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Bleomycin Pleurodesis in Malignant Pleural Effusion

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Abstract

Objectives: This is the first retrospective trial in our country to examine intrapleural bleomycin in terms of effectiveness, safety, and cost. The aim of this study was to investigate the effectiveness, safety and appropriate mode of administration of intrapleural bleomycin for pleurodesis, in the treatment of malignant pleural effusion.

Methods: Between January and July 2014, 30 patients presenting to Ibn-Alnafees teaching hospital with symptomatic malignant pleural effusions were underwent chemical pleurodesis with bleomycin via bedside thoracostomy. Only the patients with lung re-expansion after drainage entered the study. The conditions of patients were assessed and graded before and after treatment concerning pain, dyspnea, and chest radiographs.

Results: Thirty patients who underwent pleurodesis with bleomycin were available for follow-up. The patients demonstrated notable improvement in both pain and dyspnea following treatment. Permanent control of effusions, defined objectively on chest radiograph, was achieved with bleomycin treatments in 21(70%). The procedures were well tolerated and no significant adverse effects were observed.

Conclusions: This study confirms that intrapleural bleomycin carries good results in the treatment of malignant pleural effusion. Pleurodesis using bleomycin with 72 hours applied suction should be offered to every patient with malignant pleural effusion, apart from terminally ill ones, provided that a satisfying lung re-expansion has been achieved. A careful selection is essential to define the proper technique.

Keywords: Bleomycin, pleurodesis, pleural effusion, Iraq

Introduction

Malignant pleural effusion is a condition in which cancer causes an abnormal amount of fluid to collect between the thin layers of tissue (pleura) covering the outside of the lung and the wall of the chest cavity. Lung cancer and breast cancer account for about 50–65% of malignant pleural effusions. Other common causes include pleural mesothelioma and lymphoma.[1]

Once the thoracostomy tube in the pleural space drains 150 ml per day and the lung is fully expanded which is confirmed on chest roentgenogram, the next aim is to prevent reaccumulation by another procedure.[2] Pleurodesis is the process by which the pleural space is obliterated by inflammation induced through chemical or mechanical means, to achieve definitive and long-standing pleural apposition with fibrosis. Most physicians consider an expected survival beyond 2–3 months necessary to justify the risks, discomforts, and cost of pleurodesis. So, all patients with symptomatic malignant pleural effusion who are with a life expectancy of 2–3 months or more should be evaluated for pleurodesis. Those patients with a very limited life expectancy can be treated only with tube thoracostomy or thoracentesis.[3]

Agents for Pleurodesis

Chemical pleurodesis is the most commonly used method of pleurodesis. Many agents have been described for chemical pleurodesis including Talc powder, bleomycin, tetracycline, doxycycline, Corynebacterium parvum extract, silver nitrate, iodopovidone, quinacrine, interferons, interleukin-2, and several chemotherapeutics. All these pleurodesants are usually administered through a chest tube, after the drainage of the malignant pleural effusion with the drain amount less than 150 ml per 24 h.[4]

Bleomycin

Is the most widely administered antineoplastic agent with a success rate of 60–80%. Bleomycin was first discovered in 1966 when the Japanese scientist Hamao Umezawa found anticancer activity while screening culture filtrates of S. verticillus. The drug was launched in Japan by Nippon Kayaku in 1969.[5] Bleomycin used to treat Hodgkin's disease, non-Hodgkin's disease, testicular cancer, ovarian cancer, and cervical cancer. It can be given intravenously, by injection into a muscle or under the skin. It may also be put inside the chest to help prevent the recurrence of a pleural effusion due to cancer. While potentially effective against bacterial infections, its toxicity prevents its use for this purpose.[6]

The most serious complication of bleomycin is pulmonary fibrosis and impaired lung function. It has been suggested that bleomycin induces sensitivity to oxygen toxicity[7] and recent studies support the role of the proinflammatory cytokines IL-18 and IL-1beta in the mechanism of bleomycin-induced lung injury. Other side effect include fever, rash, dermatographism, hyperpigmentation, alopecia (hair loss) and Raynaud's phenomenon.[8]

