

Silver nitrate versus tetracycline in pleurodesis for malignant pleural effusions; a prospective randomized trial

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Abstract

Background: In this study, we aimed to investigate the effectiveness of silver nitrate (SN) versus tetracycline in pleurodesis among patients with malignant pleural effusion (MPE).

Methods: In this prospective randomized clinical trial, patients with unilateral MPE candidate for pleurodesis were enrolled. The patients randomly allocated in two groups for receiving 20 mL 0.5% SN or 2.5 g tetracycline diluted in 30 cc normal saline and 0.1% lidocaine, through the chest tube. Patients were followed-up immediately (during 24 h) and 1-month after the procedure for evaluating recurrence of the pleural effusion using chest radiograph. They were clinically evaluated for chest pain and/or dyspnea and fever using a questionnaire that completed by the surgeon. The results were compared with two groups.

Results: During this trial, 50 patients with MPE candidate for pleurodesis were selected and randomized into two interventional groups (25 patients in each group). Immediate and late recurrence of pleural effusion after pleurodesis were similar in two groups ($P > 0.05$). All patients in tetracycline group had fever and chest pain, but in SN group fever and chest pain were reported in 3 (12%) and 12 (48%) of patients, respectively ($P < 0.05$).

Conclusion: SN is at least as effective as tetracycline for MPE treatment. In addition, its side effects were lower than tetracycline. Other advantages of SN are its low cost, availability, and safety. For more accurate results, it is recommended to design further trials with larger sample size and with lower doses of both SN and tetracycline.

Key Words: Malignant plural effusion, pleurodesis, silver nitrate, tetracycline

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INTRODUCTION

Malignant pleural effusion (MPE) is considered as one of the most important complications of

malignancies that is related to the high rate of morbidity.^[1] In addition, almost all patients will experience debilitating dyspnea that consequently reduce the quality of life of the affected patients.^[2]

Currently available treatment for the management of MPE are pleurodesis, tunneled pleural catheters or repeated thoracentesis.^[3-5] From which pleurodesis with chemical agents is the most commonly used technique.^[3]

Pleurodesis is the obliteration of the pleural space by fusion of the visceral and parietal pleurae with fibrous

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tissue.^[6] It is suggested that chemical agents used for the procedure, locally activates the coagulation system and production of fibrogenic cytokines and consequently production of collagen.^[6]

It is well-established that an appropriate pleural sclerosing agent should be safe, widely available, inexpensive and easy to apply and should not cause significant side effects. However, the ideal agent has not identified yet, and there is not an agent meet all of the mentioned criteria.^[7] Different agents including talc, antimalarials (quinacrine, mepacrine), antineoplastic (bleomycin, 5-fluorouracil, mitomicin, etc.), antibiotics (tetracyclines, minocycline, doxycycline), silver nitrate (SN), immunomodulating and biological agents have been investigated and different results have been achieved.^[6,8-10] It seems that the ideal pleural sclerosing agent for each setting should be selected according to the characteristics of the patients and facilities of the center.

Silver nitrate and tetracycline are the most commonly used chemicals for pleurodesis. Several studies have evaluated their effectiveness and side effects separately or in comparisons with each other's and various results have been reported.^[11-14] They are also the most frequently used agents in our surgical departments but since now no study have compared their effectiveness in the treatment of MPE.

So, considering the paramount importance of quality of life in patients with MPE and selection of appropriate technique with low complication and sufficient efficacy for treatment of this group of patients, we aimed to investigate whether these chemicals could perform efficient and safe pleurodesis with less side effects and which of them is superior.

METHODS

In this prospective randomized clinical trial patients with unilateral MPE candidate for pleurodesis and admitted to the surgery Department of Alzahra Hospital affiliated to the Isfahan University of Medical Sciences were enrolled.

Patients with MPE who has the following criteria were included in the study:

- Anticipated survival longer than 1-month
- Having dyspnea or improved respiratory symptoms due to the effusion
- Cytologically or histologically confirmed MPE.

Patients with MPE who had following characteristics were excluded from the study:

- Inappropriate expansion of lungs during drainage of the effusion by tube thoracostomy
- Pulmonary involvement with tumoral mass
- Patients with air leak or history of previous pleurodesis
- History of any interpleural therapy or radiation therapy on the affected hemithorax.

The protocol of the study was approved by the regional ethics committee of Isfahan University of Medical Sciences. Written informed consent was obtained from all selected patients.

In all selected patients, a chest tube (26 F or 28 F) was placed using local anesthesia. Plural effusion was drained and the patients were prepared for pleurodesis. The patients randomly allocated in two groups for receiving 20 mL 0.5% SN (Merck; Darmstadt, Germany). Or 2.5 g tetracycline (Hakim Pharmaceutical Company-capsule 25 mg) diluted in 30 cc normal saline and 0.1% lidocaine, through the chest tube.

