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Viscum Album Versus Bleomycin for Pleurodesis among Patients with Malignant Pleural Effusion

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Abstract **OBJECTIVE:** To compare between mistletoe(Viscum album) and bleomycin as chemical agents for pleurodesis in malignant pleural effusions. **METHODS:** In this study 50 patients with pathologically confirmed, symptomatic, malignant pleural effusion irrespective of the primary tumor were studied at Suez Canal University hospital in the period of 3 years from January 2009 to December 2012. Patients were divided into 2 groups; 25 patients each: group A(pleurodesis with Mistletoe using 100mg – 5 ampoules-repeated two or three times, injected every other day) and group B(pleurodesis with Bleomycin1 iu/kg average-4 ampoules-or maximally 60 units). follow-up included postero-anterior and lateral chest radiography done after one week, month and 3 months. **RESULTS:** Most of the patients among both groups show complete remission defined as no effusion detected within four weeks of pleurodesis (72% and 56% among bleomycin and Viscum groups respectively). Significant difference was found between both groups. Recurrences were more frequent among group A (20% versus 8% in group B), $P < 0.05$. Hospital stay was shorter in the bleomycin group of patients, with a mean of (6.2) day. **CONCLUSION:** Both bleomycin and Viscum album are effective and safe agents for chemical pleurodesis, however bleomycin has some advantages over Viscum album due to its lower incidence of failure, and being more economic and for the shorter hospital stay.

Keywords: *Viscum album, malignant pleural effusion, mistletoe, bleomycin, pleurodesis*

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1. Introduction

Malignant pleural effusions cause considerable morbidity for patients affected with cancer. Patients who develop such effusions experience a reduction in the quality of life owing to symptoms such as dyspnea, chest pain and cough. Effective control of these effusions can greatly improve the quality of life of the cancer patient [1,2,3].

The aim of treatment is resolution of the pleural effusion and improvement of the clinical situation. A number of different techniques have been used.It can be done chemically and/or surgically. Pleurodesis is done to prevent recurrence of pleural effusions. The instilled chemicals cause irritation between layers of the pleura achieving symphysis between them and preventing further fluid accumulation [2,4,5]. Chemicals such as bleomycin, tetracycline, povidone iodine, doxycycline, and talc, can be introduced into the pleural space and all can be used [4-12]. However, the success rate between these agents varied greatly, some of them had good results others had negative impact, none of them is superior or have hundred percent effectiveness or convenience, with different adverse effects such as toxicity, pain, dyspnea and fever. Moreover, some are expensive others are not easily available. The multiplicity of treatment and chemicals confirms the lack of an optimal therapy [3-12].

Treatment of cancer with extracts from mistletoe was introduced at the beginning of the 20th century by Rudolf Steiner as part of anthroposophically-extended medicine [13,14,15]. Today preparations from mistletoe extracts frequently used as so-called complementary and alternative methods (CAM) [16], and the commercially available mistletoe extracts are prepared from the semi-parasitic plant Viscum album Loranthaceae (Viscum album L. or European mistletoe) [17].

A number of investigations have shown that intrapleural instillation of the Viscum album L. (mistletoe) extract is effective [18,19] in reducing the number of malignant cells in malignant pleural effusions. The efficacy was suggested to be due to the cytotoxic and immunomodulatory properties of the intrapleurally applied mistletoe extract [19,20,21,22,23].

These observations suggest that the elimination of tumor cells in the malignant pleural effusion by a non-specific activation of immune competent cells might lead to pleural sclerosis [20,21]. Intrapleural administration of mistletoe extracts is reported to result in pleurodesis, with overall response rate of 72%, and only 1.2% side effects according to the World Health Organization classification [18], so that the local treatment not only aims to induce pleurodesis but also to treat the malignant disease itself

[19]. Antony et al., [22,23] proved that the immune system plays a rule in pleurodesis and that activation of certain chemotactic molecule and interleukins in the pleural fluid itself are essential for successive pleurodesis, all these evident raise the issue of why not to use an immunomodulator agent as a chemical sclerotherapy in malignant pleural effusion Hereby we conducted this study to evaluate the results of mistletoe as a new chemical agent for pleurodesis in malignant pleural effusion and comparing its results with a well-established chemical as the bleomycin.

