Study of pleurodesis using ethanolamine oleate through ultrasound-guided pigtail
Adel M. Saeeeda, Tamer M. Alia, Ashraf A. Gomaaa, Mohamed N. Kamelb

Background  Malignant pleural effusion (MPE) is a common and serious condition that is associated with poor quality of life, morbidity and mortality.

Aim  Study of pleurodesis using ethanolamine oleate (ETH) through ultrasound-guided pigtail to evaluate the efficacy and complications of ETH and pigtail.

Design  Thirty-three patients with MPE were included and were subjected to history taking, clinical examination, chest radiographs (on admission, every day before pleurodesis to ensure complete lung expansion and to exclude pneumothorax, every day after pleurodesis till the removal of the catheter and on follow-up – 2 months after pleurodesis – to check for reaccumulation of pleural effusion), chest sonography, pleural tapping, chest computed tomography scan (in some patients), pleural biopsy using Abram's needle or through ultrasonography (in some cases), lymph node biopsy (in some cases) and spirometry before and 2 months after pleurodesis. Patients were subjected to pigtail catheter insertion using chest sonography. When the amount of effusion became less than 100 ml/day and when the chest radiography shows complete lung expansion and there is no evidence of bronchopleural fistula, pleurodesis with ETH was done. Then after 12 h, the pigtail was connected to a drainage device. Follow-up radiographs were done every day till the removal of the catheter. When the amount of the effusion became less than 100 ml/day, the catheter was removed. Assessment of the response was made after 2 months of pleurodesis. Patients were subjected to pigtail catheter removal of the catheter and on follow-up – 2 months after pleurodesis – to check for reaccumulation of pleural effusion.

Results  Complete response was 81.8% by CXR and chest ultrasound. The results of the study of Teixeira et al. [5] suggest that it is ETH itself that produces pleural fibrosis.

Conclusion  ETH injection through pigtail was safe and effective in pleurodesis of MPE.

Introduction  Despite the progress in cancer treatment, the management of malignant pleural effusion (MPE) remains palliative, with median survival ranging from 3 to 12 months [1]. The use of thoracic ultrasound in every day practice has enhanced the diagnosis of MPE and assisted in the refinement of pleural procedures [2]. Recently, the use of pigtail catheter (flexible and small bore) has emerged as an effective alternative for thoracostomy and pleural drainage. Being a less-traumatic procedure, this method creates less pain and smaller scars during and after the placement and possibly fewer procedure-associated complications [3].

Ethanolamine oleate might be a useful agent for producing pleurodesis. This agent has been used extensively as a sclerosing agent for the sclerotherapy for esophageal varices and varicose veins in the legs. Since it has been diluted with both saline and glucose in these applications, sclerosing therapy has been used for the treatment of esophageal varices and varicose leg veins since 1939 [4]. The results of the study of Teixeira et al. [5] suggest that it is ETH itself that produces pleural fibrosis.

Moreover, Salem [6] concluded that ethanolamine oleate pleurodesis through large-bore chest tube is a safe and effective method with low complication rates.

Aim  Study of pleurodesis using ethanolamine oleate through ultrasound-guided pigtail to evaluate the efficacy and possible complications of ethanolamine oleate and pigtail.

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Patients and methods

Patients
This study was conducted on 33 patients with pleural effusion admitted to Abbasia Chest Hospital since September 2014 to December 2016, in which they were diagnosed as MPE. They were subjected to the following:

(1) Full history taking with general and local chest examinations.
(2) Chest radiographs: on admission, every day before pleurodesis to ensure complete lung expansion and to exclude pneumothorax, every day after pleurodesis till the removal of the catheter and on follow-up (2 months after pleurodesis) to check for reaccumulation of pleural effusion (posteroanterior and lateral views).
(3) Complete blood picture (to exclude severe anemia, leukopenia, and thrombocytopenia), liver function tests and renal function tests (to exclude advanced liver and/or renal diseases), coagulation profile (to exclude any bleeding tendency).
(4) Pelvi-abdominal sonography (to exclude patients with liver cirrhosis and to search for primary malignancy or metastasis), chest sonography.
(5) Pleural tapping and the aspirated fluid was sent for chemical and cytological examinations, no need for bacteriological assessment.
(6) Chest computed tomography (CT) scan was done in some patients to detect pleural thickening or the underlying masses (cytology, Abrams and lymph node biopsy did not require CT before, but if the patient was not diagnosed by the previous methods CT was done to detect pleural thickness for ultrasound-guided biopsy).
(7) Pleural biopsy using Abram’s needle or through ultrasonography was done in some cases in Abbasia Chest Hospital and was sent for histopathological examination.
(8) Lymph node biopsy was done in some cases and sent for histopathological examination (axillary lymph node excisional biopsy was done outside Abbasia Chest Hospital and the slides were re-examined in the Pathology Laboratory in Abbasia Chest Hospital).
(9) Spirometry just before pleurodesis (after fluid drainage and complete lung expansion) and 2 months after pleurodesis.

