The outcome of Pleurodesis in Malignant Pleural Effusion

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Waleed M. Hussen*  FIBMS (ThCVS), FACS, MRCS, FRCS (Glasgow)
Ali H. Said** FIBMS (ThCVS)
Osama Elhassani** FIBMS, CABA & IC (Anesthesia)

Abstract:
Background: Accumulation of fluid in the pleural space, which is malignant in nature, is secondary to lung, breast or ovarian tumors. Malignant effusion secondary to metastatic Adeno Ca is most commonly seen in males and breast Ca is most commonly seen in females. It indicates advanced disease and reduced survival.

Objectives: Is to study prospectively the outcome of pleurodesis in thirty patients with malignant pleural effusion by using two different agents Bleomycin and Talc.

Patient and methods: Data of thirty patients with malignant pleural effusion collected and analyzed using a form to categorize them according to their age, gender, presenting features, imaging studies and procedure performed to drain the fluid and to arrange chemical pleurodesis.

Results: Eighteen patients were male; twelve patients were female in a ratio of 1.5:1. The youngest was 52 years old while the oldest was 81 years old. The mean age was 65.8 ±7.34. Cough and dyspnea were the most frequent presenting features. Imaging studies showed that seven patients had definite effusion with an underlying mass. Eight patients had right sided effusion with an underlying mass while the remaining eleven patients had effusion only. Twenty patients received (Talc) and ten patients received Bleomycin with comparable recurrence rate of the effusion, in seven patients out of 20 in Talc (35%) and in three out of 10 patients receiving Bleomycin (30%).

Conclusion: Both (Talc and Bleomycin) can be used with comparable results and recurrence

Key words: pleurodesis, malignant effusion, Bleomycin, Talc

Introduction:
Malignant pleural effusion (PE) 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 PE. Other common causes include pleural mesothelioma and lymphoma. [1] Neoplasms of the lung, breast, ovary, and lymphomas constitute more than 75% of cases of malignant PE [2]. Metastatic adenocarcinoma is the most common type. Lung cancer in male patients. Breast cancer in female are the most common underlying cause. A positive pleural effusion for malignant disease reflects an advanced stage and inoperability for surgery. Involvement of the lymphatic drainage system by malignancy is the primary mechanism by which pleural metastases cause PE. This leads to the accumulation of the fluid which normally leaves the pleural space [3] Signs and symptoms of a PE vary depending on the underlying disease, but dyspnea, cough, and pleuritic chest pain are common. Chest X-ray usually confirms the presence of a PE, but if doubt exists, ultrasound or computed tomography (CT) scans are definitive for detecting small effusions and for differentiating pleural fluid from pleural thickening. [4] Except for patients with obvious heart failure, thoracentesis should be performed in all patients with more than a minimal PE of unknown origin (i.e., larger than 1 cm height on lateral decubitus radiograph, ultrasound, or CT). Analysis of the pleural fluid yields valuable diagnostic information or definitively establishes the cause of the PE. [5]. Cytology is positive in approximately 60 percent of malignant PE [6]. CT findings suggestive of malignant disease are the presence of pleural nodules or nodular

*Corresponding Author: College of Medicine, University of Baghdad and Medical City Teaching Complex. Email dr.waledmustafa@yahoo.com
**Medical City Teaching Hospital
Alihagabe10@gmail.com
drjalhassani@yahoo.com
pleural thickening, or infiltration of the chest wall or diaphragm. Positron emission tomography seems promising for differentiating between benign and malignant pleural diseases (sensitivity 97 % and specificity 88.5 % in one study) [7]. 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 is name pleurodesis. Many agents have been described for chemical pleurodesis including Talc powder, Bleomycin, tetracycline, doxycycline, silver nitrate, iodopovidone, quinacrine, interferons, interleukin 2, and several chemotherapeutics [8] Bleomycin is the most widely administered antineoplastic agent with a success rate of 60–80%. Tetracycline and doxycycline are also commonly used for pleurodesis and have similar clinical success rates, although they are associated with intense pleuritic pain [9]. Talc, although talc is the most effective pleurodesant, it is not without complications with rare reports indicating that the incidence of acute respiratory distress syndrome (ARDS) can be as high as 1–9% due to intense pleuritis [10]

