Efficacy and safety of intrapleural cisplatin versus silver nitrate in treatment of malignant pleural effusion

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Introduction Malignant pleural effusion is a frequent problem. Pleurodesis is performed to prevent its recurrence. New, effective, and safe sclerosing agents are needed.

Aim The aim of this was to compare efficacy and safety of silver nitrate solution 0.5% versus cisplatin in achievement of pleurodesis in malignant pleural effusion.

Patients and methods Prospective randomized single-blinded clinical trial performed at Chest, Clinical Oncology and Nuclear Medicine and Pathology Departments, Mansoura University, from February 2016 to March 2017. A total of 60 patients (26 male and 34 female) with malignant pleural effusion were divided into two groups: first group included 30 patients who were managed with silver nitrate pleurodesis, and second group included 30 patients who were managed by intrapleural cisplatin injection. The success rate of pleurodesis was considered if there was no clinical or radiological recurrence of effusion for 1 month after intervention.

Results There were significant improvements in cough, chest pain, and dyspnea in the two groups after 1 month versus that before pleurodesis. The success rate of pleurodesis in silver nitrate group was 90 versus 76.7% in cisplatin group, without significant difference (P=0.166). Chest pain was reported in 26.7% in silver nitrate group and 13.3% in cisplatin group, and fever was reported in 33.3% in silver nitrate group and 20.0% in cisplatin group. Recurrence was reported in 10% in silver nitrate group and in 23.3% in cisplatin group.

Conclusion Silver nitrate and cisplatin were nearly equally effective, safe, and less expensive agents in achievement of pleurodesis in patients with malignant effusion with high success rate and low complications.

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Introduction

Malignant effusion is a frequent presentation complicating nearly all malignant tumors. The primary tumors causing it are lung cancer followed by breast cancer and lymphomas [1].

Pleurodesis is done for malignant pleural effusion to improve symptoms and prevent its recurrence. Chemical pleurodesis is performed by intrapleural instillation of sclerosing materials such as bleomycin and talc [2]. The use of talc may be followed by systemic embolization, acute respiratory distress syndrome (ARDS), and respiratory failure [3]. Pharmaceutical talc is not available in many countries including Egypt [4].

Light [5] advised use of silver nitrate 0.5% for pleurodesis by its intrapleural injection as an accepted alternative. Cisplatin is a chemotherapeutic drug widely used for management of malignant effusion as sclerosing agent, exhibiting a 45–67% success rate for pleurodesis [6].

The aim our study was to compare the efficacy (success rate) and safety (complications) of silver nitrate solution 0.5% versus cisplatin in pleurodesis for treatment of malignant effusion.

Patients and methods

A prospective single-blinded randomized clinical trial was conducted in which patients who had malignant effusion were injected through pleural catheter with silver nitrate 0.5% in one group and cisplatin in the other group. All cases were assessed clinically and radiologically after 1 month for the success rate.

This study was done at Chest, Clinical oncology, and Pathology Departments, Mansoura University, Egypt, from February 2016 to March 2017. It included 60 patients, 26 male and 34 female, with malignant pleural effusion. They were divided into silver nitrate group (30 patients), with mean age of 57.70±12.44 years, and cisplatin group (30 patients), with mean age of 58.37± 13.85 years.

Ethical approval was obtained from Institutional Research Board of Faculty of Medicine, Mansoura University (code no: MS/16.01.108). After detailed

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explanation of the study protocol, all patients signed their written consents.

The study included symptomatic patients with malignant effusion. Patients who had history of allergy to cisplatin or silver nitrate, shifted mediastinum to the same side of effusion, thickened pleura with entrapped lung, uncorrected bleeding disorders, renal failure, or uncompensated cardiac comorbidities were excluded from this study. Included patients were randomly selected according to sealed envelope method and divided into two groups regarding the use of agents for pleurodesis injected through pleural catheter: silver nitrate group, treated with intrapleural silver nitrate 0.5%, and cisplatin group, treated with intrapleural cisplatin.