2. Methods

2.1. Study Population

In this study 50 patients with pathologically confirmed, symptomatic, malignant pleural effusion irrespective of the primary tumor were studied at Suez Canal University hospital in the period of 3 years from January 2009 to December 2012.

Patients with documented, symptomatic, malignant pleural effusion of both sexes were included in the study. Patients with previous history of tube thoracostomy, pleurodesis or thoracotomy, other causes of pleural effusion rather than malignancy, severely ill Patients were excluded.

2.2. Examination Technique and Study Variables

All of the studied patients were subjected to history taking, lines of management of primary lesion, operations, radiotherapy and chemotherapy, and complications, and any other chronic illnesses.

Basic investigations were done including laboratory investigations, pathological confirmation of the diagnosis and radiological investigations, CT scan of the chest if needed.

Intercostal tubes-sized 32fr. were inserted in 5th intercostal space mid-axillary line under local anesthesia for all patients in both groups for gradual evacuation and assessment of physical, chemical and pathological characters of the effusion. Pleurodesis will be done when there is less than 100mls drainage per day, a chest X-ray is performed to ascertain whether the pleural effusion has resolved or not. Pleurodesis was done using Mistletoe in group (A) using 100mg (5 amp.) repeated for two to three times (according to response) and injected every other day. In group (B) pleurodesis was done using Bleomycin 1 iu/kg average (4 amps).

Symptoms associated with the injection of the sclerosing agent were treated accordingly, opioids were used for pain management based on the severity and paracetamol was used as antipyretic for fever control.

Late postoperative follow-up included postero-anterior and lateral chest radiography done after one week, month and 3 months. Then, the outcome was determined through Follow up of patient condition for symptoms of respiratory discomfort and radiological evidence of recurrence of pleural effusion. Data were collected and analyzed.

3. Results

A total number of 50 patients equally randomized to the two treatment groups for pleurodesis. Patients in both groups were more or less matched as regarding age and sex. More than half of the studied patients in both groups were males (60% and 52% among bleomycin and Viscum groups respectively) with no statistically significant difference Table 1.

Table 1. Demographic distribution of the studied patients and co-morbidity

		Bleomycin group (n=25)		Viscum group (n=25)		P Value
		No.	%	No.	%	
Mean age		52 years(±0.9)		54 years(±1.3)		NS (0.8)
Sex (Male)		15	60%	13	52%	NS (0.4)
DM		3	12%	2	8%	NS (0.3)
Hypertension		3	12%	2	8%	NS (0.3)
Chronic liver disease		2	8%	1	4%	NS (0.19)
Chronic renal disease		1	4%	1	4%	NS
Presenting symptom						
	Dyspnea	25	100%	25	100%	NS
	Cough	25	100%	25	100%	NS
	Sleeplessness	23	92%	22	88%	NS (0.8)
	Loss of appetite	20	80%	20	80%	NS
	Easy fatigability	7	28%	6	24%	NS (0.9)

Most of the studied patients in both study groups have no co-morbid diseases. The most common diseases were diabetes mellitus and hypertension. About 8-12% of the patients in both groups were either diabetics or hypertensive with no significant difference, dyspnea and cough was evident among all patients in both groups at time of presentation Table 1.

The most common malignancies among the studied patients as an average were breast cancer (32%), bronchogenic carcinoma (18%), and mesothelioma (14%). No statistically significant difference was reported between both groups, except as regard the renal cell carcinoma group was significantly higher in the bleomycin group, detail pathology presented in Table 2.

Table 2. Studied patients according to primary malignancy

Pathological Diagnosis	Bleomycin group . %	Viscum group %	P Value
Breast cancer	28%	36%	0.16
Bronchogenic carcinoma	16%	20%	0.27
Mesothelioma	16%	12%	0.29
Renal cell carcinoma	12%	4%	P < 0.001
Hepatocellular carcinoma	8%	4%	0.19
Lymphoma	4%	4%	NS
Uterine carcinoma	8%	8%	NS
Bladder carcinoma	4%	8%	0.19
Ovarian carcinoma	4%	4%	NS

Before pleurodesis all patients have been subjected to thoracentesis at least once. But the percentage of patients that had thoracentesis twice were (44% and 36% among bleomycin and Viscum groups respectively), no statistically significant difference was reported between both groups as regard numbers of thoracentesis setting before pleurodesis.