Patients and Methods:
Study type and setting: A prospective study of thirty patients who were referred to the Thoracic and Vascular Department of the Surgical Subspecialties Hospital (Ghazi Al-Hariri Hospital) with malignant PE, for chemical pleurodesis, or admitted to the Department with Pleural effusion, cytology of which turned to be malignant in nature so planned for pleurodesis.
Study design: the data were taken from the patients’ files, and analyzed in relation to age, gender, presenting features, imaging (ultrasound, chest X-ray, and computerized tomography), procedure performed and the results of the obtained cytology.
Study period: the data were collected for a period of seven months, from the first of February 2019 until 31 August 2019.
Ethical considerations: The study was approved by the Iraqi Board for Medical Specializations in Thoracic and Cardiovascular Surgery. All participants were informed about the study and a verbal consent was taken from each one of them or their families if they were unable to do it.

Interventional Methods: The pleural effusion was drained by tube thoracostomy under local anesthesia in the safety triangle, in the surgical ward or the theater, by aseptic condition by the senior residents or on call surgeon. The patients were kept in the ward until all the fluid was drained or were discharged with drain in place till full drainage. After total evacuation was achieved . The pleurodesis considered and usually done with sclerosant agents. We used Bleomycin (30mg in 50 cc normal saline) and talc (3g diluted in 50cc normal saline and xylocaine added for pain relief ). The tube was clamped for 4-6 hours, de-clamped for 4-6 hours under suction then the tube is removed, and patient is discharged home.

Statistical analysis:
Data management was done by the use of IBM® SPSS® (Statistical Package for the Social Sciences) Statistics Version 23. The Chi-square was used for analyzing categorical data, and the independent samples T-test was used for numerical and normally distributed data. The Binary logistic regression model was used for predicting odd’s ratio for recurrent PE. All analyses were done with 95% confidence intervals (CI). P-values less than 0.05 were considered statistically significant.

Results:
There were 18- males representing 60% of the study sample, 12 females (40%) were females. The youngest patient was 52 years old, the oldest patient was 82 years old, both were males .The mean age of the study sample was 65.8 ±7.43 years. The distribution of the study sample according to age and gender is illustrated in Figure (1).
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Table (1): Distribution of the patients by presenting complaint and past medical history of the study group

| Variables             | Number | %   |
|-----------------------|--------|-----|
| Presenting complaint  |        |     |
| Cough and Dyspnea     | 17     | 56.7|
| Dyspnea               | 11     | 36.7|
| Dyspnea and chest pain| 2      | 6.7 |
| Smoking               |        |     |
| Current smoker        | 16     | 53.3|
| Ex-smoker             | 9      | 30.0|
| No                    | 5      | 16.7|

All patients were sent for chest X-ray, U/S, and CT scan, which revealed that 11 (36.7%) had left sided mass and effusion, eight (26.7%) had right sided mass and PE, while the remaining 11 (36.6%) patients showed effusions with no detectable mass by imaging. The ultrasound study revealed that males had slightly lower aspirated fluid compared to females, as males had a mean of 1611.1 ± 699.5 ml, compared to 1700 ± 555.9 ml in females. Lower values were observed in metastatic Adeno Ca (MAC), and the talc group as shown in table (2).

Table (2): distribution of the volume of the pleural fluid aspirated according selected variables

| Variables                      | Talc             | Bleomycin         | P-value |
|--------------------------------|------------------|-------------------|---------|
| Gender                         | Mean ± SD        | Mean ± SD         |         |
| Female                         | 1700 ± 555.9     | 1783.3 ± 767.9    | 0.329   |
| Male                           | 1611.1 ± 699.5   | 1613.5 ± 628.3    |         |
| Histology                      |                  |                   |         |
| SCC                            |                  | 1810.0 ± 744.5    | 0.020*  |
| MAC                            |                  | 1565.0 ±579.7     |         |
| MM                             | 1600**           |                   |         |
| Type of drug used for pleurodesis|                  |                   |         |
| No                             | 1650 ± 610.9     | 1640 ± 721.4      | 0.969** |
| Yes                            |                  |                   |         |
| Recurrence                     |                  |                   |         |
| No                             | 16.7             |                   |         |
| Yes                            | 30.0             |                   |         |

*: Independent samples T-test, **: Chi-square test

Twenty patients received talc injection 66.667% of the study group, while the remaining 10 patients received Bleomycin. The latter group was significantly older, but there was no gender or recurrence risk difference (Table 3).