Pathological diagnosis was done by pleural fluid cytology or histopathological examination of pleural biopsy taken with Abram needle or medical thoracoscopy. After diagnosis of malignant effusion, partial relief of symptoms after first therapeutic thoracocentesis, and patient acceptance to be included, the patients were subjected to the following:

(1) Clinical evaluation for cough, chest pain, and dyspnea that scored before pleurodesis and after 1 month of pleurodesis. Cough was evaluated according to Belfiore *et al.* [7], chest pain was scored by McGill pain questionnaire [8], and dyspnea was scored according to modified Medical Research Council (mMRC) scoring of dyspnea [9].
(2) Radiological evaluation: chest radiograph of the posteroanterior view was done at presentation, 1 day after injection of the pleurodesis agent, and follow-up after 1 month. Computed tomography (CT) of the chest was done at presentation and 1 month after injection of the pleurodesis agent. Grading of effusion was done according to Mironov *et al.* [10] as follows: effusions filling less than one-third were mild, one-third to two-thirds were moderate, and more than two-thirds of hemithorax were massive effusions.
(3) Pleurodesis technique: chest tube (28 Fr intercostal tube; Medic Co., Cairo, Egypt) or small-bore catheter (Angiocath 12 Fr, Lenacath; Haidylena Co., 6th October, Egypt) was inserted at the site of maximal pleural fluid collection guided with chest sonography after intradermal and subcutaneous injection of 7–10 ml lidocaine 2%. Evacuation of the pleural space was done at a rate of 1–1.5 l/day. After complete lung inflation and fluid drainage became less than 150 ml/day, the pleurodesis agent was injected.
    (a) Silver nitrate group: after intrapleural injection of 10 ml lidocaine 2%, 20 ml of 0.5% silver nitrate was injected intrapleurally according to Light [5].
    (b) Cisplatin group: after intrapleural injection of 10 ml lidocaine 2%, 25-mg cisplatin dissolved in 50-ml normal saline was injected intrapleurally according to Seto *et al.*[11].

    After injection of the pleurodesis agent, the pleural catheter was locked for 2 h, the patient was rotated, and then was opened and allowed to drain the remaining fluid. At the drainage of the less than 200 ml/day, pleural catheter was removed.
(4) Successful pleurodesis was determined as no recurrence of effusion on chest radiograph or CT for 1 month after pleurodesis according to Lee *et al.* [12]. Patients were followed up weekly in the first month for the success rate and complications.

Statistical analysis

Statistical analysis was done by SPSS (Statistical Package for Social Sciences), version 22 (International Business Machines Corporation, New York, USA). Qualitative data were presented as number and percentage. For quantitative data, student *t*-test was used to compare the two groups. Paired sample *t*-test was used to compare the results before and after therapy in the same group. *P* is significant if less than 0.05.

Results

A total of 71 patients who had malignant effusion were recruited in our study, but 11of them were excluded (four had shifted mediastinum to the same side of effusion, three had thickened pleura with entrapped lung, one patient had uncorrected bleeding disorder, and three refused to complete the study). The remaining 60 patients were managed as two groups: silver nitrate group was managed with silver nitrate pleurodesis and cisplatin group was managed with intrapleural cisplatin injection.

Silver nitrate group comprised 30 patients (18 female and 12 male), with mean age of 57.70±12.44 years and cisplatin group embodied 30 patients (16 female and 14 male), with mean age of 58.37±13.85 years. Both groups were age, sex, and smoking habit matched ($P>0.05$).

In the silver nitrate group, the pathological diagnosis was metastatic poorly differentiated adenocarcinoma in

83.3%, metastatic undifferentiated carcinoma in 10.0%, and lymphoma in 6.7%. In the cisplatin group, the pathological diagnosis was metastatic poorly differentiated adenocarcinoma in 90.0%, metastatic undifferentiated carcinoma in 6.7%, and mesothelioma in 3.3%. The most frequent primary origin of metastatic pleural effusion was lung – 26.7% in silver nitrate group and 33.3% in cisplatin group – and breast – 30.7% in both groups.

small-bore catheter (SBC) was used in 80% of silver nitrate group and in 70% of cisplatin group, whereas large-bore catheter was used in 20% of silver nitrate group and in 30% of cisplatin group, without significant difference between the two groups (P=0.371).