Procedure of Pleurdesis

Conventional pleurodesis: In the traditional approach to chest-catheter pleurodesis, a short-term catheter is inserted intrapleurally, either blindly or by image guidance for the drainage of the pleural fluid and instillation of a sclerosing agent. The tube is removed when minimal fluid remains to be drained. Most experts recommend that the sclerosant be instilled only when catheter drainage has decreased to less than 150 ml/day. When bleomycin is used it is given in a dose of 60 mg as a slurry, in a 200-ml saline solution, to which 20 ml of 7.5% ropivacaine is added to decrease associated pain. The tube is clamped for 8 h, and the patient turned in different

positions. After 8 h, the drain is connected to slow suction of 20 cm of H_2O for 24 h. At the end of the procedure, the patient can be discharged from the hospital. The tube is left in place, until less than 100 ml to 150 ml of fluid is drained in 24 h. Chest roentgenograms are obtained 1 month after the procedure and then monthly for 3 months. Further follow-up is needed as per the type of tumor and the onset of respiratory symptoms.[9]

Video-assisted thoracoscopic surgery pleurodesis: Talc poudrage is performed by videothoracoscopy, under general anesthesia and selective one-lung ventilation. Any residual fluid is aspirated, loculations are divided when present, pleural biopsies are taken if necessary, and lung reexpansion is confirmed. Chest X-rays are obtained at 1 and 2 weeks. If pleurodesis is achieved, the pleural catheter is removed, usually 2 weeks after the procedure.[10]

Survival After Pleurodesis

The most difficult question to answer is the improvement of survival with pleurodesis. As such, pleurodesis is purely a palliative procedure and it only decreases the mortality out of respiratory compromise and thus improving quality of life and survival. Multiple clinical factors have been used to estimate survival after pleurodesis, including the organ of origin of malignancy, cell type (adenocarcinoma, squamous, small cell, etc.), stage of the tumor, characteristics of the pleural fluid, and performance level. Unfortunately, in spite of careful selection, 32% of patients do not survive 30 days after pleurodesis.[11] The American Thoracic Society/European Respiratory Society guideline for the management of malignant pleural effusion recommends that pleurodesis should be limited to patients with pleural fluid pH values greater than 7.30, because of the direct correlation between low pH and poor short-term survival.[12] Among the criteria now in common use, performance status is the most important for estimating post-pleurodesis survival.[13]

Aim of the Study

The aim of the study was to investigate the effectiveness, safety and appropriate mode of administration of intrapleural bleomycin for pleurodesis, in the manegment of malignant pleural effusion.

Materials and Methods

This is a retrospective study of 30 patients who had been admitted to Ibn Al-Nafees teaching hospital overperiod of six months (from January to June 2015) who had been followed the next six months. For most patients confirmed the Diagnoses of pleural effusion with the help of a chest radiograph or ultrasonography. A few patients showed the presence of pleural effusion the CT scan. The pleural fluid was aspirated and cytological evaluation was done with other routine and special investigations, if needed. The medical records plus surgeon note of these patients with the diagnosis of malignant pleural effusion were reviewed. Information relevant to patients variables with regard to patients age, sex, presenting symptoms, radiographic findings (chest x-ray and CT scan) had been assessed. IF suspected or confirmed for malignancy, the search for the primary was done with appropriate investigations. All the patients were further investigated for staging and metastasis. All patients after a full pre-operative preparations including basic and specific investigations underwent formal chest tube and the malignant pleural effusion was drained. All of our patients had immediate post-operative course, patients were discharged home in a good condition and recurrence was seen in 9 patients.

Results

Of 30 patients with malignant pleural effusion 18 of them were female constituting (60%) and the rest (12 patients) were male constituting (40%). The youngest patient was a 34-years old woman, and the oldest was a 72 years old man. Most of the patients (12 patients (40%)) fall between 50–60 years old. The distribution of our patients as regard their age and sex is shown in Figure 1.

In our study the most common cause of malignant pleural effusion was breast cancer 53.3% followed by bronchogenic carcinoma 36.6% as shown in the Table 1.

Of 30 patients, recurrence of malignant pleural effusion was seen in 9 patients. Pleural fluid cytology was positive in 12 patients only and the recurrence was seen in 6 of them as shown in the Table 2.

In our study recurrence rate is higher in soft tissue sarcoma 50% followed by breast cancer 31.2% as shown in the Table 3.