Table (3): Age, gender and recurrence in relation to drug used for pleurodesis

| Variables     | Talc     | Bleomycin | P-value |
|---------------|----------|-----------|---------|
| Age           | 63.65 ± 5.93 | 70.2 ± 8.47 | 0.020*  |
| Gender        | No. (%)  | No. (%)   |         |
| Male          | 13(56.0) | 5 (50.0)  | 0.774** |
| Female        | 7 (35.0) | 5 (50.0)  |         |
| Recurrence    | No. (%)  | No. (%)   |         |
| No            | 13 (65)  | 7 (35)    | 0.999** |
| Yes           | 7 (35)   | 3 (30)    |         |
Recurrence of effusion after pleurodesis in 10 patients (33.3 %)
Further analysis using binary logistic regression revealed that the recurrence was not related to gender, type of injection, smoking or alcohol consumption. It was inversely correlated with age, with younger patients being more likely to develop recurrence. As shown in Table (4), where the odd’s ratio represents the increasing the risk of recurrence.

Table (4): risk stratification of recurrent pleural effusion after chemical pleurodesis

| Variables       | Odd’s ratio | Lower CI | Upper CI | P-value |
|-----------------|-------------|----------|----------|---------|
| Age             | 0.775       | 0.646    | 0.930    | 0.006   |
| Gender          | 3.408       | 0.458    | 25.366   | 0.231   |
| Talc injection  | 1.034       | 0.129    | 8.312    | 0.975   |
| Smoking/Alcohol*| 0.301       | 0.071    | 1.285    | 0.105   |

Discussion:
The age distribution and the male: female ratio of the patient in the current study contradicts the results of Zakaria (2018) in Iraq who studied 30 cases of malignant PE admitted to Ibn Al- Nafees Teaching Hospital. He reported that most patients were between 50-60 years of age with 60% of them were females; which was attributed to the fact that Al-Amal Hospital(close to ibn al nafess hospital) which contributes to 53.3 % of the patients, referred the majority of advanced breast cancer cases (11). In a study by Nikbaksh et al (2011), studied 51 cases of malignant PE in Iran, and reported that their mean age was 60.3±15.8 years and 62% of them were females, and 40% of cases had breast cancer (12). The Iraqi Cancer Registry reported in 2009 that breast cancer was responsible for 19.6% of the cases of PE followed by bronchogenic cancer that was responsible for 10 % of cases (13). All of our patients suffered from dyspnea, which in 56.7% of the cases was associated with cough, and in 6.7% was associated with chest pain. This was comparable with results of Rafiee et al (2014) in Iran who studied 42 cases with malignant PE, and reported that 90.5% of patients presented with dyspnea (14). Some patients may initially be asymptomatic, but eventually the majority will develop dyspnea, that requires treatment to alleviate symptoms (15). The mean volume of pleural fluid aspirate in our study was 1646.7 ± 637.2 ml, and the amount had no statistically significant differences between genders, histology of tumors, type of drug used for pleurodesis and recurrence. This amount was lower than results of Nikbaksh et al (2011), in which the mean amount of pleural fluid was 2282±848.69 ml, and was not related to outcome of pleurodesis [12]. In another study done by Lumachi et al in Italy (2012), who studied factors affecting the survival of patients having talc pleurodesis, reported the mean volume of PE was 2005.7±1078.9 ml, and that it was not related to the survival of patient (16). Options to relieve dyspnea resulting from malignant PE may include, therapeutic pleural aspiration, drainage and injection of sclerosant agents or thoracotomy. If a sclerosing agent is too used, complete drainage of the PE is very important to increase success rate of the procedure, so the treatment should be tailored for each patient, and the amount is highly individualized, so it is quite difficult to compare between different study populations (17-18). The recurrence rate of malignant PE in our patients who treated with talc was 35%, while for those who treated with Bleomycin it was 30%. The recurrence rate from other studies is shown in the table 5:

Table (5): The recurrence rate in different studies

| Author     | Place/date | Type of sclerosant | Recurrence Rate |
|------------|------------|--------------------|-----------------|
| Diacon et al (19) | Switzerl Land/2000 | Talc vs bleomycin | Talc group (13%) after one month and (13%) after six months Bleomycin group (41%) after one month and (65%) after six months |
| Haddad et al (20) | Brazil/2004 | Talc vs bleomycin | Talc group (9.8%) after one month and (27.8%) after six months Bleomycin group (12.4%) after one month and (32.2%) after six months |
| Saka et al (21) | Japan/2018 | Talc vs bleomycin | Talc group (12%) Bleomycin group (16.7 %) |
| Our study | Iraq/2020 | Talc vs bleomycin | Talc group (35%) Bleomycin group (30%) |

