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Malignant pleural effusion biomarkers as predictor for chemical pleurodesis success

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KEYWORDS

MPEs;
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Abstract *Background:* 42–77% of exudative pleural effusions are due to malignant diseases (Marel et al., 1993) [1]. This study aimed to evaluate the value of biochemical parameters of the pleural aspirate in predicting success of chemical pleurodesis in adult patients with malignant pleural effusion.

Patients and methods: This prospective study included 30 adult patients with malignant pleural effusion diagnosed by clinical examination, Chest CT scanning and closed pleurocentesis. Patient ages were mean of 60.4 ± 7.8 years, multiple sessions of closed pleurocentesis were carried out followed by insertion of an intercostal tube. The pleural aspirate was then sent for chemical analysis to detect Glucose, pH, and LDH. Pleurodesis was then done either by using Tetracycline (group A), or Bleomycin (group B). All patients were then followed up for success of the pleurodesis process within one month.

Results: Within one month of follow-up, rates of clinical response to treatment in group A (Tetracycline) were successful in 40%; versus group B (73.3%). Complete response (CR) occurred in group A cases (20%); versus 33.3% in group B; whereas partial response (PR) occurred in 3 cases of group A; versus 6 cases of group B; and treatment failure (TF) occurred in 9 of group A cases versus 4 of group B cases. None of our patients died. Morbidity occurred in the form of mild-to-moderate.

The success of the pleurodesis was closely-associated with higher glucose and pH levels together with a low LDH level in the pleural fluid.

Conclusion: The success of pleurodesis is usually higher when the pleural fluid pH and glucose levels are high & the LDH level is low in MPE.

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Introduction

The visceral pleura (enveloping the entire surface of the lungs), and the parietal pleura (covering the inner surface of the chest

wall, mediastinum and diaphragm); are deficient only at the hilum where the bronchi, pulmonary vessels and nerves enter the lung substance [2].

Although normally, 0.1–0.2 mls/kg/body weight of a plasma ultrafiltrate exist as a thin layer of fluid between the parietal and visceral pleural layers, the rate of turn-over of pleural fluid in humans is rapid and may exceed 1 L/day. And the volume of fluid normally present in the pleural space is small (of the order of 5–15 ml) [3,4].

Pleurodesis, from the Greek pleura and desis (binding together) is intended to achieve a symphysis between parietal and visceral pleura [5]. The most common indication for this procedure is MPEs; less common are pneumothorax and recurrent benign pleural effusions. The methods of pleurodesis include intrapleural instillation of a sclerosant agent, surgical abrasion with a dry gauze sponge and videothoracoscopy. The instillation of sclerosant agent is performed through a conventional large-bore or a more comfortable small – bore chest tube and recently through videothoracoscopy [6–12]. The mechanism of pleurodesis is based on pleural irritation in order to create an inflammatory reaction leading to fibinogenesis [12]. The cellular and molecular mechanisms involved in pleurodesis include the activation of the coagulation cascade of the pleura; fibrin deposition; fibroblast recruitment, activation and proliferation; and collagen deposition [6,14].

About 25% of effusions do not require therapy; the effusions are small and stable. MPEs caused by lymphomas, breast cancer, small cell lung cancer, or ovarian cancer may respond to systemic chemotherapy or hormonal therapy. Repeated percutaneous draining of effusions may lead to tumour growth along the needle track and through the chest wall. Patients who have received extensive prior systemic therapy and those with chemotherapy-resistant tumours, like non-small cell lung cancer, are not likely to respond to systemic therapy [12–15].

Palliative approaches to the management of malignant pleural effusions are necessary in such patients [16]. Patients with symptomatic MPEs whose underlying cancer is unlikely to respond to systemic treatment should have their pleural fluid drained. Patients with relatively large (> 1000 ml) recurrent effusions whose symptoms resolve with drainage and whose lung can fully expand are candidates for palliation. Two general approaches to the palliative management of symptomatic pleural effusions are chest tube drainage with instillation of a sclerosing agent and thoracoscopic drainage of the pleural effusion under local or general anaesthesia with intraoperative sclerosis of the pleural space [15,17].