The presenting symptoms were dyspnea in all patients of both groups, cough was present in 90% of silver nitrate group and 60% of cisplatin group, and chest pain was present in 36.7% of silver nitrate group and 40% of cisplatin group.

There were no significant differences between both groups in cough, chest pain, and dyspnea scores at start of treatment or after 1 month of pleurodesis. There was significant decrease in the cough, chest pain, and dyspnea scores in both groups after 1 month versus that before pleurodesis as shown in Table 1.

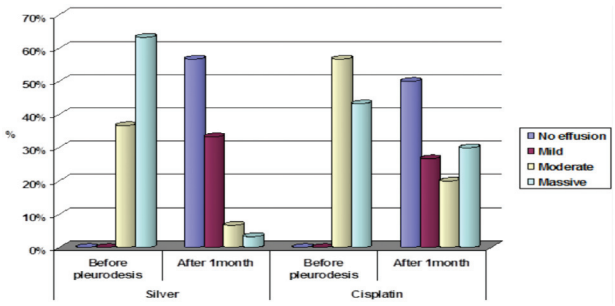
Moderate pleural effusion was present in 36.7% of silver nitrate group and in 56.7% of cisplatin group. Massive pleural effusion was present in 63.3% of silver nitrate group and in 43.3% of cisplatin group. Statistically significant decrease in the amount of effusion was seen from massive and moderate to mild, and no effusion after 1 month of pleurodesis in both groups (P<0.001) was present as shown in Fig. 1.

The success rate of pleurodesis by silver nitrate in silver nitrate group was 90% (27 of 30 patients) whereas the success rate of pleurodesis by intrapleural cisplatin was 76.7% (23 of 30 patients), and no statistically significant difference was present between both groups (P=0.166) as shown in Table 2.

Regarding the complications of pleurodesis, chest pain was recorded in 26.7% in silver nitrate group and 13.3% in cisplatin group which was controlled by analgesics. Empyema was recorded in 6.7% in silver nitrate group and managed by antibiotic therapy. Fever was recorded in 33.3% in silver nitrate group and 20.0% in cisplatin group. Abdominal pain was recorded in 6.7% in silver nitrate group and 20.0% in cisplatin group. Vomiting was recorded in 3.3% in silver nitrate group and 26.7% in cisplatin group (statistically significant; P=0.002). There was no procedure-related mortality as shown in Table 3.

As shown in Table 4 regarding hospital stay, the total hospital stay was 7.77±3.73 days in silver group and 8.43±3.84 days in cisplatin group. Time

Figure 1



Radiological response of pleural effusion after 1 month of pleurodesis

Table 1 Clinical scores of cough, chest pain, and dyspnea before pleurodesis versus 1 month after pleurodesis

Symptoms	Silver nitrate group (n=30) [median (minimum–maximum)]	Cisplatin group (n=30) [median (minimum–maximum)]	Significance
Cough			
Before pleurodesis	2 (0–2)	2 (0–2)	0.834
After 1month	1 (0–1)	1 (0–2)	0.796
P (before vs. 1 month)	<0.001*	0.003*	
Chest pain			
Before pleurodesis	2 (0–3)	2 (0–3)	0.857
After 1 month	1 (0–2)	1 (0–2)	0.587
P (before vs. 1 month)	0.002*	0.006*	
Dyspnea			
Before pleurodesis	4 (3–4)	4 (3–4)	1.000
After 1 month	1 (1–2)	2 (1–3)	0.161
P (before vs. 1 month)	<0.001*	<0.001*	

*P value significant.

before pleurodesis was 5.90±3.08 days in silver group and 6.57±3.21 days in cisplatin group. Time after pleurodesis was1.80±1.03 days in silver group and 1.90±0.84 days in cisplatin group, and there was no statistically significant difference between both groups (P=0.498, 0.415, and 0.683, respectively).

Figures 2 and 3 show two cases that were managed by silver nitrate and cisplatin pleurodesis.

