and bleomycin, in pleurodesis of malignant pleural effusions. Inclusion criteria included symptomatic patients with cytologically proved malignant pleural effusions hospitalized in our hospital over a period of 22 months. Exclusion criteria included allergy to doxycycline or bleomycin, past history of sclerotherapy, systematic chemotherapy immediately prior to or in the next 2 months after sclerotherapy, and unwillingness to continue the study. The study was approved by ethics committee of the hospital. Written informed consent was signed by all patients. The technique of pleurodesis has been explained elsewhere.[16,17]

After fluid evacuation, the patient was randomized to treatment with either bleomycin 45 mg or doxycycline 600 mg. The latter was mixed with 50 ml normal saline and 10 ml of 1% lidocaine. The therapeutic sclerosing agent was injected in the pleural space through the tube. Then, it was closed to wall suction for 1 hour while the patient was seated for 1 hour. It is demonstrated that doxycycline rapidly diffuses in pleural space and there is no need to rotate the patient.[18] Thereafter, the tube was reopened to wall suction. When the drainage was less than 100 mL/day, the drainage catheter was removed. Upright chest X-rays (CXRs), posteroanterior and lateral views, were taken before and after the procedure. CXRs were repeated 10 days and 2 months later to compare the fluid levels. The radiologic response was defined by the fluid level observed in costophrenic and vertebrophrenic angles. No more accumulation of pleural fluid was determined as mild effusion. Accumulation of fluid in less than 50% of pulmonary fields was set as moderate pleural effusion, whereas fluid accumulation covering more than 50% of pulmonary fields was determined as severe pleural effusion. The amount and frequency of fluid drainage up to 3 months after the procedure were registered. The clinical response was set based on the prevalence of different severities of dyspnea before and after intervention. It was classified as no dyspnea, mild dyspnea (difficult respiration during heavy physical activities), moderate dyspnea (dyspnea during regular daily physical activities), and severe dyspnea (difficult respiration at rest). The radiologic and clinical response rates between the two groups were compared using Chi-square test. SPSS software, version 10 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. *P* values less than 0.05 were considered significant. Complications of the procedure including dyspnea, local chest pain, and fever were recorded before and after the procedure; 10 days and 2 months later. Supportive measures were applied to resolve the symptoms after sclerotherapy.[19-21]

RESULTS

Forty-two patients with malignant pleural effusion were randomized to sclerotherapy with either doxycycline or bleomycin. The mean age of patients was 68 years. Thirty patients were male. No patient expired or lost to follow-up within 3 months after sclerotherapy.

Fourteen male and seven female patients with a mean age of 66.5 years received doxycycline sclerotherapy. Ten men and no woman had past history of smoking. The minimum, maximum, and mean values of tobacco exposure were 10, 30, and 21 pack year, respectively. Eleven patients had metastatic carcinoma. Others had mesothelioma (three patients), squamous cell carcinoma (three patients), bronchogenic carcinoma (two patients), and lymphoma (two patients). Complications of doxycycline sclerotherapy included dyspnea [Table 1], local chest pain in 15 patients and fever in seven patients. The mean time of having chest pain was 2.5 days after the intervention. The mean time of appearance of fever was 11 h after the procedure.

Sixteen male and five female patients with a mean age of 69 years received bleomycin sclerotherapy. Fourteen men and no woman had past history of smoking. The minimum, maximum, and mean values of tobacco exposure were 3, 35, and 21.5 pack year; respectively. Thirteen patients had metastatic carcinoma. Others had mesothelioma (two patients), squamous cell carcinoma (one patient), bronchogenic

carcinoma (three ones), and lymphoma (two patients). Complications of bleomycin sclerotherapy included dyspnea [Table 1], local chest pain in 17 patients and fever in five patients. The mean time of having chest pain was 1 day after the intervention. The mean time of appearance of fever was 3 h after the procedure.

Prevalence of dyspnea was not significantly different between the two groups before and immediately after sclerotherapy. But, the prevalence of dyspnea and its different severities, 10 days and 2 months after intervention were significantly different between the two groups [Table 1].

Prevalence of mild, moderate, and severe pleural effusions was not significantly different between doxycycline and bleomycin sclerotherapy before and immediately after the procedure, and also 10 days later [Table 2]. But, 2 months after intervention, the difference in radiologic response rates between the two groups was significant. In other words at this time, 67% of patients in doxycycline group showed mild pleural effusion, whereas 71% of patients in bleomycin group had moderate effusion [Table 2]. Three months after sclerotherapy, nobody in doxycycline group and one patient in bleomycin group had pleural fluid drainage (P = 0.5). There was also no difference in frequency of chest pain and fever and their durations between the two groups.

Prevalence of different severities of dyspnea and pleural effusion based on underlying malignancies 2 months after sclerotherapy in the two groups are presented in Tables 3 and 4.