Aim of Work: The aim of the present study was to evaluate the role of assessing the predictive value of certain biochemical parameters (present in the pleural aspirate) in assessment of the adequacy and efficiency of two pleurodesing agents namely Tetracyclin and Bleomycin which were injected intrapleurally via conventional tube thoracostomy.

Patients and methods

Patient groups

Patient groups included 30 adult patients aged between 45 and 72 years (mean of 60.4 ± 7.8 years). There were 25 smokers (83.3%), and 22 (73.3%) lived within industrial areas. All

patients presented with malignant pleural effusion due to different types of thoracic malignancies that were diagnosed by clinical examination and special investigations (Chest CT scanning and closed pleurocentesis). Patients were categorized into two groups:

- (A) Tetracyclin group: (15 patients).
- (B) Bleomycin group: (15 patients).

Inclusion criteria

Presence of MPEs with: (1) Dyspnoea that improved after large-volume thoracocentesis with subsequent recurrence of a symptomatic pleural effusion. (2) No radiographic evidence of conditions that might prevent lung re-expansion (i.e. visceral pleural entrapment or atelectasis as a result of bronchial occlusion). (3) Pleural fluid cytologic studies or pleural biopsies that are +ve for malignant cells. (4) No endobronchial obstruction; acceptable patient performance status and life expectancy.

Exclusion criteria

Presence of MPEs with: (1) Inability to lie in the lateral decubitus position. (2) Previously attempted, ipsilateral pleurodesis. (3) Any change in the chemotherapy regimen within 4 weeks before the patient entered the study (4) radiation therapy 2 weeks before referral for pleurodesis.

Methodology

Preoperative preparation and patient evaluation

A thorough clinical examination including the patient's history was carried out. Preoperative investigations included plain chest X-rays in different positions, CT of the thorax, in addition to the routine lab tests (full blood picture, blood coagulation, renal and hepatic function tests). In all patients, multiple sessions of closed pleurocentesis were carried out and the pleural aspirate was then sent for chemical analysis. This was followed by insertion of a 28-FG intercostal tube under local anaesthesia in the 6th IC space connected to underwater seal system. When the drainage of the intercostal tube reached ≤ 150 ml/day, pleurodesis was then done either by using Tetracycline (group A = 15 patients), or Bleomycin (group B = 15 patients). All patients were then followed up over one month for success of the pleurodesis process which was declared by clinical, and radiological measures, and when the amount of daily pleural drainage dropped down to 150 ml or less.

Doses

In all patients, intrapleural injection of 10–15 ml 1% lidocaine was done before the instillation of either: (A) tetracyclin as a suspension of 20 mg/kg of tetracycline powder obtained from tetracyclin capsule (maximum of 2 g) in 50 ml of normal saline administered through the tube [18] or (2) Bleomycin as 60 mg (minimum) or 150 mg (maximum) per instillation.

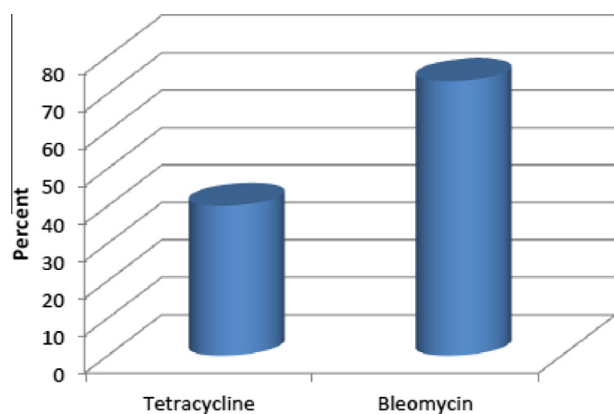


Figure 1 Incidence of clinical success between tetracycline and bleomycin groups.