Table 2 Success rate of pleurodesis in both groups

Success rate	Silver nitrate group (n=30) [n (%)]	Cisplatin group (n=30) [n (%)]	χ^2	P
Success	27 (90.0)	23 (76.7)	1.920	0.166
Failed	3 (10.0)	7 (23.3)		

Discussion

Malignant pleural effusions are usually presented by dyspnea and chest pain. Rapid reaccumulation and repeated thoracocentesis cause burden to both patient and physician [13].

Pleurodesis is a well-established method for rapidly accumulating malignant effusions. The sclerosing agent should be effective, low cost, widely accessible, safe, and easy to use [14]. Complete lung expansion and the radiological apposition of both parietal and visceral pleura are the most important factors for successful pleurodesis [15].

SBC was used in 80% of silver nitrate group and in 70% of cisplatin group, whereas large-bore catheter was

Table 3 Immediate complications after pleurodesis

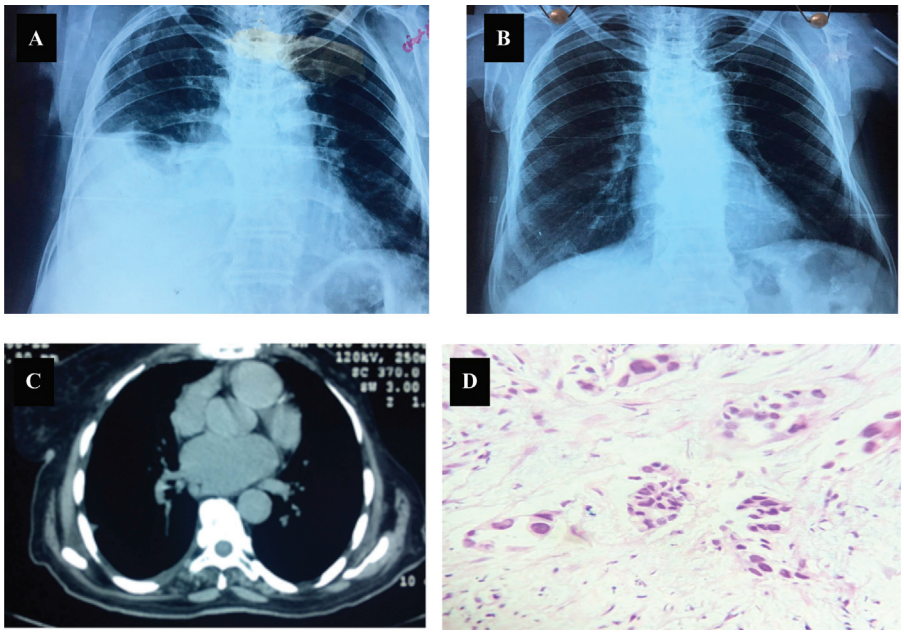
	Silver nitrate group (n=30) [n (%)]	Cisplatin group (n=30) [n (%)]	χ^2	P
Chest pain	8 (26.7)	4 (13.3)	1.667	0.197
Empyema	2 (6.7)	0 (0.0)	2.069	0.150
Fever	10 (33.3)	6 (20.0)	1.364	0.243
Abdominal pain	2 (6.7)	6 (20.0)	2.308	0.129
Vomiting	1 (3.3)	8 (26.7)	9.231	0.002*

*P value significant.

