Original Article

Bleomycin in the treatment of 50 cases with malignant pleural effusion

Novin Nikbakhsh (MD) [*1]
Ali Pourhasan Amiri (MD) [2]
Danial Hoseinzadeh (MD) [3]

1- Department of Surgery, Babol University of Medical Sciences, Babol, Iran.
2- Department of Internal Medicine, Babol University of Medical Sciences, Babol, Iran
3- Babol University of Medical Sciences, Babol, Iran.

*** Correspondence:**
Novin Nikbakhsh, Department of Surgery, Shahid Beheshti Hospital, Babol Univesity of Medical Sciences, Babol, Iran

E-mail: novinsu@hotmail.com
Tel: 0098 111 2252071
Fax: 0098 111 3232665

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Abstract

Background: Patients with symptomatic malignant pleural effusion (MPE) may gain profit from pleurodesis for relief of dyspnea and in preventing the accumulation of fluid or air in the pleural space. Pleurodesis methods are palliative and regard the patient's symptoms and underlying disease condition that are different. The purpose of this study was to assess the efficacy of bleomycin in the treatment of malignant pleural effusion.

Methods: From March 2003 to August 2009, 50 cases of malignant pleural effusion referred for chemical pleurodesis. Malignant pleural effusion was diagnosed by cytotogical examination of pleural fluid after thoracosynthesis. Pleurodesis was done by pleural fluid instillation of bleomycin. The severity of effusion with response to treatment was compared.

Results: Nineteen (38%) cases were males and 31 (62%) were females. The mean age of these patients was 60.3±15.8 years (range=31 to 85 years). The majority of patients had breast cancer and lung adenocarcinoma. The mean volume of pleural fluid drained was 2282±848.69^{cc} (range 800-4500 ^{cc}). Pleural effusion was mild in 2 (4%) patients, moderate in 25 (50%) and severe in 23 (46%). There was no statistically significant difference between the response to treatment and the amount of effusion (p=.087). Complete response was seen in 33 (66%) patients, partial response in 11 (22%) and failure to treatment in 6 (12%). There was no relationship between the response to treatment and tumor type. There was not any complication in 33 (66%) patients, but fever was seen in 2 (4%) and chest pain in 7 (14%) and both of them in 8 (16%).

Conclusion: The results show that pleurodesis with bleomycin has improved the symptoms of 88 percent of patients without causing any significant complications. Although pleurodesis does not have any effect on patients' survival, it has positive impact on their lives continuously by enhancing the quality of life.

Keywords: Pleural effusion, Malignancy, Pleurodesis, Bleomycin.

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Some clinical conditions such as congestive heart failure, cirrhosis, acute pancreatitis, rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, drug reaction, myocardial infarction, benign tumors, mesothelioma, metastatic tumor to pleural membrane (such as lymphoma, lung and breast cancer), lymphatic obstruction and pleural amyloidosis may lead to pleural effusion (1). Malignancies are the common cause of recurrent pleural effusion (2). Malignant pleural effusion (MPE) affects more than 200000 people in the USA (3). The most common cause of this effusion is lung, breast, and ovarian cancers and lymphoma, with breast and lung malignancies alone account for approximately 75% of these effusions (4). This effusion is often diffuse and leads to dyspnea and chest discomfort, therefore, the patient's quality of life may disrupt with cough and dyspnea.

In these patients, life expectancy is not more than few months and the cause of death is regarded to the underlying disease manner. Patients with symptomatic malignant pleural effusion (MPE) may gain profit from pleurodesis for relief of dyspnea and prevent accumulation of fluid or air in the pleural space (5). Pleurodesis includes mechanical abrasion of pleural layers or intrapleural administration of a chemical agent that lead to the inflammation of pleural layers. These methods are palliative and regard to the patient's symptoms and underlying disease condition are different (6).

In recurrent malignant pleural effusion, patients need to repeated aspiration for symptoms relief and pleurodesis may impress to reach this goal with efface the pleural space (7). Unfortunately, in 10%- 40% of patient reaccumulation of fluid occurs and leads to the recurrence of dyspnea that extremely depends on the sclerosing agents use for pleurodesis (8). Different chemical agents such as: talk, bleomycin, doxycycline and minocycline are used for pleurodesis that none of them is absolutely ideal and all of them have some adverse side effects.

Mortality does not increase during pleurodesis process but the adverse side effects depends on the chemical agent used such as fever, gastrointestinal pain and discomfort, pleuritic chest pain and less common complications that include respiratory failure, cardiovascular disturbance, systemic inflammatory response, empyema and reduction of lung capacity that may occur (9).

An ideal chemical agent must have some characteristics such as being inexpensive, no adverse/side effects or less availability (8-10). Mindfully to the high prevalence of malignant pleural effusion and decrease of quality of life, in the latest months of these patients' life pleurodesis can make it better so we decided to evaluate the effect of pleurodesis with bleomycin in 50 patients with malignant pleural effusion.