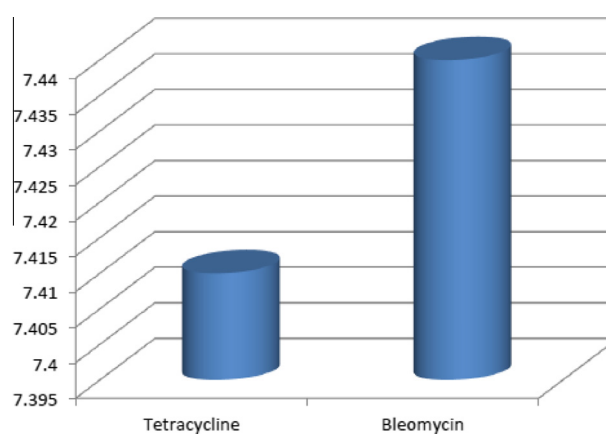


Figure 3 Mean pH between tetracycline and bleomycin groups.

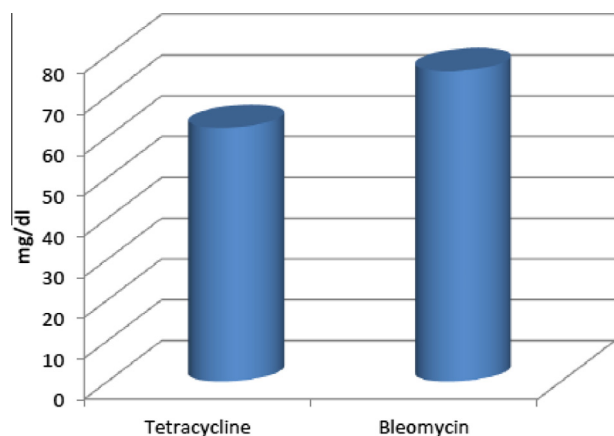


Figure 2 Mean glucose levels (mg/dl) between tetracycline and bleomycin groups.

Criteria of response: [19–21]

Complete response (CR)

No reaccumulation of fluid within the first 30 days as determined by clinical examination & chest X-ray.

Partial response (PR)

Symptomatic, minimal fluid recurrence, not requiring aspiration within the initial 30-day evaluation period.

Treatment failures (TF)

Reaccumulation of pleural fluid necessitating re-aspiration of fluid in less than 30 days.

The chest tube was then clamped and patients were repositioned every 15 min for 2 h to ensure a uniform dispersion of the agents. After 24 h, the tube was connected to 15-cm water suction. It was removed when drainage was < 50 ml/8 h and chest X-ray film indicated full expansion of the lungs.

Special investigations

Determination of pleural fluid pH

The pleural fluid obtained via aspiration by closed thoracocentesis was sent for chemical analysis. One of the parameters measured was the pH which had a role in predicting success of pleurodesis. Pleural fluid was collected for pH determination in a manner analogous to that for arterial blood gases. All samples were collected anaerobically in a syringe rinsed with 0.2 ml of heparin (1:1000) and quickly analysed within 30 min of collection. Pleural fluid pH is stable for at least 2 h using this technique and the reproducibility is + 0.01 pH units [22]. The pleural fluid total protein, LDH and glucose concentrations were determined by standard autoanalyzer techniques [23,24].

Statistical analysis

Data were statistically described in terms of mean \pm standard deviation (\pm SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t* test for independent samples in comparison with normally distributed data and Mann Whitney *U* test for independent samples when data were not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency was less than 5. *p* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The causes of malignant effusion were matched well in the two groups: metastatic adenocarcinoma and equally mesothelioma in 5 cases (33.3%); metastatic squamous cell carcinoma and lymphoma in 2 cases (13.3%); and one case of malignant lymphoma (6.6%) (Table 1).