The sclerosant was injected to the patients in each group. The patients were placed in right and left decubitus, prone and supine positions for 10–15 min. The chest tube was unclamped after 1 h and removed when the amount of drained fluid reached to <100 cc. After removal of the chest tube, chest radiograph was performed for confirmation of the appropriate lung reexpansion. The patients were clinically evaluated for chest pain and/or dyspnea and fever using a questionnaire that completed by the surgeon.

Chest pain was recorded using a linear scale of 1–3 (1: Mild, 2: Moderate and 3: Sever). Patients were said to have dyspnea or chest discomfort if they have the symptoms more severe than that experienced before the procedure.

Patients were said to have fever if they had oral temperature >37.5°C.

Patients were followed-up immediately (during 24 h) and 1-month after the procedure for evaluating recurrence of the pleural effusion using chest radiograph. Characteristics of the patients were recorded, using a questionnaire. The data in two studied groups were compared.

Statistical analysis

Data analyzed using SPSS version 18 (SPSS Inc., Chicago, IL, U.S.A.) software. Qualitative variables were presented as number (%) and compared in studied

groups using Chi-square test. Quantitative variables were presented as the mean \pm standard deviation. The comparison of quantitative and qualitative variables between studied groups was done using one *t*-test and Chi-square test, respectively.

RESULTS

During this trial, 50 patients with MPE candidate for pleurodesis were selected and randomized in two interventional groups (25 patients in each group). The consort diagram of the study is presented in Figure 1.

Characteristics of the patients allocated in two interventional groups are presented in Table 1.

Frequency of recurrence rate of plural effusion and complications of pleurodesis including fever, pain and dyspnea and/or chest discomfort in two studied groups are presented in Figure 2.

Chest pain after pleurodesis was severed and moderate in 16 (64%) and 9 (36%) of patients in tetracycline group, respectively.

Moderate and mild chest pain after pleurodesis were reported in 1 (4%) and 11 (44%) of patients in SN group, respectively.

DISCUSSION

In this trial, we have investigated both effectiveness and complications of SN versus tetracycline in pleurodesis

for MPE. The results indicated that effectiveness of the two agents was similar but regarding the complications, SN was a more appropriate agent.

As mentioned, there is much debate regarding selection of the most appropriate chemical agent for pleurodesis. According to the report of a review study, the most effective agents are oral forms of tetracycline derivatives, quinacrine, SN, iodopovidone, and talc.^[15,16]

Though many novel agents such as doxycycline have been introduced also,^[17] but we studied the effectiveness of agents which most commonly used in our settings. However, Shouman *et al.* have indicated that the most important factors for choosing a sclerosing agent in developing countries are the drug availability and cost.^[18]

In this study, breast and lung cancer were the most common types of malignancies that result in MPE in both studied groups. It was in line with other studies. Previous studies indicated that about 75% of MPE are secondary to the lungs, breast cancers or lymphoma.^[19] In another study in 50–65% of cases of MPE, lung and breast cancer were the most frequent causes.^[20]

The success rate of pleurodesis in SN and tetracycline groups were 76% and 84%, respectively. Though our results were similar to the rates have been reported in previous studies,^[21-23] but comparing the effectiveness of studied agents with other studies is so difficult due to the fact that different doses of the agents and various techniques for pleurodesis including tube size, differences in tube thoracostomy procedure and various definitions for success rate was applied.^[20,21]