Inclusion criteria
Simple, free and reaccumulating pleural effusion (e.g. MPE).

Patients with one or more of the following were excluded from the study:
Terminal cases, failure of the lung to expand after tube thoracotomy, bleeding tendency proved by partial time, partial thromboplastin time, and clotting time, advanced liver and/or renal diseases, bone marrow depression (severe anemia, leukopenia thrombocytopenia), bronchopleural fistula, presence of trabeculations, tuberculosis pleural effusion, and empyema.

Methods
Patients with MPEs as diagnosed by cytological or histopathological examination in Abbasia Chest Hospital since September 2014 to December 2016 were subjected to the following:

(1) Chest sonography:
Thoracic sonography can show loculations or residual fluid due to tube malfunctioning, which could impair the efficacy of the sclerosing agent, and guided thoracentesis. Indeed, the presence of loculated effusions is regarded as one of the main factors determining the failure of pleurodesis [7]. Chest sonography has been reported to be very sensitive in identifying the presence of residual pleural effusions, allowing very small volumes of pleural fluid to be detected. Such sensitivity and the possibility of being easily performed at the bedside make chest sonography the first-choice technique for evaluation and monitoring of pleural effusions [8].

(2) Pigtail catheter insertion using chest ultrasonography – pigtail size: 8.5–14 F; method of pigtail insertion: the trocar technique for image-guided drainage procedures is performed by direct puncture of the fluid collection using a trocar needle and insertion of a catheter. The trocar is removed after the catheter position has been optimized under image guidance [9].

When the amount of effusion became less than 100 ml/24 h and when the chest radiography shows complete lung expansion and there is no evidence of bronchopleural fistula, pleurodesis with ethanolamine oleate (ETH) was done according to Miller and Sahn [10]: 0.6 ml atropine sulfate intramuscular 30 min before the procedures, Analgesia: ketoprofen 100 mg, intramuscular, 30 min before the procedures, with intrapleural injection of 25 ml of ETH and 10 ml xylocaine 2%. Closure of the pigtail catheter: the patient was turned to the supine, prone right and left lateral decubitus and sitting positions so that ETH...
comes in contact with all pleural surfaces. The patient will be kept in each position for 15 min.
(a) After 12 h from the injection, the pigtail was connected to a drainage device (urine collecting bag).
The urinary collection bag or the urosac functions on the same principle as the specially designed chest drainage bags, and therefore can be used as a cheap and easily available substitute. Urosac used as a chest drainage bag has been shown to be a safe, effective, and economical alternative in several studies [11].
(b) Follow-up radiographs were done every 24 h till the removal of the catheter.
(c) When the amount of the effusion became less than 100 ml/24 h, the catheter was removed.

(3) Assessment of the response (after 2 months of pleurodesis).
According to Foresti [12] and Seaton et al. [13], the effectiveness of pleurodesis was assessed as follows:
(a) Complete response (CR: total resolution of pleural effusion).
(b) Partial response (PR: formation of asymptomatic loculated effusion).
(c) No response: (NR: reaccumulation of pleural effusion to the amount seen at presentation).

Data management and analysis
The collected data was revised, coded, tabulated, and introduced to a PC using statistical package for the social sciences (SPSS 15.0.1 for Windows; SPSS Inc., Chicago, Illinois, USA). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics
(1) Mean±SD, and range for parametric numerical data, while median was used for nonparametric numerical data.
(2) Frequency and percentage of non-numerical data.