Within one month of follow-up, the rates of clinical response to treatment in group A (Tetracycline) were successful in 6 cases (40%); versus 11 cases in group B (73.3%). Complete

Table 1 The cause(s) of malignant effusion in the two study groups.

| Cause (s) of malignant effusion | Result (No. & %) | |
|------------------------------------|---------------------------------------|------------------------------------|
| | Grp A (<i>n</i> = 15) (tetracycline) | Grp B (<i>n</i> = 15) (bleomycin) |
| Metastatic adenocarcinoma | 5 (33.3%) | 5 (33.3%) |
| Metastatic squamous cell carcinoma | 2 (13.3%) | 2 (13.3%) |
| Mesothelioma (epithelial) | 5 (33.3%) | 5 (33.3%) |
| Malignant myeloma | 1 (6.6%) | 1 (6.6%) |
| Lymphoma | 2 (13.3%) | 2 (13.3%) |
| Hodgkin | 1 (6.6%) | 1 (6.6%) |
| Non-Hodgkin | 1 (6.6%) | 1 (6.6%) |

Table 2 Treatment response percentage in the two groups.

| Parameter | Result | |
|-----------------------------|-------------------------|----------------------|
| | Grp A (Tetracycline) | Grp B (Bleomycin) |
| Total number of patients | 15 | 15 |
| <i>Clinical outcome</i> | | |
| I. Success% | 6 (40%) | 11 (73.3%) |
| Complete response (CR)% | 3 (20%) | 5 (33.3%) |
| Partial response (PR)% | 3 (20%) | 6 (40%) |
| II. Treatment failure (TF)% | 9 (60%) | 4 (26.6%) |

response (CR) occurred in 3 of group A cases (20%); versus 5 cases (33.3%) of group B; whereas partial response (PR) occurred in 3 cases of group A; versus 6 cases (40%) of group B; and treatment failure (TF) occurred in 9 of group A cases (60%) versus 4 (26.6%) of group B cases (Tables 2 and 3).

The biochemical parameters in the pleural fluid & rates of response in the two study groups are displayed in Table 4.

As for the mortality and the morbidity complications in the two study groups: no mortality occurred in both groups. Morbidity occurred in the form of mild-to-moderate chest pain (lasting only for few days) in 4 of group A cases (26.6%) versus one patient (6.6%) in group B cases. Hyperpyrexia occurred in 3 patients (20%) of group A, versus a single case (6.6%) in group B cases. Nausea and vomiting occurred in 4 patients of group B cases (26.6%) (Table 5).

The statistical comparison concerning the rate of response to the pleurodesis agents used is displayed in Table 6.

Discussion

It has been estimated that up to 15% of lung cancer patients will initially present with a MPE and that as many as 46% will develop a pleural effusion at some point in their disease process. In those with advanced breast cancer, effusions can be seen in half of all patients. The most important symptom associated with MPE is dyspnoea [17]. The traditional approach to MPE has been to attempt obliteration of the pleural space thereby removing the potential space where fluid can accumulate and cause symptoms. This is achieved by introducing a sclerosing agent to the pleural space, stimulating inflammation and fibrosis while maintaining apposition between the visceral and parietal pleural surfaces. Several different sclerosing agents have been used, most commonly talc, tetracycline,

doxycycline, bleomycin and silver nitrate with talc generally felt to be the most effective [14].

The aim of the present study was to evaluate the role of assessing the predictive value of certain biochemical parameters (present in the pleural aspirate) in assessment of the adequacy and efficiency of two pleurodesing agents namely Tetracycline and Bleomycin which were injected intrapleurally via conventional tube thoracostomy. The follow-up period in our study was 30 days and this agreed with a study by Ruckdeschel et al. [25] that stated that future trials should likely assess effectiveness in 60 days rather than 90 days (done in their study) since all reports with more than a handful of patients, including their own comment on the extraordinary rate of systemic progression and death in the first month after initiating therapy. In addition, the vast majority of fluid recurrence is in the first 30 days [26,27].