DISCUSSION

A malignant pleural effusion (MPE) is defined by the presence of cancer cells in the pleural space.[22] Most malignant pleural effusions in patients older than 60 years are induced by metastatic carcinoma.[4] Similarly, the mean age of patients in the current study was 68 years and over 57% of their malignant pleural effusions were caused by metastatic carcinoma. The most common side-effect of intrapleural doxycycline or bleomycin has been chest pain.[19-21,23,24] Over 76% of patients in the present study experienced chest pain after pleurodesis.

This study evaluated the radiologic and clinical responses of two different sclerotherapy agents, doxycycline and bleomycin, in pleurodesis of malignant pleural effusions. Different studies reported various response rates based on underlying malignancies and the extent of disease.[12-16] No dyspnea, mild dyspnea. and moderate dyspnea; 10 days and 2 months after sclerotherapy, were significantly less frequent in doxycycline group compared with bleomycin group in the current study. Although no one in any group demonstrated severe pleural effusion 2 months after intervention, the doxycycline group revealed

Table 1: Prevalence of different severities of dyspnea, before and after the procedure, and 10 days and 2 months later in each group

Dyspnea	Type of sclerotherapy	Number of patients (percentage)			
		Before sclerotherapy	After sclerotherapy	10 days later	2 months later
No	Doxycycline	3 (14)	4 (21)	5 (24)	4 (21)
	Bleomycin	1 (5)	2 (9.5)	0	0
Mild	Doxycycline	1 (5)	7 (33)	5 (24)	6 (28.5)
	Bleomycin	0	14 (67)	12 (57)	7 (33)
Moderate	Doxycycline	5 (24)	7 (33)	7 (33)	5 (24)
	Bleomycin	1 (5)	5 (24)	9 (43)	13 (62)
Severe	Doxycycline	12 (57)	3 (14)	4 (21)	5 (24)
	Bleomycin	19	0	0	1 (5)
P value		0.1	0.1	0.005	0.01

The significance level is 0.05

Table 2: Prevalence of different severities of pleural effusion, before and after the procedure, and 10 days and 2 months later in each group

Pleural effusion	Type of sclerotherapy	Number of patients (percent)			
		Before sclerotherapy	After sclerotherapy	10 days later	2 months later
Mild	Doxycycline	0	20 (95)	17 (81)	14 (67)
	Bleomycin	0	16 (76)	15 (71)	6 (28.5)
Moderate	Doxycycline	9 (43)	1 (5)	4 (19)	7 (33)
	Bleomycin	4 (19)	5 (24)	6 (28.5)	15 (71)
Severe	Doxycycline	12 (57)	0	0	0
	Bleomycin	17 (81)	0	0	0
P value		0.18	0.18	0.7	0.01

The significance level is 0.05

Table 3: Prevalence of different severities of dyspnea based on underlying malignancy, 2 months after sclerotherapy in each group

Dyspnea	Type of sclerotherapy	Number of patients, 2 months after pleurodesis				
		Metastatic carcinoma	Mesothelioma	Pulmonary squamous cell carcinoma	Bronchogenic carcinoma	Lymphoma
No	Doxycycline	3	1	1	0	0
	Bleomycin	0	0	0	0	0
Mild	Doxycycline	2	1	0	2	1
	Bleomycin	4	0	1	2	0
Moderate	Doxycycline	3	0	1	1	0
	Bleomycin	8	2	0	1	2
Severe	Doxycycline	3	1	0	0	1
	Bleomycin	1	0	0	0	0
Total number of patients	Doxycycline	11	3	2	3	2
	Bleomycin	13	2	1	3	2

The significance level is 0.05

Table 4: Prevalence of different severities of pleural effusions based on underlying malignancy, 2 months after sclerotherapy in each group

Pleural effusion	Type of sclerotherapy	Number of patients, 2 months after pleurodesis				
		Metastatic carcinoma	Mesothelioma	Pulmonary squamous cell carcinoma	Bronchogenic carcinoma	Lymphoma
Mild	Doxycycline	7	2	2	2	1
	Bleomycin	5	0	0	1	0
Moderate	Doxycycline	4	1	0	1	1
	Bleomycin	8	2	1	2	2
Severe	Doxycycline	0	0	0	0	0
	Bleomycin	0	0	0	0	0
Total number of patients	Doxycycline	11	3	2	3	2
	Bleomycin	13	2	1	3	2

The significance level is 0.05

significantly less frequent moderate pleural effusion compared with the bleomycin group. There were no significant differences in other measurements between the two groups. Bleomycin is generally much more expensive than doxycycline.[4,25] Given the lower cost of the latter, its well-tolerance and its satisfactory radiologic and clinical response after 2 months in patients with malignant pleural effusion, this study supports the long term role of doxycycline over bleomycin in sclerotherapy of malignant pleural effusions. Further investigations with larger sample sizes are needed to confirm the results of this study.