Analytical statistics
(1) Student's t-test was used to assess the statistical significance of the difference between two study group means.
(2) Mann–Whitney U-test was used to assess the statistical significance of the difference of a nonparametric variable between two study groups.
(3) Fisher’s exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.
(4) Paired t-test was used to assess the statistical significance of the difference between two means measured twice for the same study group.
(5) Wilcoxon signed rank test was used to assess the statistical significance of the difference of a nonparametric numerical variable measured twice for the same study group.

P-value: level of significance
(1) P value of more than 0.05: nonsignificant.
(2) P value of less than 0.05: significant.
(3) P value of less than 0.01: highly significant.

Results
Patients with right pleural effusion were 18 (54.5%) patients, while patients with left pleural effusion were 15 (45.5%) patients.
CR was 81.8% of study cases while NR/PR was 18.2% of the study cases (Table 1).
Patients having mesothelioma (diagnosed by pleural biopsy by Abrams or through ultrasound-guided biopsy) were 16 (48.5%), while patients having metastatic adenocarcinoma (diagnosed by cytology by pleural fluid aspiration and lymph node biopsy) were 17 (51.5%) (Table 2).
Lactate dehydrogenase (LDH) in pleural effusion is significantly high in patients with NR/PR than in patients with CR (Table 3).
Pleurodesis complications were fever (21.1%), chest pain (33.3%), nausea (24.2%), vomiting (12.1%), and hypotension (6.1%) (Table 4).
Pigtail duration till pleurodesis ranged from 3 to 13 days. Pigtail complications were (pigtail obstruction) (3.03%), (chest pain) (3.03%), and (obstruction and pain) (12.12%) (Table 5).

<table>
<thead>
<tr>
<th>Table 1 Patients’ response among studied cases</th>
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<tbody>
<tr>
<td>Response according to CXR and US</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Response according to CXR and US</td>
</tr>
<tr>
<td>No/partial response</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
</tbody>
</table>

US, ultrasound.
No significant difference as regards actual (measured) FEV1/FVC% before and 2 months after pleurodesis among all cases. There was mild decrease in FVC and FVC% before and after pleurodesis among all studied cases; however, it was highly significant (Table 6).

Discussion

Recurrent pleural effusions are a common clinical problem in patients with advanced neoplastic disease, and the treatment is mostly palliative. When life expectancy is not too short, pleurodesis is considered the most valid option [14].

This is a prospective single (one) arm clinical trial in which 33 patients with MPE were enrolled. Patients with right pleural effusion were 18 (54.5%) patients, while patients with left pleural effusion were 15 (45.5%) patients. Moreover, 16 (48.5%) patients were diagnosed as malignant pleural mesothelioma, while 17 (51.5%) patients were diagnosed as metastatic adenocarcinoma but no statistically significant differences were found between the studied groups regarding the different reported pathologies and pleurodesis outcome.

In the present study, LDH in pleural fluid was significantly high in the NR/PR patients compared with CR patients whereas changes in glucose and protein were nonsignificant.

In his study, Shoukry [15] showed similar results. He reported that pleural fluid levels of LDH is the most sensitive marker that discriminated those with failed pleurodesis from those with successful pleurodesis, where the cutoff points that discriminated success from failure is LDH more than 1023 IU/l and with increasing LDH more than 1023 IU/l, there was increased probabilities of pleurodesis failure. Whereas in the present work the cutoff points that discriminated success from failure is LDH more than 954 IU/l and with increasing LDH more than 954 IU/l, there was increased probabilities of pleurodesis failure.

In the present study, 27 (81.8%) patients showed CR; three (9.1%) patients showed PR; and three (9.1%) patients showed NR according to CXR and chest sonography findings 2 months after pleurodesis.

The results of the present study were in harmony with Salem [6], who reported CR in 85%, PR in 5%, and NR in 10% of 20 patients with MPE who underwent pleurodesis using ethanolamine olate through large-bore chest tube.

However, the results in the present study were not consistent with Lisete et al. [5], who demonstrated that the intrapleural injection of ETH produced pleurodesis in a dose-dependent manner. In rabbits that received 100 mg ETH, satisfactory pleurodesis was obtained in 50%. ETH also produced microscopic pleural fibrosis in a dose-dependent manner. The underlying lung and the contralateral lung had at the most only slight amounts of fibrosis or inflammation. The induced changes did not differ whether the diluent was

| Table 3 Comparison between no/partial response and complete response cases as regards pleural fluid biochemistry |
|------------------------------------------------------|-------------------------------------------------|--------|---|-----------|
| No/partial response (mean±SD) | Complete response (mean±SD) | t | P | Significance |
| Glucose | 166.83±104.20 | 120.85±65.59 | 1.911 | 0.177 | NS |
| Protein | 5.07±0.49 | 4.57±0.61 | 3.347 | 0.077 | NS |
| LDH | 954.33±590.40 | 518.88±342.71 | 5.927 | 0.021 | S |

LDH, lactate dehydrogenase; S, significant; *Student’s t-test.
dextrose 50 or saline. No pleurodesis resulted when dextrose 50 alone was given.