Tetracycline, the agent used most commonly in the past, is no longer commercially available. At the present time, bleomycin, doxycycline HCl (Vibramycin) or tetracycline HCl (Hostacycline) and talc remain the agents most commonly used [28,29]. Doxycycline has been advocated as a replacement for tetracycline; however, recent reports suggest that up to two thirds of patients will require multiple treatments [30]. This is less than optimal in these patients with limited life expectancy. Few recent trials compared doxycycline to tetracycline as a pleurodesing agent. However, tetracycline has been compared with bleomycin in many recent randomized trials [31]. A statistically significant difference was noted favoring bleomycin, which was effective in 64% compared to only 33% in the tetracycline group. Our study results conformed well to the previous result as clinical success occurred in 11 patients (73.3 3%) who received bleomycin, versus only 6 patients (40%) who took tetracycline. Moreover, treatment failure occurred more with the tetracycline group (9 patients, 60%); versus the bleomycin group (4 patients, 26.6%) [32,33] (see Fig. 1).

The tetracycline derivative doxycycline is an alternative sclerosant with reported success rates of about 80%. Studies differ regarding the influence of tumour type on the success rate of pleurodesis. Some studies report no differences [32].

Twenty-one patients, 12 with normal pleural fluid pH (7.30 or greater) and 9 with low pleural fluid pH (less than 7.30) were treated with tube thoracostomy and intrapleural tetracycline for symptomatic, recurrent pleural effusions. The twenty patients with low-pH malignant effusion had a significantly greater positivity on initial pleural fluid cytologic examination, a shorter mean survival and a poorer response to tetracycline

Table 3 Response of the malignant effusion to the pleurodesing agent.

| Cause of malignant effusion | Response to the pleurodesing agent | | | | | | |
|-----------------------------|------------------------------------|---------------------------------------|----|----|------------------------------------|----|----|
| | No | Grp A (<i>n</i> = 15) (tetracycline) | | | Grp B (<i>n</i> = 15) (bleomycin) | | |
| | | CR | PR | TF | CR | PR | TF |
| Metastatic adenoca | 5 | 1 | 1 | 3 | 2 | 2 | 1 |
| Metastatic Squamous cell ca | 2 | 1 | - | 1 | - | 1 | 1 |
| Mesothelioma (epithelial) | 5 | 1 | 1 | 3 | 2 | 2 | 1 |
| Malignant myeloma | 1 | - | - | 1 | - | 1 | - |
| Lymphoma | 2 | - | 1 | - | 1 | - | - |
| Hodgkin | | - | - | | - | - | 1 |
| Non-Hodgkin | | | | | | | |

I. Success = CR: Complete Response or PR: Partial response. II. Failure = TF: Treatment Failure.

Table 4 Biochemical parameters in the pleural fluid & rate of response in the study groups.

| Cause of malignant effusion | Response to the pleurodesing agent | | | | | | | |
|--|---------------------------------------|------|-----------------|-----------|------------------------------------|------|-----------------|-----------|
| | Grp A (Tetracycline) (<i>n</i> = 15) | | | | Grp B (Bleomycin) (<i>n</i> = 15) | | | |
| | Result | pH | Glucose (mg/dl) | LDH (U/L) | Result | pH | Glucose (mg/dl) | LDH (U/L) |
| <i>Metastatic adenoca (5)</i> | | | | | | | | |
| Patient (1) | CR | 7.41 | 113 | 352 | CR | 7.42 | 120 | 222 |
| Patient (2) | PR | 7.37 | 90 | 330 | CR | 7.43 | 112 | 238 |
| Patient (3) | TF | 7.27 | 48 | 2420 | PR | 7.38 | 68 | 2200 |
| Patient (4) | TF | 7.29 | 50 | 2348 | PR | 7.32 | 55 | 2019 |
| Patient (5) | TF | 7.23 | 49 | 2232 | TF | 7.24 | 45 | 1199 |
| <i>Metastatic Squamous cell ca (2)</i> | | | | | | | | |
| Patient (6) | CR | 7.37 | 110 | 412 | PR | 7.37 | 83 | 320 |
| Patient (7) | TF | 7.28 | 49 | 1100 | TF | 7.23 | 28 | 1117 |
| <i>Mesothelioma (epithelial) (5)</i> | | | | | | | | |
| Patient (8) | CR | 7.43 | 128 | 180 | CR | 7.44 | 122 | 144 |
| Patient (9) | PR | 7.32 | 110 | 390 | CR | 7.45 | 125 | 133 |
| Patient (10) | TF | 7.22 | 33 | 1230 | PR | 7.29 | 102 | 760 |
| Patient (11) | TF | 7.24 | 42 | 2288 | PR | 7.31 | 106 | 910 |
| Patient (12) | TF | 7.27 | 50 | 2104 | TF | 7.21 | 51 | 1521 |
| <i>Malignant myeloma (1)</i> | | | | | | | | |
| Patient (13) | TF | 7.23 | 39 | 2433 | PR | 7.34 | 89 | 236 |
| <i>Lymphoma (2)</i> | | | | | | | | |
| <i>Hogkin</i> | | | | | | | | |
| Patient (14) | PR | 7.33 | 103 | 388 | CR | 7.45 | 113 | 134 |
| <i>Non-Hodgkin</i> | | | | | | | | |
| Patient (15) | TF | 7.23 | 48 | 2100 | TF | 7.26 | 46 | 1498 |