It can be seen from the table above that talc was superior to Bleomycin in reducing recurrence of PE, in the first three studies which was in contradiction to our results. The primary cause for this discordance was the use of Talc powder by video assisted thoracoscopic surgery (VATS) in most of the patients in the studies, which is not a routine procedure in our country. More than quarter of our patients had Ca lung, (26.66%) with unknown primary tumor location, while Zakaria M did not report any case with unknown primaries (11). This could be attributed to the fact that our patients with unknown primary tumor location, then had other
investigations to discover the primary tumor site, and this was comparable with the results of Ebata et al in Japan (2015) who investigated patients presenting with malignant PE as a first cancer diagnosis, and reported that 28.9% had unknown primary, and that malignancy of the lung was the most common primary tumor in those patients after further investigation/surgeries (22). In another study done by Clive et al (2014) multi-center study, the reported details for possible primaries causing malignant PE were breast and lung cancer (23). Post thoracostomy site wound infection, happened in 3 of our patients (10%), while the (Ebata T. et al 2015)(22) showed three patients out of 100 patients (3%) were treated for wound infection.

No mortality was seen in our study which is similar to the results of (Clive AO, et al 2014) (23).

**Conclusion:**
Both (Talc & Bleomycin) can be used with comparable results and recurrence rate.

**Recommendations:**
The future use of VATS with patients, who can tolerate the procedure (plurodesis), allows the increasing use of talc powder and decreases the recurrence rate.

**Conflict of interest:**
None

**Author’s contributions:**
Waled M. Hussen: contributed to study conception, study design, data analysis and interpretation, drafting of the manuscript.
Ali H. Said, Osama Elhassani: contributed to study conception, study design data analysis and interpretation.

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ناتج الالتصاق الجنبي في انصباب الجنب الخبيث

الاستاذ الدكتور وليد مصطفى حسين كلية الطب / جامعة بغداد الجراح الاختصاصي الدكتور علي هاشم سيد مستشفى بغداد التعليمي المختر الاشتاري الدكتور هاشم سيد مستشفى بغداد التعليمي

المقدمة: تراكم السوائل في التجويف الجنبي، وهو خبيث في الطبيعة، ناتوي لأورام الرئة والثدي أو المبيض. يعتبر الورم الغدي النقيلي الأكثر شيوعًا في الذكور وورم الثدي الأكثر شيوعًا في الإناث. إنه يشير إلى تقدم المرض وانخفاض نسبة النجاة.

الهدف: هو الدراسة المستقبلية لثلاثين مريضا يعانون من انصباب الجنبي الخبيث الذي تم أجريا له عملية الالتصاق جنبي كيميائي.

المريض والطرق: تم جمع وتحليل بيانات ثلاثين مريضا يعانون من انصباب جنبي خبيث. تم التخليل باستخدام نموذج تصنيفهم وفقًا لعمرهم ونوع الجنس والعلامات السريرية والتصوير الشعاعي والإجراءات التي تم إجراؤها لسحب السوائل وترتيب الالتصاقات الجبلي الكيميائي.

النتائج: ثمانية عشر مريضا من الذكور. اثنا عشر مريضا من الإناث. كان أصغرهم يبلغ من العمر 52 عامًا وكان الأكبر عمره 81 عامًا. كان متوسط العمر 65.8 ± 7.34. كانت أكثر الاعراض شيوعًا هي السعال وضيق التنفس. أظهرت دراسة التصوير الشعاعي أن أحد عشر مريضا يعانون من انصباب جنبي أيسر مع ورم في الرئة. وكان ثمانية مرضى يعانون من انصباب جنبي ايمن مع ورم في الرئة. بينما كان لدى المرضى المتبقين انصباب فقط تم إجراء عملية الالتصاق الجنبي الكيميائي باستخدام (Talc) لعشرين مريضا وتم إجراء عملية الالتصاق الجنبي الكيميائي باستخدام (Bleomycin) لعشرة مرضى. معدل مقارب لنسبة انصباب عشرين مريضا بينهم.

الخلاصة: إن معدلات التكرر بالانصباب كانت مقارنة في استخدام كل من (Talc & Bleomycin).

مفتاح الكلمات: الالتصاق الجنبي، الاصباب الخبيث، البليومسين، التك