The difference between the present study and Lisete et al. [5] study may be due to that the later was performed on rabbits and not humans.

Shouman et al. [16] have compared different substances for pleurodesis in MPE through a chest tube. As regards the success rates they found that they were 66.7, 73, 60, 66.7, and 26.7% for tetracyclin, talc slurry, iodopovidone, bleomycin, and tube alone, respectively. And these success rates were lower than that of the present study because of the high LDH in pleural effusion of patients who underwent pleurodesis by tetracyclin, talc slurry, iodopovidone, bleomycin, and tube alone and they were 1710±546, 1810±248, 1890±395, 1860±395 and 1410±475 IU/l, respectively, in comparison to LDH in the pleural effusion in the present study which was mean 600.53±425.16 in all studied cases.

The results of the present work were not in accordance with Herrington [17] who evaluated doxycycline as a pleurodetic agent. Out of 12 patients with MPE, eight (66.6%) achieved a CR; two (16.6%) had a PR; and two (16.6%) had NR. Moreover, these success rates are lower than that of the present work.

The difference may be due to the difference in the number of the studied patients between Herrington [17] study and the present work.

Barbetakis et al. [18] have studied the results of chemical pleurodesis with mitoxantrone in MPE from breast cancer. At 60 days, the overall response was 78.5% (CR: 53.5% and PR: 25%) which was lower than that of the present study.

The difference occurred because Barbetakis et al. [18] studied only MPE from breast cancer.

In the present study, adverse effects of ethanolamine oleate were absent in 14 (42.4%) patients and present in 19 (57.6%) patients. They were mild and occurred within the day of pleurodesis in the form of fever that did not exceed 38°C, in seven (21.2%) patients and responded to simple antipyretics; mild chest pain occurred in 11 (33.3%) patients which responded to simple analgesics, nausea in eight (24.2%) patients, vomiting in four (12.1%), and hypotension in two (6.1%) patients which responded to saline infusion. There were no mortality, no life-threatening complications, no adult respiratory distress syndrome, no respiratory failure, no acute pneumonitis, no granulomatous pneumonitis, no cardiac arrhythmias,

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Table 4 Complications of pleurodesis using ethanolamine oleate among the studied cases

<table>
<thead>
<tr>
<th>Pleurodesis complications</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Present</td>
<td>19 (57.6)</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>No</td>
<td>26 (78.8)</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>No</td>
<td>22 (66.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>No</td>
<td>25 (75.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>No</td>
<td>29 (87.9)</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>No</td>
<td>31 (93.9)</td>
</tr>
</tbody>
</table>

Table 5 Pigtail duration and complications among the studied cases

<table>
<thead>
<tr>
<th>Pigtail complications</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>27 (81.8)</td>
</tr>
<tr>
<td>Present</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Type of pigtail complications</td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>1 (3.03)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (3.03)</td>
</tr>
<tr>
<td>Obstruction and pain</td>
<td>4 (12.12)</td>
</tr>
</tbody>
</table>

Table 6 Comparison between spirometry results before and 2 months after pleurodesis among all the studied cases

<table>
<thead>
<tr>
<th></th>
<th>Before pleurodesis (mean±SD)</th>
<th>2 Months after pleurodesis (mean±SD)</th>
<th>t</th>
<th>P</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>1.66±0.73</td>
<td>1.54±0.70</td>
<td>4.188</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FVC%</td>
<td>46.99±11.53</td>
<td>43.04±9.94</td>
<td>3.532</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.48±0.67</td>
<td>1.34±0.60</td>
<td>3.801</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FEV1%</td>
<td>52.22±13.34</td>
<td>46.66±10.38</td>
<td>3.362</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>88.94±7.22</td>
<td>86.91±7.85</td>
<td>1.742</td>
<td>0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

HS, highly significant; *Paired t-test; Complete response (CR: total resolution of pleural effusion).
no empyema, no prolonged fever, no severe chest pain, no visual loss, and no allergic reactions were noted.