Regarding history of previous surgery there is no statistically significant difference between both groups. The most common surgery was mastectomy that was performed among 32% of the studied patients Table 3.

Two (8%) patients in the bleomycin group had fever, while only one (4%) had fever in the Viscum group, as regards pain only two (8%) patients suffered of pain in the bleomycin group but no one in the Viscum group had pain, and in those patients narcotics were given for pain control.

Most of the patients among both groups showed complete remission defined as no effusion detected within four weeks of pleurodesis (72% and 52% among bleomycin and Viscum groups respectively). But there were higher success rate among the Bleomycin group with statistically significant difference. Regarding number of patients showing no success was more among Viscum group 28% versus 8% in bleomycin group with significant difference Table 4.

Table 3. Tumor therapy prior to pleurodesis

Tumor therapy before pleurodesis	Subcategory	Bleomycin group (n= 25)		Viscum group (n=25)		P Value
		No.	%	No.	%	
Radiotherapy		5	20%	4	16%	0.3
Chemotherapy		13	52%	15	60%	0.4
Surgical management						
	Mastectomy	7	28%	9	36%	0.7
	Nephrectomy	2	8%	1	4%	0.3
	Cystectomy	1	4%	1	4%	NS
	Hysterectomy	2	8%	2	8%	NS

Table 4. Outcome of pleurodesis

Outcome (after 4 weeks)	Bleomycin group		Viscum group		P Value
	No.	%	No.	%	
Complete remission	18	72%	13	52%	P < 0.003
Partial remission	5	20%	5	20%	NS
No success	2	8%	7	28%	P < 0.001
Mean hospital stay	(6.2) 6days(±0.8)		(12.6) 12days(±1.2)		P < 0.006

Among our patients we found that the period of hospital stay was shorter in patients of the bleomycin group with a mean of (6.2) days but those of the Viscum group had hospital stay of (12.6) days showing significant statistical difference Table 4.

4. Discussion

Malignant pleural effusion is considered an indicator of advanced disease with a poor prognosis, and with rare chance of long term survival. Palliative treatment includes repeated thoracentesis, catheter thoracostomy with sclerotherapy, or rarely pleuro-peritoneal shunt creation [1,2,3,4,5].

Treatment options for malignant pleural effusions are determined by the symptoms and performance status of the patient, the primary tumor and its response to systemic therapy, lung re-expansion after pleural fluid evacuation, and expected survival [2,3,5].

The present study was conducted aiming at describing the difference in the efficacy of pleurodesis between Mistletoe versus Bleomycin in management of patients with malignant pleural effusion in Suez Canal University hospital.

A total of 50 patients with malignant pleural effusion were enrolled in the study after meeting our inclusion and exclusion criteria. They were equally randomized to one

of two treatment groups for pleurodesis. The first group was subjected to intra-pleural instillation of bleomycin while in the second group Viscum album was used.

Traditionally, the most common approach for a persistent, recurrent malignant effusion has been large-bore chest tube drainage followed by instillation of a sclerosing agent, Chemical pleurodesis is a palliative treatment intended to obliterate the pleural space. A previous systematic review by **Walker-Renard and othe**rs [5] and **Rodriguez-Panadero** [4] for patients with recurrent, symptomatic, malignant pleural effusions treated with chemical pleurodesis showed that tetracycline, doxycycline, bleomycin, and talc have been the agents most commonly used to produce pleurodesis. Among our patients in the bleomycin group the mean age was 52 years with (60%) men. While in the study of **Ruckdeschel JC and colleague*s*** [6], the mean age for patients in bleomycin group was 61 years with 17 men (44%) and 21 women (56%). While mean age among bleomycin group in the study of ***Zimmer and colleagues [7]*** was 68 years, and in the study held by ***Diacon and colleagues*** [8] in a total of 31 patients was 69.3 years.

Dyspnea and cough were evident among all our patients at time of presentation, while the least common presenting symptom was easy fatigability (28%). ***Zimmer and colleague*** [7] reported that the most common presentation of their patients is gradual onset of dyspnea and 30% had bilateral effusion. While according to ***Ruckdeschel and colleagues*** [6] over three-fourths of their patients were presented with dyspnea, also ***Patz and colleagues*** [10] reported that most of their patients present with progressive dyspnea, cough, or chest pain that compromises their quality of life.