CR: complete response, PR: partial response, TF: treatment failure.

Table 5 Morbidity and mortality complications in the study group.

| Complication | Result (no & % to group cases) | |
|---|---------------------------------------|------------------------------------|
| | Grp A (<i>n</i> = 15) (Tetracycline) | Grp B (<i>n</i> = 15) (Bleomycin) |
| *Mortality | None | None |
| *Morbidity: | 7 (46.6%) | 6 (40%) |
| Chest Pain (mild-moderate for few days) | 4 (26.6%) | 1 (6.6%) |
| Hyperpyrexia | 3 (20%) | 1 (6.6%) |
| Nausea & Vomiting | — | 4 (26.6%) |
| Seizures or Convulsions | — | — |
| No complication(s) | 8 (53.3%) | 9 (60%) |

pleurodesis compared with 40 patients with normal-pH malignant effusions [23]. In our study, similar findings and morbidity complication rate were found.

Before studying the relationship between glucose and pH levels in pleural fluid and their effect on pleurodesis success we should emphasize that according to studies primarily

Table 6 Statistical comparison of the rate of response to the pleurodesis agents used.

| Clinical response | Grp A (n = 15) (tetracycline) | Grp B (n = 15) (bleomycin) | Row totals |
|-------------------|-------------------------------|----------------------------|------------|
| CR | 3 | 5 | 8 |
| Column% | 20 | 33.30 | |
| Row% | 37.5 | 62.50 | |
| Total% | 10 | 16.60 | 26.60 |
| PR | 3 | 6 | 9 |
| Column% | 20 | 40 | |
| Row% | 33.30 | 66.60 | |
| Total% | 10 | 20 | 30 |
| TF | 9 | 4 | 13 |
| Column% | 60 | 26.60 | |
| Row% | 69.20 | 30.70 | |
| Total% | 30 | 13.30 | 43.30 |
| Total | 15 | 15 | 30 |
| Total% | 50 | 50 | 100 |
| Clinical Success% | 6/15 (40%) | 11 (73.3%) | |

$P = 0.40258$ Column: Vertical arrangement of results Row: Horizontal arrangement of results.

published by the group from denver [34,22,35]. The mechanisms that cause pleural fluid glucose and pH to drop are intimately related since glucose metabolism brings about intra-pleural H^+ ion generation and the cells in the pleural fluid as well as those in the lining play an active role in this metabolic process. The abnormal pleural membrane, a result of tumour infiltration and fibrosis appears primarily responsible for Low pH and glucose [36]. There is impaired glucose transfer from blood to pleural fluid and vice versa in patients with low pH but not in normal – pH malignant effusions. Glucose in pleural fluid is metabolized into the end products CO_2 and Lactic acid at a rate similar to normal – pH MPE.