Table 4 Hospital stay of the studied patients

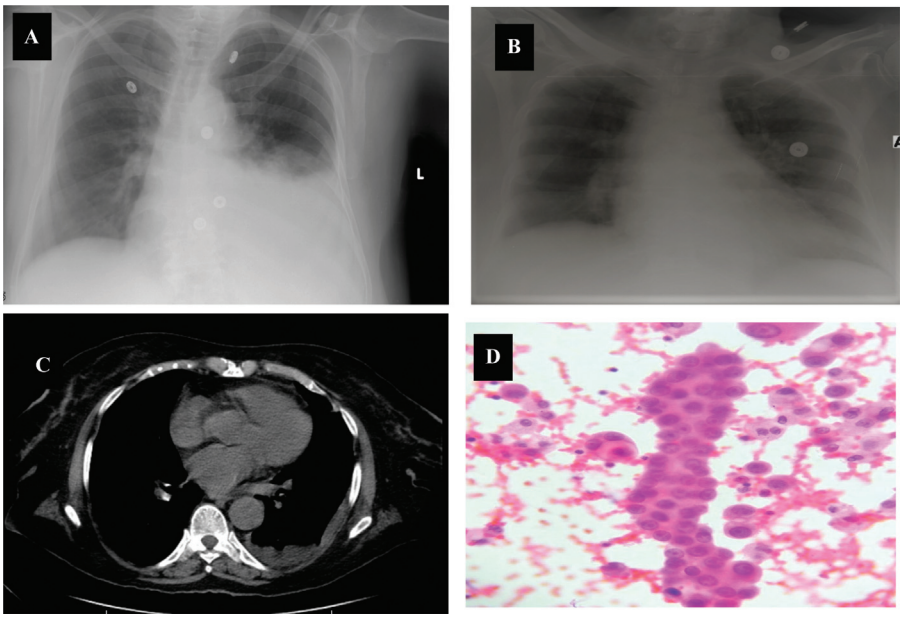
	Group A (silver nitrate) (n=30) (mean±SD)	Group B (cisplatin) (n=30) (mean ±SD)	t	P
Total hospital stay	7.77±3.73	8.43±3.84	0.682	0.498
Time before pleurodesis	5.90±3.08	6.57±3.21	0.821	0.415

Figure 2



A 65-year-old woman was presented with cough, dyspnea, and chest pain 3 years after left mastectomy for breast cancer. She was treated with silver nitrate pleurodesis. (a) CXR at presentation. (b) Chest X ray (CXR) after 1 month. (c) Computed tomography after 1 month. (d) Histopathology: metastatic poorly differentiated adenocarcinoma of primary breast origin. H&E, 400

Figure 3



A 57-year-old woman with 2 years of ovarian cancer was presented with cough, and dyspnea. She was treated with cisplatin pleurodesis. (a) CXR at presentation. (b) CXR after 1 month. (c) Computed tomography after 1 month. (d) Histopathology: metastatic undifferentiated carcinoma of primary ovary origin. H&E, 400

used in 20% of silver nitrate group and in 30% of cisplatin group (P=0.371). A study by Saffran *et al.* [16] reported that pleurodesis for malignant effusion using small-bore pig-tail catheter produced comparable result to that of large-bore tube. Those data are further supported by the study of Parulekar *et al.* [17] who compared the success rate of pleurodesis using talc, tetracycline, and bleomycin through small pleural catheter and large-bore chest tube. The success rates were not different between the groups. Caglayan *et al.* [18] used small-bore catheter in comparison with large-bore chest tube for pleurodesis using povidone–iodine and concluded that successful pleurodesis was similar regardless of the type of inserted pleural catheter.

Successful pleurodesis was defined by no recurrence of pleural effusion on the same side on a chest radiograph or CT at 1 month after chemical pleurodesis [12]. Longer follow-up was difficult because of the death associated with malignant effusion, with a mean survival of 3 months [19].

In silver nitrate group, the success rate of pleurodesis by silver nitrate 0.5% was 90% (27 of 30 patients), and these results were comparable to the study by Menna *et al.* [15], in which injections of silver nitrate (1%) produced a successful pleurodesis in 89% of patients after thoracoscopic talc poudrage failed pleurodesis. Our success rate was slightly less than Paschoalini *et al.* [20] who showed that after 1 month, successful pleurodesis was shown in 96% of those who received silver nitrate (0.5%) versus 84% of those who were managed by talc slurry. In the study by Terra *et al.* [21], 63 patients with malignant effusion were managed by silver nitrate (0.5%) pleurodesis. After 30 days, the overall effectiveness of pleurodesis was 95.8%. The slight differences between our results and the previous studies could be explained by different number of patients, different doses of silver nitrate, and previous pleurodesis in some of their patients.