Among our patients the most common malignancies in the bleomycin group were breast cancer (28%), bronchogenic carcinoma (16%), mesothelioma (16%), renal cell carcinoma (12%) and (24%) of other primary tumor. And also in the study of ***Patz and colleagues*** [10]. Twenty patients (38%) had breast carcinoma, (15%) had lung carcinoma, and (10%) had ovarian carcinoma. So regarding type of primary malignancy, breast cancer was the commonest primary malignancy followed by bronchogenic carcinoma in our study and the study of ***Patz and colleague*** [10]. While in the study of ***Ruckdeschel JC and colleagues*** [6] bronchogenic carcinoma patients were (34%), more than breast cancer patients, but this reflects that these types of tumors are the most common types causing malignant pleural effusion.

Regarding history of previous surgery, the most common surgery in our study was mastectomy that was performed in 28% of the studied patients. While the most common form of tumor therapy performed for our studied patients prior to pleurodesis was chemotherapy (52% among bleomycin groups).

Complete remission is defined as there is no pleural effusion four weeks from the pleurodesis, partial remission is defined as recurrence of pleural effusion within four weeks after pleurodesis that did not required further interference neither tube thoracostomy nor thoracentesis, failure or no response if no change had happened and if the patient still need further interference despite pleurodesis [4,5,6,10]. According to ***Patz and colleagues*** [10] none of their patients had systemic chemotherapy immediately prior to or during the 30-day interval following sclerotherapy, while 68% of the patients in ***Ruckdeschel and colleagues*** [6] study had previous surgery prior to pleurodesis, 42% had previous irradiation but not during the last two weeks before pleurodesis, and 45% had chemotherapy. Most of the other published papers of all previous studies give no idea about history of previous tumor therapy prior to or after pleurodesis, however this is an important issue as surgery, and irradiation and/or chemotherapy have an impact on the prognosis of the disease and the general condition of the patient. For each of our patients, an ntercostal tube-sized 32fr. was inserted in 5th intercostal space mid-axillary line under local anesthesia in both groups for gradual evacuation. Pleurodesis was done when there is less than 100mls drainage per day, a chest X-ray is performed to ascertain whether the pleural effusion has resolved or not. Among our patients we found that the period of hospital stay was shorter in patients of the bleomycin group with a mean of (6.2) day. Chest tubes were removed within 5 days in 79% of patients in the study of ***Patz and colleagues [10]*** (mean, 4.6 days; range, 2 to 11 days). According to ***Zimmer and colleague*** [7], the mean hospital stay was 6.5 days among bleomycin group, while in ***Diacon and colleagues*** [8] study the mean hospital stay in bleomycin group was 7.7 days.

The period of hospital stay in most patients in all studies were in the range of 5 days to 1 week reflecting the short hospital stay, when combined to high efficacy, total costs in most of the previous studies favored bleomycin pleurodesis, as the main cost-driving factor, was the shorter time spent in the hospital.

Most of our patients showed complete remission defined as no effusion detected within four weeks of pleurodesis (72% among bleomycin groups), with 8% failure rate. The success rate in our study is higher than ***Patz and colleagues*** [19] among the patients in bleomycin group, this may be due to our good patient selection as we have excluded severely ill patients, patient with encysted pleural effusion and patients with associated pleural thickening.

Mistletoe extracts are commonly used in cancer patients; review of 16 trials investigating the efficacy of mistletoe extracts in cancer patients claimed that they improve quality of life (QOL), psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy [13,16].

In healthy adults increasing numbers of blood granulocytes were noted after application of a lectin-rich mistletoe preparation, as well as an increased production of granulocyte-macrophage colony-stimulating factor (GMCSF) [23,24], and the induction of tumor necrosis factor- alpha (TNF-alpha) [22]. There is clear evidence that the application of mistletoe extracts induced IgG anti-lectin antibodies [19,20,21,22].

Mistletoe preparations (Viscum album L.) were used for pleurodesis and found to be of low side effects and simple in administration [18,19]. Lectin induce apoptosis, the natural cell death, viscotoxins lead to cell lyses so that the local treatment not only aims to induce pleurodesis but also to treat the malignant disease itself [18,19,20].