Methods

Fifty patients with malignant pleural effusion (MPE) who referred to Thoracic Surgery Department of Beheshti General Hospital, Babol, Iran for chemical pleurodesis between March 2003 and August 2009 were reviewed. In all patients, MPE were documented with cytological examination of pleural fluid after thoracosynthesis. In all of the patients, the expected survival was at least 1 month with karnofsky score of 50 or more and none of them has previously systemic chemotherapy with bleomycin. Before pleurodesis, the size of pleural effusion was assessed by a posteroanterior chest radiography and was classified as ″mild″, when it was filled less than 33% of hemithorax, ″moderate″, when it was filled 34%–67% of the hemithorax (extending from the diaphragm to the pulmonary hilum), and massive, when it was filled more than 68% of the hemi thorax (exceeding the hilar region).

After local anesthesia, a conventional large-bore chest tube (28-32 French) was placed into the pleural space in the 6th-7th intercostals space in the posterior axillary line. The proper position of tube and complete lung expansion was controlled by chest radiography, 3-4 hours after tube insertion. After radiographic demonstration of full lung expansion, less than 100 ^{cc} daily drainage of plural fluid, 60 units of bleomycin dissolved in 50 ^{cc} of sterile normal saline solution were instilled into the pleural space via chest tube. Then the tube was clamped for 4 hours and the patient's position was rotated to prone supine and left and right lateral decubitus positions for every 20 minutes. Thoracostomy tube was removed when the daily drainage was less than 200 ^{cc}. In all of the patients, control radiography was taken after chest tube removal. The follow-up of patients in Outpatient clinics in our hospital was done in 1, 3, 6 months after chemical pleurodesis.

The response to treatment was assessed with clinical symptoms and followed up by chest radiography and was classified as: "complete response" no clinical or radiological reacumulation of fluid, "partial response", small amount of fluid reacumulation but no recurrence of symptoms and did not require thoracosynthesis, however, "Failure" has fluid recurrence with clinical manifestation or requiring thoracosynthesis.

Patients that had complained of dyspnea without any effusion in chest radiography were defined as complete response. It seems that the cause of dyspnea in these patients must be considered as underlying disease and not to as failure of chemical pleurodesis.

After chemical pleurodesis with bleomycine, the most important adverse effects were fever and pain. All evidences of pain and fever in the first 24 hours after pleurodesis were registered. The data were analyzed with SPSS version 16 and use of t-test for continues variables, Chi square test for comparison of proportions. The response rate was compared using the Chi-square test. The significant level for all the tests was carried out at the 0.05.

Results

Primary tumors site and type are summarized in table 1. The majority of patients had breast cancer and lung adenocarcinoma. The mean volume of pleural fluid drained was 2282±848.69^{cc} (range 800-4500^{cc}), there was no statistically significant difference between the treatment and the amount of fluid drained (p=.521). Pleural effusion was mild in 2 (4%) patients, moderate in 25 (50%) and severe in 23 (46%). There was no statistically significant difference between the different malignancies and severity of effusion (p=.355) and between the response to treatment and amount of effusion (p=.087) (table 2). Complete response was seen in 33 (66%) patients, partial response in 11 (22%) and failure to treatment in 6 (12%). Response to treatment with regard to primary tumor type is shown in table 1 that there was no relationship between response to treatment and tumor type.

There was not any complication in 33 (66%) patients, but fever was seen in 2 (4%) and chest pain in 7 (14%) and both of them in 8 (16%). There was no relationship between type of malignancy and complication statistically (p= 0.288). After six months follow up, 6 months survival was 64%. It means that 32 (64%) patients were alive after 6 months and 18 (36%) died (table 1). There was no statistically difference between the types of malignancy and 6 months survival (p=0.843). Thirty-two patients remained alive after 6 months, there were 12 (37.5%) males and 20 (62.5%) females and from the dead patient, there were 7 (38.9%) males and 11 (61.1%) females. The patients sex and 6 months survival did not have any statistical relationship (p=0.579). Six months survival and response to treatment with regard to primary tumor type are shown in table 1. Survival did not have any significant relationship with the response to treatment (p=0.542).

Table 1: primary tumor site, response to treatment and 6 month survival depending on the primary tumor site

Primary tumor type	Partial response N (%)	Complete response N (%)	Failure N (%)	Total N (%)
Breast	5 (25)	13 (65)	2 (10)	20 (40)
Lung				
Adenocarcinoma	2 (18.2)	8 (72.7)	1 (9.1)	11 (22)
Sqamouse cell	0	0	1 (100)	1 (2)
Small cell	0	1 (100)	0	1 (2)
Adenocystic	0	1 (100)	0	1 (2)
Gastric				
Adenocarcinoma	0	2 (66.7)	1 (33.3)	3 (6)
Cardia				
Adenocarcinoma	1 (33.3)	1 (33.3)	1 (33.3)	3(6)
esophagus	0	2 (66.7)	1 (33.3)	3 (6)
Ovary	0	2 (100)	0	2 (4)
Pancreas	0	1 (100)	0	1 (2)
Lymphoma	0	1 (100)	0	1 (2)
Cervical mass(SCC)	0	1 (100)	0	1 (2)
Thyroid(PTC)	1 (100)	0	0	1 (2)
Kidney	1 (100)	0	0	1 (2)
Total	10 (20)	33 (66)	7 (14%)	50 (100)