In cisplatin group, the success rate of pleurodesis by intrapleural cisplatin was 76.7% (23 of 30 patients). Our rate was more than that obtained by Rusch *et al.* [22] who found that the response rate was 49%. Tohda *et al.* [23] also had a similar trial on 70 patients, and the success rate was 46%. The response rate of Lung Cancer Study Group [24] was only 49%. Kim *et al.* [25] reported a higher success rate (97.3%); they studied 37 of 40 patients managed with intrapleural cisplatin and cytarabine. In a study by Seto *et al.* [11], the response rate was 83%. The differences between our results and these studies seem to be caused by different number of patients, inclusion criteria, and treatment methods. Lung Cancer Study Group 861 study enrolled cases with resistance to systemic chemotherapy. In the study by Kim *et al.* [25], intrapleural chemotherapy was the initial treatment before systemic chemotherapy, but in our study, most of the patients received chemotherapy

before or during pleurodesis. The success rate of pleurodesis by silver nitrate was more (90%) than that of intrapleural cisplatin (76.7%) but without significance (P=0.166).

Regarding the complications in the current study, in silver nitrate group, chest pain was recorded in 26.7%,which was controlled by analgesics. Empyema was recorded in 6.7% which was managed by antibiotics and drainage. Fever was recorded in 33.3%, abdominal pain was recorded in 6.7%, and vomiting in 3.3% of patients. Those complications were controlled without intensive care unit admission, and there was no procedure-related mortality. Our results were comparable to Terra *et al.* [21], in which 29% of patients developed fever after silver nitrate solution slurry, and chest pain was reported in 10% of their patients. Infection was reported in two (3%) cases, as cellulitis at drainage area in one case and empyema in the other case that was treated with chest tube drainage with systemic antibiotics. Fever was found in one patient 2 days after pleurodesis. Vargas *et al.* [26] reported that lower concentrations will decrease theses adverse effects with an effective pleurodesis. In a study by Paschoalini *et al.* [20], pain was not a serious complication, but in our study, pain was a frequent complication but not significant.

In the cisplatin group, chest pain was reported in 13.3%, fever in 20.0%, abdominal pain in 20.0%, and vomiting was reported in 26.7% of cases. In a study by Rusch *et al.* [22], they used high doses of cisplatin intrapleural for pleurodesis, and they reported more complications as leukopenia and/or thrombocytopenia that resolved without sequelae of infection or bleeding in 9%, nausea and vomiting in 88% of their patients as well as chest pain in 77% of their patients. In the study by Kim *et al.* [25], one patient had reversible myelosuppression, and three patients had vomiting. Both wound infection and empyema complicated two patients. Pain was relatively tolerable and was managed with analgesics; they used high doses of cisplatin intrapleural for pleurodesis which causes more systemic absorption with more systemic complications. In the study by Seto *et al.* [11], the incidence of complications reported in their study was low, including nausea, vomiting, dyspnea, and infection (4, 3, 1, and 1%, respectively), whereas 90% of the patients had gastrointestinal complications. When comparing both groups regarding complications, only vomiting was significantly higher in cisplatin group.

Regarding hospital stay, our results were comparable to those of Caglayan *et al.* [18] (3.05 days in the large-bore tube group and 5.74 days in the small-bore catheter group); Mohsen *et al.* [27] in which the time of tube drainage till pleurodesis was 4.5 days; and El-Morsy *et al.* [28] (4.5 days compared with pleurodesis through SBC 6.5 days, regardless of the agent used). In the study by Rafei *et al.* [1], the mean time from drainage of effusion to pleurodesis was 10.8 days, and the mean time to removal of tube after pleurodesis was 33.6 h.

Advantages of silver nitrate and cisplatin are their availability throughout the world and low cost. In Egypt, the cost for 20 ml 0.5% silver nitrate solution is US$0.25 and for cisplatin 25 mg is US$1.50, unlike talc, which is not available and more costly, 5 g talc is US$2.00 [20]

In conclusion, silver nitrate and cisplatin were nearly equally effective, safe, and inexpensive agents in the achievement of pleurodesis in cases with malignant pleural effusion with high success rate and low tolerable complications.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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