In our study, suction was applied in 13 patients (43.3%) and recurrence of malignant pleural effusion in these patients was seen in 3 patients (23%) only (Table 4).

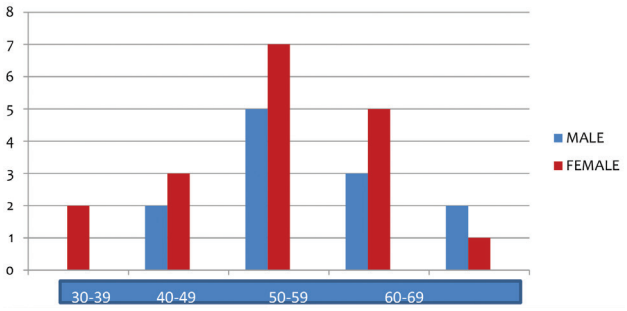

Fig. 1 **Age and sex distribution of patient with malignant pleural effusion.**

Table 1. **Causes of malignant pleural effusion**

Primary tumor	Male		Female		Total	
Breast cancer	0	0%	16	53.3%	16	53.3%
Bronchogeniccarcinoma	9	30%	2	6.6%	11	36.6%
Soft tissue sarcoma	2	6.6%	0	0%	2	6.6%
Renal cell carcinoma	1	3.3%	0	0%	1	3.3%

Table 2. **The effect of the pleural fluid cytology on recurrence rate**

	No of patients	Recurrence	Percentage
Pleural fluid cytology +ve	12	6	50%
Pleural fluid cytology –ve	18	3	16.6%

Table 3. **Recurrence rate according to the type of tumor**

Type of tumor	Number	Recurrence
Breast cancer	16	5
Bronchogenic carcinoma	11	3
Soft tissue sarcoma	2	1
Renal cell carcinoma	1	0

Table 4. **Effect of suction on recurrence rate**

	Number	Recurrence
With suction	13	3 (23%)
Without suction	17	6 (35.2%)

Discussion

Of 30 patients with malignant pleural effusion 18 of them were female constituting (60%) and the rest (12 patients) were male constituting (40%). The male to female ratio was 1:1.5. This results are inconsistent with the results obtained in India in which male to female ratio was 2.5:1.[52] The higher incidence of malignant pleural effusion in females is due to higher incidence of breast cancer in AL-Amal Hospital which contributes to 53.3% of the cases. Most of the patients (40%) fall between 50–60 years old. In our study the most common cause of malignant pleural effusion was breast cancer 53.3% followed by bronchogenic carcinoma 36.6%. This is inconsistent with the study obtained in India in which the major primary cancers were lung cancer followed by lymphoma and breast cancer.[52] This difference between these studies may be due to the lack of screening program for breast cancer in Iraq and the increasing incidence of cancer in the last years due to radiation exposure due to internationally banned weapons. In our study, pleural fluid cytology was positive for malignant cells in 40% only while in India pleural fluid cytology was positive in 60%.[52] This difference may related to factors such as the type of tumor; the tumor burden in the pleural space; and the expertise of the cytologist. Each patient included in our study signed the informed consent approved by our institutional ethics committee. All procedures were carried out in the minor procedures room. In all patients, the skin was prepaired with alcoholic clorhexidine and the surgical field isolated with sterile drapes. After local anesthetic (lidocaine 2%) administration, pleural drainage was carried out with 28–32 Fr chest tubes using the trocar technique. After that, underwater seal bottle was connected to the drain.

Proper chest tube position was evaluated immediately after the procedure according to adequate pleural fluid evacuation, absence of hemorrhagic events and physical examination. Evaluation was performed by a trained investigator that followed a pre-established protocol, checking for potential complications of catheter placement (respiratory insufficiency, bleeding, pain and cough). If the chest tube was working properly, the patient was transferred to the ward after 1 hour of observation and radiological examination were considered unnecessary.

In our patients, the drain was kept in place until the daily output was <100 mL/day. The patients underwent a chest radiography; if chest X-Ray showed pulmonary expansion greater than 90% of the affected hemithorax, the patient was selected for pleurodesis. If complete chest expansion did not occur (trapped lung), pleurodesis was not performed and the patient was excluded from the trial. Patients selected for pleurodesis underwent bleomycin introduction through the thracostomy tube (60 mg in 50 mL of saline solution and 5 mL lidocaine 2%). Systemic analgesia was administered only when necessary. The drain was kept closed for 3 hour; after this, the drain was opened and the patient kept on sucker for 72 hours then discharged and instructed to return in 1 week. Complications after pleurodesis were actively searched after bleomycin instillation and in each visit through physical examination and a standardized questionnaire.