CONCLUSION

Pleural effusions did not change with use of doxycycline and bleomycin in short time but long-term results of doxycycline sclerotherapy was better than bleomycin sclerotherapy in malignant pleural effusions that was supported by this study. However, additional studies with larger sample size are necessary to confirm the results.

ACKNOWLEDGMENT

The authors gratefully acknowledge authorities at the Islamic Azad University Najafabad branch for financial support of this study.

REFERENCES

1. Marchi E, Teixeira LR, Vargas FS. Management of malignancy-associated pleural effusion: Current and future treatment strategies. Am J Respir Med 2003;2:261-73.
2. American Thoracic Society. Management of malignant pleural effusions. Am J Respir Crit Care Med 2000;162:1987-2001.
3. Antunes G, Neville E. Management of malignant pleural effusions. Thorax 2000;55:981-3.
4. Andrews CO, Gora ML. Pleural effusions: Pathophysiology and management. Ann Pharmacother 1994;28:894-903.
5. Dimitriadis KA. Malignant pleural effusions. Arch Oncol 2001;9:2.
6. Bielsa S, Hernandez P, Rodriguez-Panadero F, Taberner T, Salud A, Porcel JM, Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung 2011;189:151-5.
7. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004:CD002916.
8. Benko I, Molnar TF, Horvath OP. Palliative treatment of malignant pleural effusions by video-assisted thoracoscopic surgery. Acta Chir Hung 1999;38:131-3.
9. Lee YC, Baumann MH, Maskell NA, Waterer GW, Eaton TE, Davies RJ, *et al*. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: Survey of pulmonologists. Chest 2003;124:2229-38.
10. Tan C, Sedrakyan A, Browne J, Swift S, Treasure T. The evidence on the effectiveness of management for malignant pleural effusion: A systematic review. Eur J Cardiothorac Surg 2006;29:829-38.
11. Antunes G, Neville E, Duffy J, Ali N. Pleural Diseases Group, Standards of Care Committee British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. Thorax 2003;58:ii29-38.
12. Kuzdzal J, Sladek K, Wasowski D, Soja J, Szlubowski A, Reifland A, *et al*.

Talc powder vs doxycycline in the control of malignant pleural effusion: A prospective, randomized trial. Med Sci Monit 2003;9:PI54-9.
13. Bilaceroglu S, Guo Y, Hawthorne ML, Zhu Z, Stathopoulos GT, Lane KB, *et al.* Oral forms of tetracycline and doxycycline are effective in producing pleurodesis. Chest 2005;128:3750-6.
14. Dikensoy O, Zhu Z, Donnelly E, Stathopoulos GT, Lane KB, Light RW. Combination therapy with intrapleural doxycycline and talc in reduced doses is effective in producing pleurodesis in rabbits. Chest 2005;128:3735-42.
15. Cerimagic Z, Guska S, Pilav I, Banjanovic B. The using doxycycline in procedure chemical pleurodesis of malignancy pleural effusion. Med Arh 2006;60:360-3.
16. Porcel JM, Salud A, Nabal M, Vives M, Esquerda A, Rodriguez-Panadero F. Rapid pleurodesis with doxycycline through a small-bore catheter for the treatment of metastatic malignant effusions. Support Care Cancer 2006;14:475-8.
17. Elpern EH, Krueger J, Kimsey J, Silver M. The technique of pleurodesis. J Crit Illn 1994;9:1105-10.
18. Dryzer SR, Allen ML, Strange C, Sahn SA. A comparison of rotation and nonrotation in tetracycline pleurodesis. Chest 1993;104:1763-6.
19. DiBardino DJ, Vanatta JM, Fagan SP, Awad SS. Acute respiratory failure after pleurodesis with doxycycline. Ann Thorac Surg 2002;74:257-8.
20. Liao H, Guo Y, Jun Na M, Lane KB, Light RW. The short-term administration of Ketoprofen does not decrease the effect of Pleurodesis induced by talc or Doxycycline in rabbits. Respir Med 2007;101:963-8.
21. Fyfe AJ, McKay P. Toxicities associated with bleomycin. J R Coll Physicians Edinb 2010;40:213-5.
22. Heffner JE, Klein JS. Recent advances in the diagnosis and management of malignant pleural effusions. Mayo Clin Proc 2008;83:235-50.
23. Bleomycin in malignant pleural effusion. Choose talc pleurodesis. Prescrire Int 2011;20:291.
24. Walker-Renard PB, Vaughan LM, Sahn SA. Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 1994;120:56-64.
25. Dikensoy O, Light RW. Alternative widely available, inexpensive agents for pleurodesis. Curr Opin Pulm Med 2005;11:340-4.

Source of Support: Islamic Azad University Najafabad Branch.
Conflict of Interest: None declared.