Due to abnormal pleura in patients with low pH effusions, the rate of transport of CO_2 and lactic acid out of pleural space is slowed and accumulation occurs resulting in decreased pleural fluid pH [36,37]. Rodriguez-Panadero and Mejias [40] and Heffner et al. [43] also stated in their studies that pleural fluid glucose and pH correlate very well when the glucose level is < 60 mg/dl ($P < 0.001$). At higher glucose levels, there is poor correlation ($P < 0.05$) (see Fig. 2).

In Group A patients in our study a significant positive correlation was found between pH and glucose levels in pleural fluid that is to say that when the glucose level increased in pleural fluid the pH value also increased and when glucose levels were low, pH values were also low. There was also a significant

negative correlation between glucose levels and LDH value in pleural fluid i.e. as glucose levels increased, LDH values decreased. This meant that the malignant infiltration process of the pleura was less severe (less LDH) resulting in better glucose transfer into the pleural cavity (more glucose in pleural fluid) and better transport of its metabolic products (CO_2 and Lactic acid) thus resulting in higher pH values of pleural fluid (Table 4). As regards Group 2 patients the same correlations were found between glucose, LDH and pH values but were statistically insignificant (Tables 7 and 8, see Figs. 3 and 4).

Bleomycin is the most widely used antineoplastic agent used for pleurodesis with a success rate of 60–80%. Tetracycline, doxycycline and talk are also recommended. A study compared bleomycin with tetracycline and found that both have similar clinical success rates, but tetracycline caused intense pleuritic pain. [38] Jansen JP and his coworkers evaluated talk and found similar results [39].

In our study, the success of the pleurodesis process showed a clear relationship with glucose and pH levels in pleural fluid as in both groups and in all the observed results, more aggressive involvement causing treatment failure (TF), was associated with a very low pH and Glucose value and a markedly-elevated or high LDH result; whereas clinical success (CR, or PR) was found to occur in association with a lower LDH, a higher glucose and pH levels (Table 4). The low

Table 7 Statistical analysis differences in mean and standard deviation of biochemical parameters in pleural aspirate.

| Variables | Grp A (n = 15) (tetracycline) | Grp B (n = 15) (bleomycin) | t-Value | P Value |
|-----------------|-------------------------------|----------------------------|---------|---------|
| Glucose (mg/dl) | | | 1.320* | 0.1614* |
| mean | 62.2 | 76.1 | | |
| SD | 22.12 | 13.2 | | |
| pH | | | −0.452* | 0.5358* |
| mean | 7.410 | 7.44 | | |
| SD | 0.1654 | 0.1431 | | |
| LDH (U/L) | | | −0.689* | 0.5760* |
| mean | 670.22 | 976.1 | | |
| SD | 543.21 | 1045.2 | | |

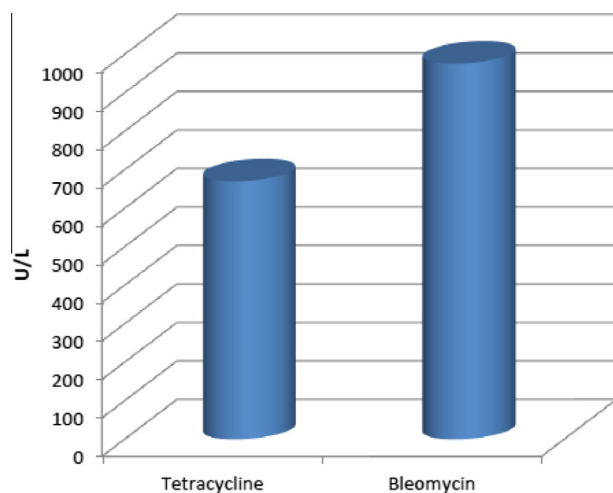
* = No Statistical significance.