Table 2: Response to treatment regarding to severity of effusion and 6 month survival

	Partial response N (%)	complete response N (%)	Failure N (%)
Death within 6 month	4 (36.4)	13 (39.4)	1 (16.7)
Alive after 6 month	7 (63.6)	20 (60.6)	5 (83.3)
Mild effusion	0	2 (100)	0
Moderate effusion	4 (16)	15 (60)	6 (69.6)
Severe effusion	7 (30.4)	6 (24)	0

Discussion

In this study, the mean age of patients was 60.28±15.76 in which 38 percent were males and 62 percent were females. Effusion was mild in 2 patients (4%), moderate in 25 (50%) and severe in 23 (64%). In all similar studies, the patients mean age was more than 60 years old and males proportion was lower than females, which is in consistence with our study. In the study by Ong et al. pleurodesis was done on 38 patients using bleomycin on 20 patients; the mean age of their patients was 66.3±11.7 years and male to female ratio was 8 to 12. Pleural effusion was located on the left side in 8 patients and right side in 12 patients and was moderate in 10 but large in other 10 patients (10).

In the study by Martinez-Morgon et al., 31 patients were under pleurodesis with bleomycin; the mean age of patients was 60±15 years and male to female ratio was 12 to 19 years (11). In Zimmer study on 33 patients, 14 patients were under pleurodesis using bleomycin with the mean age of 68±4.4 years and male to female ratio of 4 to 10. Pleural effusion was observed on the left side in 4 patients and the right side in 10 patients (12). In our study, the most frequent cancers were breast (40%) and lung adenocarcinoma (22%). Similar to the present study, Martinez-Morgon reported breast and lung cancer as the most prevalent cancers in their study, in which 10 patients were detected with breast cancer, 7 with lung cancer, 2 with gastric cancer, 2 with lymphoma and 10 patients with other types of cancer (11).

Whereas, in Ong study, the cases of lung cancer were more than breast cancer 9 cases had lung cancer, 7 breast cancer, and 4 patients with other types of cancer (10). Unlike our study, no breast cancer was reported, in the patients of Zimmer study; lung, ovarian and other types of cancer were found in 8, 2 and 4 patients, respectively (12). In the present study, improvement was partial in 11 (22%) patients and was completed in 33 (66%); treatment failure was also observed in six patients (12%). In Ong study, treatment success (no recurrence of pleural effusion to one month after treatment) was found in 14 out of 20 (70%) patients. After one month follow up, no recurrence was seen in 12 patients, mild pleural effusion in three patients, moderate in three patients and severe in no patient (10). In Martinez-Morgon study, recurrence of pleural effusion was detected in 20 out of 31 patients; follow-up was not possible in 14 patients, and after 6 months follow-up of the remaining 17 patients, 14 patients (82%) showed completed recovery, 2 patients (12%) partial improvement and 1 patient (6%) treatment failure (11). In Zimmer's study, 79% of patients showed none or minimal effusion after treatment, which is considered as treatment success. Moderate and severe effusion was observed in two to one patient respectively (12). In Hamed, Moores, Ostrowski and Kessinger studies, treatment success rate were 66%, 64%, 81% and 62% in order (13-16). In our study, from the total patients, 33 (66%) did not present any complications, while 2 patients (4%) showed fever, 7 patients (14%) pleuretic pain and 8 (16%) pleuritic pain with fever. In Ong study, from a total of 20 patients, fever was observed in 4 cases and pleuritic pain in 2 cases after the treatment. In addition, empyema, dyspnea or death were not found in any patients (10). Martinez-Morgon reported presence of pain in 10 patients (32%), fever in 6 patients (19%) and nausea and vomiting in one patient (3%) postoperatively (11). In Zimmer's study, pain and shortness of breath was scored from zero (absence) to 10 (presence even with the pain) and were compared before and after the treatment. The mean follow up of patients was 1.7 months. Pain score was reduced from 4.1 to 2.4 and dyspnea from of 2.9 to 2 (12). In our study, after 6 months follow up, the patients' 6-month survival was 64 percent, i.e. 32 patients (64%) were alive and 18 patients (36%) died after this period. Median survival in patients under pleurodesis with bleomycin was 5 months in Ong's study (10). In Martinez-Morgon study with mean follow-up of 7 months, 16 out of 31 patients died and median survival was 9 months in these patients (11). Chemical pleurodesis is a treatment option which is often implemented to control symptoms of malignant pleural effusion. Effectiveness of this method is associated to the inflammatory response leading to reduced fibrinolytic activity and decreased damage to mesothelial cells and stimulated fibroblast infiltration (13). Ideal matter for pleurodesis should possess safety and good efficacy and be used in the shortest possible time.

Bleomycin is an antineoplastic antibiotic from Streptomyces Verticillus which is attached to DNA and inhibits its synthesis by causing DNA breakage. Bleomycin is now widely used because of its properties to sclrosing pleurodesis and control malignant pleural effusion (14-16).

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