Ramadan et al. [19] compared the results of medical pleurodesis, using four different chemical agents: bleomycin ampoules, doxycycline capsules, povidone iodine solution, and 5-fluorouracil ampoules, in cases of MPE, as regards efficacy, safety, availability, and cost, using large-bore chest tubes. Pleurodesis complications for bleomycin cases (chest pain 60%, fever 30%, empyema 20%), for doxycycline (chest pain 60%, fever 30%, empyema 10%), for iodopovidine (chest pain 50%, fever 50%), for 5-fluorouracil (chest pain 40%, fever 40%, empyema 10%).

For the previous four sclerosing agents chest pain had occurred in a rate higher than that of the present study because of the use of only 10 ml lidocaine 2% which was a dose lower than that used in the present study, also the use of a large-bore chest tube in Ramadan et al. [19] study increased the pain. And as regards fever and empyema, they occurred because of the long tube duration that was present in Ramadan et al. [19] study and reached up to mean 7.1±2.5 days in 5-fluorouracil; whereas, it was mean 6.09±2.4 days in the present work.

In the present study, pigtail complications were present only in six (18.2%) patients and were in the form of pigtail obstruction in one (3%) patient, chest pain in one (3%) patient, and obstruction and pain together in four (12.1%) patients. No extrapleural catheter placement no perforation of intrathoracic organs, no perforation of abdominal organs, no diaphragmatic laceration, no empyema, no pulmonary edema, and no Horner's syndrome were noted.

The present study was inconsistent with Roberts et al. [20] who have found that 5% of pigtail catheter placements were associated with serious complications (hemothorax, pneumothorax, and hepatic perforation) and the overall complications of catheter use occurred in 20% of patients and included failure to drain, dislodgement, kinking, empyema, and disconnection, which were not present in the present study.

This occurred because Roberts et al. [20] did not use ultrasound guidance.

In the present study, ultrasound guidance was used during pigtail catheter insertion and this prevented the occurrence of the complications that might occur during pigtail insertion such as extrapleural placement, thoracic or abdominal organ perforation or development of pneumothorax and also this helped in avoiding potential iatrogenic complications of invasive procedures.

The results of the present study resemble to some extent Liu et al. [21] who reviewed patients who underwent pigtail catheters (size from 10 to 16 Fr) under ultrasound guidance for drainage of pleural effusions of various etiologies and pneumothoraces. Only 10 (3.0%) drains had complications due to the procedure, including infection (1.2%), dislodgement (1.2%), wound bleeding at the puncture area complicated with hemothoraces (0.3%), and lung puncture (0.3%). There was no significant difference in success rate when different catheter sizes were used to treat pleural diseases.

However, in the present study and the study of Liu et al. [21] pigtail complications were minimal, and this was due to the application of ultrasound.

In the present study, there was a very mild decrease in FVC and FVC% in patients with CR, 2 months after pleurodesis.

This is not in agreement with Salem [6], who reported nonsignificant change in FVC and FVC% before and after pleurodesis in cases of MPE.

The difference between the present study and Salem [6] study may be due to the difference in the period between doing pleurodesis and doing spirometry in the two studies which was 2 months in the present study and 1 day in Salem [6] study or because of the anticancer treatment that the patients received during the two months following pleurodesis in the present study, and this may be considered a confounding factor.

The results of the present study had several limitations; the results of the present work represent one hospital in which the number of studied patients was too small for a proper evaluation of the adverse effects and the success rate of ethanolamine oleate pleurodesis. Besides, the period of follow-up was only 2 months, but this short period of follow-up was to avoid loss of patients due to death.

Despite the progress in cancer treatment, the management of MPE remains palliative, with median survival ranging from 3 to 12 months [1].
Further long-term studies, including larger periods of follow-up (every 2 months for 6 months) and larger number of patients who can undergo pleurodesis using ethanolamine oleate are required.

Conclusion
Ultrasound-guided pigtail catheter insertion was usually safe with little chance for complications.

Ethanolamine oleate pleurodesis is an easy, cheap, effective, and safe procedure with minimal adverse effects in the 2 months follow-up period and ethanolamine oleate is an available substance.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References