Table 8 Pearson product Moment correlation coefficients “*r*” between the different biochemical parameters in the pleural aspirate.

| Variable | Glucose | | pH | | LDH | |
|-----------------|-----------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | Grp A | Grp B | Grp A | Grp B | Grp A | Grp B |
| Glucose (mg/dl) | $r = 1.000$ $P = -$ | $r = 1.000$ $P = -$ | $r = 0.4814$ $P = 0.016$ | $r = 0.0332^*$ $P = 0.813^*$ | $r = 0.5422^*$ $P = 0.044^*$ | $r = 0.1372^*$ $P = 0.054^*$ |
| pH | $r = 0.5916^*$ $P = -0.0332^*$ | $r = 0.9817^*$ $P = 0.017^*$ | $r = 1.000$ $P = -$ | $r = 1.000$ $P = -$ | $r = .7814^*$ $P = .005^*$ | $r = .0852^*$ $P = .916^*$ |
| LDH (U/L) | $r = -.5422^*$ $P = .022^*$ | $r = .1372^*$ $P = .635^*$ | $r = .6724^*$ $P = .0741^*$ | $r = -.7815^*$ $P = .055^*$ | $r = 1.000$ $P = -$ | $r = 1.000$ $P = -$ |

r = Correlation coefficient.

* Significance.

**Figure 4** Mean LDH levels (U/L) between tetracycline and bleomycin groups.

glucose level despite high pH in some patients could be explained by the study by Rodriguez-Panadero and Mejias [40] who found that estimated pleural fluid volume had a greater influence on glucose levels than on pH values and this finding may be due to an increase in glucose consumption of fluid cells whether they are malignant or not [40].

A study by Nikbakhsh et al. [41] shows that pleurodesis with bleomycin has improved the symptoms of 88% of the 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.

The results of our study, thus, indicate that pleurodesis success is much more liable if pleural fluid pH is > 7.30 and pleural glucose levels are > 60 mg/dl. Below these values, pleurodesis failure is common. Several studies reported conforming results such as Rodriguez-Panadero and Mejias [40] and Heffner et al. [43], who attempted pleurodesis in 62 patients having MPEs evaluated after a month. They stated that these findings were the consequence of the close relationship found between low pleural glucose and pH levels and the extension of lesions observed during follow-up [40].

In a study by Sanchez-Armengol and Rodriguez-Panadero [42], 64 patients with MPE of different aetiology were subjected to thoracoscopic pleurodesis. Out of these 5 patients had glucose level < 60 mg/dl and pH < 7.20 . The results of pleurodesis were 3 partial responses (PR) and 2 failures (F); a success rate of 60%. 59 patients had a glucose level > 60 mg/dl and pH > 7.20 . The results of pleurodesis were 46 CR, 100 PR and 3 TFs; a success rate of 94.9%. These results are also in agreement with the results of our study. Results from previous studies suggest that physiologic measurements such as pleural fluid pH and glucose levels and morphologic measures of disease progression such as those determined during thoracoscopic exploration of the pleura are indicative of prognosis. In 1988, for example Sahn and Good [23] demonstrated the prognostic importance of pleural fluid pH and survival in patients with malignant pleural effusions. Mean survival was only 2 months if pleural fluid pH was < 7.30 , whereas mean survival was 10 months if pleural fluid pH was > 7.30 . A significant association between both pleural fluid pH and glucose and survival was noted by Rodriguez and Lopez [40–43]. Patients with pleural fluid pH < 7.30 had a mean survival of only 2 months, compared to 5 months if pleural pH was > 7.30 . In addition, patients with pleural fluid pH < 7.30 and pleural fluid glucose < 60 mg/dl had a shorter mean survival than patients with higher pH and glucose values (1.4 months VS 5.4 months respectively).

Conclusion

The success rate of pleurodesis should be assessed in relation to biochemical parameters such as LDH in pleural fluid in addition to pH and Glucose level as in patients with MPE, the success of pleurodesis is usually higher when the pleural fluid pH and glucose levels are high, and the LDH level is low. A low pH, and glucose level, and a high LDH in MPEs have a poorer outcome of pleurodesis.

Conflict of interest

We have no conflict of interest to declare.

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