After thoracostomy tube removal, a return visit was scheduled to the 30th post catheter insertion day, for clinical evaluation and a new chest X-Ray. Thereafter, the visits were each 3 months. On all the return visits, new chest X-Ray and the occurrence of complications were evaluated. If the patients were symptomatic and there was evidence of fluid accumulation on the chest X-Ray, a thoracentesis was performed. If there was doubt between fluid accumulation and tumor progression or lung infiltration, a chest CT scan was performed Patients were followed until death or until the end of the study in December, 2016.

In our study no complications were observed during chest tube placement or pleurodesis. Post-pleurodesis complications included empyema (1 patient). The average drainage time was 5.1 days. The recurrence rate observed in patients that were alive 30 days after pleurodesis was 30% (9/30 patients). This is higher than the rate observed in Sao Paulo study in which the recurrence rate was 13.9%. In our study 13 patients underwent suction for 72 hours after bleomycin instillation and the recurrence rate in these patients was 23% while in the remaining 17 patients pleurodesis had been done without suction with recurrence rate of 35.2%. Such difference in success rates reinforces the benefit of suction application in pleurodesis. Out of 30 patients pleural fluid cytology was positive in 12 patients with 50% recurrence rate while in the remaining 18 patients with negative pleural cytology the recurrence rate was 16.6%. So positive pleural fluid cytology may correlate with high invasiveness of the disease with high recurrence rate. The recurrence rate also depend on the type of the primary cancer with high recurrence rate in soft tissue sarcoma (50%) (Only 2 cases) followed by breast cancer (31.2%) and bronchogenic carcinoma (27.2%). In our study, additional procedures were necessary in 2 patients (6.6%) due to malignant pleural effusion recurrence.

The prognosis associated with malignant pleural effusion is generally poor. Survival depends on the primary cancer and the patient's performance scale. Out of 30 patients who could be followed up for a minimum of six months, 22 patients (73.4%) died. Only 8 (26.6%) patients were alive after six months. There are however, potential limitations to this study. The retrospective study design could have introduced systemic bias, including patients who were unavailable for follow up. This problem was eliminated by using data that were derived from a 180-day period with complete outcome information for statistical analysis. Furthermore the quality of life was not documented in the months following the procedure. Successful pleurodesis show marked improvement in

dyspnea. In spite of the fact that patients with trapped lung had been excluded from the pleurodesis trial, we followed them, and we have found some significant results. From a clinical perspective, the most important finding was the high empyema rate (30%) in those who had trapped lung with long-term drainage.

Conclusion

- Malignant pleural effusion commonly complicates an underlying malignancy, lung cancer is the most common in males and breast cancer in females. Breast cancer is the commonest cause of malignant pleural effusion in our study 53.3% followed by bronchogenic carcinoma 36.6%.
- Thoracostomy drainage and chemical pleurodesis are the best palliative measures in the management of malignant pleural effusion. In our study, bleomycin pleurodesis was safely performed with good efficacy and a accepted complication rate.
- In this study, the strategy used enabled adequate control of pleural effusion symptomatology and was associated with the level of recurrence higher than that observed in the literature.
- The recurrence rate of malignant pleural effusion was lower in those who underwent suction for 72 hours after bleomycin pleurodesis than those without suction.
- The recurrence rate of malignant pleural effusion was higher in patients with positive pleural fluid cytology. So positive pleural fluid cytology may related to high invasiveness of the disease with high recurrence rate.
- The recurrence rate of malignant pleural effusion was higher in soft tissue sarcoma (only 2 cases) followed by breast cancer and bronchogenic carcinoma. So the recurrence rate depends on the type of the primary cancer.

Recommendation

- Suction for 72 hours better to applied for every patient with malignant pleural effusion after instillation of bleomycin.
- Breast cancer screening Campaigns better to encouraged as breast cancer is the commonest cause of malignant pleural effusion in our country.

Conflicts of Interest

None.

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