Kim and colleagues [18] compared Viscum album with doxycycline for pleurodesis in patients with malignant pleural effusion in the Internal Department of the University Hospital Seoul, Korea.

According to ***Kim and colleagues*** [18] 30 patients with malignant pleural effusions with the following primary tumors: lung cancer (23 patients) (77%), breast cancer (4 patients) (13%), cancer of uterine cervix, gastric cancer and unknown primary cancer (1 patient each) were included in the study , and in the translated published paper they give no data about sex and age groups of the patients.

But in our own study we had 25 patients in the Viscum group, 13 men (52%) and with mean age of (55) years. among our Viscum group we had (36%) with breast cancer, (20%) with bronchogenic carcinoma, (12%) with mesothelioma.

When we came to compare their results to ours we found that the success rate according to ***Kim and colleagues*** [18] was 81 % of the patients treated with Viscum showing a complete response, while it was 52 % of the patients in our study.

As regard the post pleurodesis side effects, (8%) of the patients in the bleomycin group had fever and at the same percentage others had pain, which is similar to other study as **Ruckdeschel JC and colleague*s*** [6], reported that (9%) of his patients in the bleomycin group had fever and (7%) had pain, mean while the only side effect in the Viscum group was fever in one patient (4%) and no one had pain. If we reviewed the results of other studies we will find that it differs greatly from one to other as Sahn SA [3] in his review reported that lung cancer is the most common cause of malignant effusion, dyspnea and cough were the most common presentation, talc poudrage or slurry was the most successful, but fever and pain was a common post instillation complaint, F. Rodriguez-Panadero [25] reported in another study that talc instillation some time is associated with high incidence of failure due to activation of fibrinolysis process and Harrison LH Jr [26] said it should be avoided in some **cases.** Although bleomycin appears to be effective in clinical practice, its main drawbacks are cost and systemic absorption, with risk of significant toxicity [6,7,12]. Antony and others used tetracycline and proved to be effective but its parenteral form is no longer available and the remaining stock is decreasing rapidly, and it had high incidence of post instillation pain and some times fever requires heavy analgesia [5,11,12]. Moreover, a relatively high rate of late recurrences has been reported [4]. While the alternative of tetracycline; the Doxycycline, has average effectiveness of 72% but it often requires repeated doses, sometimes for more than 2 weeks, which is seen as a drawback and high incidence of local chest pain after instillation [9,10]. **Balassoulis G et al**., reported a complete response was seen in (48%) patients, a partial response was seen in (31%), and (21%) patients did not respond to pleurodesis by Erythromycin which is also is another newly used agent. Also he denoted that chemical pleurodesis can be palliative for symptomatic malignant pleural effusions, and the extent of the successful is a function of tumor bulk, pleural fluid pH, and the choice of sclerosing agent [27]. Sahn SA [3] reported that thirty percent of non responder had a pleural fluid PH < 7.3, and we should mention that other studies [28,29] highlighted the importance of the PH of the effusion as one of the factors that determine the efficacy and the response, but unfortunately we did not include this issue in our study and this should be considered as one of its limitation. At last we should clear that although mistletoe is considered as an agent with anticancer property, its result is a little bit lower than the bleomycin, and it seams that the hypothesis reported by lynch TJ [2] that the effectiveness of a chemical sclerosing agent in pleurodesis is related to the ability to produce pleuritis rather than its antitumor effect.

In summary: pleural effusions still have a significant negative draw back on the quality of life in patients with malignancy. Therapy in these patients should be simple, safe, efficacious, and cost-effective, while minimizing the over all hospital stay. Chemical pleurodesis has become a common palliative approach and effective with a variety of agents. Both agents used in our study are effective in pleurodesis with comparable effect. However bleomycin has the upper hand regarding incidence of complete remission with statistically significant result, and it showed nearly the same universal results of the many previous studies and with shorter hospital stay.

5. Conclusion

Both bleomycin and Viscum album are effective and safe agents for chemical pleurodesis, **Bleomycin** has some advantages over Viscum album due to its lower incidence of failure, and being more economic and for the shorter hospital stay. **Viscum** has satisfactory over all results (complete and partial remission in 72%), it has a higher rate of failure and need repeated instillation than with bleomycin.

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