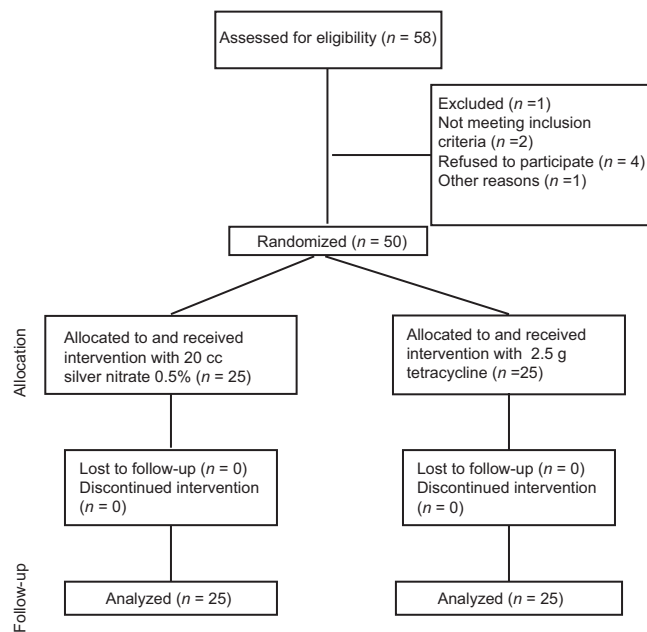


Figure 1: Consort diagram of the study

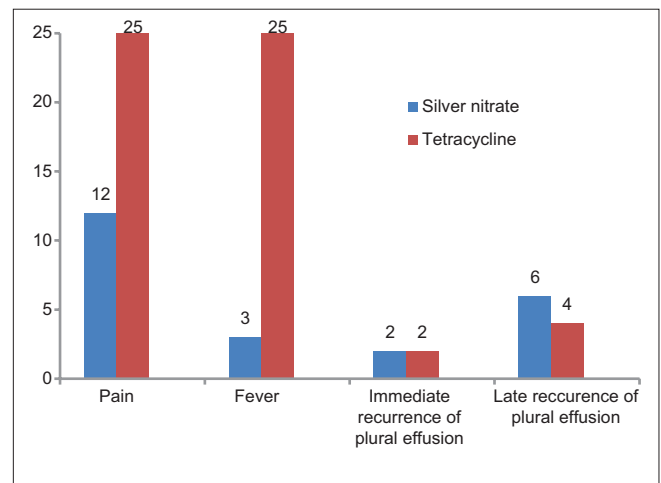


Figure 2: Frequency of recurrence rate of plural effusion and complications of pleurodesis including fever, chest pain and/or dyspnea in patients with malignant plural effusion allocated to received silver nitrate and tetracycline

Table 1: Characteristics of the patients with malignant plural effusion allocated to received silver nitrate and tetracycline

Variables	Silver nitrate (n=25) (%)	Tetracycline (n=25) (%)	P
Sex (female/male)	10/15	11/14	0.50
Age (years)	49*	48*	0.6
Type of cancer			
Lung	11 (44)	12 (48)	0.9
Breast	5 (20)	4 (16)	
Lymphoma	4 (16)	4 (16)	
Leukemia	2 (8)	1 (4)	
Uterus	1 (4)	2 (8)	
Pancreas	1 (4)	-	
Kidney	1 (4)	-	
Prostate	-	1 (4)	
Stomach	-	1 (4)	

*Median

Success rate of the two studied agents was similar in the current study.

There were few studies that compare these two therapeutic agents. Most of them were experimental and compared the agents with others. In addition, there was not any clinical trial for comparing the two agents. The first experimental study that compared the effectiveness of SN versus tetracycline was carried out in rabbits by Vargas *et al.* in Brazil. They showed that intrapleural injection of 0.50% SN produced an effective pleurodesis as well as 35 mg/kg tetracycline with no significant side effects. They concluded that SN is comparable to tetracycline.^[22]

There were many studies regarding the effectiveness of SN and tetracycline.^[11-14]

Evidences indicated that tetracycline stimulates mesothelial cell release of growth factors for fibroblast proliferation and deposition of collagen. It is dose-dependent effective inhibitors of the matrix-degrading metalloproteinase (MMP) activity in the pleural fluid. Therefore, it reduces the activity of MMPs and remodels the tissues by normal repairs not fibrosis.^[23]

The doses of tetracycline that used in current study was higher than prior studies (2.5 g vs. 0.5–1.5 g in other studies),^[11,24] whereas the success rate of studies which used lower doses of tetracycline were similar to ours, so it is recommended to study different doses of tetracycline for pleurodesis in patients with MPE.

The effectiveness of SN for pleurodesis is due to its induced caustic injury to the mesothelium, and its effectiveness has been proven in many experimental and few clinical studies.^[11,25,26] According to that

studies SN 0.5% could be an appropriate alternative to tetracycline with low adverse effects.^[22] In addition, recent studies have demonstrated the effectiveness of low dose SN that is, 0.1% for pleurodesis.^[27] It could be also used in some conditions such as an early bronchopleural fistula.^[28] In our study, SN had similar success rate to tetracycline and lower side effect. Its priority to tetracycline was its lower adverse effects. Considering that a lower dose of SN (0.1) could have a similar effect and obviously lower adverse consequences, so further studies for evaluating different doses of SN would be more practical.

The main limitation of our study was the small sample size of patients.

The strength of the current study was its design. Because most of the previous studies were experimental and in animals, and there were few clinical trials in this field.

CONCLUSION

The findings of the current study showed that SN is at least as effective as tetracycline. In addition, its side effects were lower than tetracycline. Other advantages of SN are its low cost, availability and safety. For more accurate results, it is recommended to design further trials with larger sample size and with lower doses of both SN and tetracycline.

In addition, it seems that comparing the effectiveness and complications of other low-cost agents with SN would be more helpful to obtain more accurate and practical results in this field.

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