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Rapid pleurodesis in symptomatic malignant pleural effusion☆

Erkan Yildirim[a,*], Koray Dural[a], Rasih Yazkan[a], Nurullah Zengin[b], Dilsad Yildirim[a], Nesimi Gunal[a], Unal Sakinci[a]

[a]*Department of Thoracic Surgery, Ankara Numune Education and Research Hospital, Ankara, Turkey*
[b]*Department of Medical Oncology, Ankara Numune Education and Research Hospital, Ankara, Turkey*

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Abstract

Objective: The objective of the study was to see whether a rapid method of pleurodesis was superior to the standard protocol in patients with symptomatic malignant pleural effusion. **Methods**: Between January 2000 and February 2003, a prospective randomised trial was carried out in a sequential sample of 27 patients with malignant pleural effusions documented cytopathologically. Twelve patients were allocated to group 1 (standard protocol) and 15 to group 2 (new protocol). A small-bore catheter (12 Fr) and oxytetracycline (35 mg/kg of body weight) were used in both groups. In group 1, patients had drainage until radiological evidence of lung re-expansion was obtained and the amount of fluid drained was less than 150 ml/day, before oxytetracycline was instilled. The catheter was removed when the amount of fluid drained after instillation was less than 150 ml/day. In group 2, patients had the oxytetracycline instilled in a fractionated-dose manner following frequent aspirations at 6 h intervals. The catheter was removed when the total amount of fluid drained after instillation of the oxytetracycline [OT] was less than 150 ml/last three aspirations. Response was evaluated at 1, 3 and 6 months after pleurodesis. **Results**: There was no statistically significant difference in the demographic features, site of the primary tumour, disease characteristics, and response rates in any evaluation period in both groups ($P>0.05$). However, the number of days of drainage and hospitalisation, and the cost were significantly lower in the second group ($P<0.001$). **Conclusions**: This new pleurodesis method provided shorter hospital stay resulting in superior cost-effectiveness and palliation without sacrificing the efficacy of pleurodesis.

Keywords: Pleural diseases; Pleurisies; Malignant pleural effusion; Pleurodesis; Methods; Efficacy; Treatment

1. Introduction

The management of patients with malignant pleural effusions can present significant diagnostic and therapeutic challenges [1].

Symptomatic pleural effusions in patients with advanced cancer is a common problem that causes significant morbidity and can negatively affect patients' quality of life for their remaining months. Several palliative treatment options are available. Repeated needle thoracocentesis, tube thoracostomy, chemical or biologic pleurodesis, pleurectomy, and pleuroperitoneal shunt [2].

Pleurodesis aims to achieve a symphysis between parietal and visceral pleural surfaces, in order to prevent accumulation of fluid or air in the pleural space [3]. Rapid pleurodesis methods should be improved in the light of effective palliation in these patients suffering from continuing challenges.

In the current study, we aimed at comparing the efficacy of the novel rapid pleurodesis method with the standard protocol. Fractionated doses of oxytetracycline (OT) were administered with frequent aspirations of the pleural fluid at 6 h intervals in an attempt to keep both pleurae in close contact. The main objective of the present research was to reduce the amount of time the patient should spend at the hospital after the intervention with equal efficacy.

2. Materials and methods

2.1. Study design

A prospective, randomised method was utilized to compare standard method of pleurodesis with the proposed new rapid pleurodesis process in patients with symptomatic malignant pleural effusion. The institutional review board for human studies has approved the treatment protocols. The procedures used were in accordance with the recommendations found in the Helsinki Declaration of 1975.

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*Corresponding author. Asagiövecler Mh. 79.Sk. 8/3 06460 Dikmen-Cankaya, Ankara, Turkey. Tel.: +90 312 482 72 79; fax: +90 312 310 34 60.
E-mail address: erseyda@yahoo.com (E. Yildirim).

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The same researchers performed all procedures in the same institution. The pathological diagnosis was proved by either cytological examination of the pleural effusion or pleural biopsy.

With their consents, patients were randomly assigned to one of two identified groups. The technique used in the first group ($n=12$) was the standard protocol and for the second group ($n=15$) it was the new proposed method. A small-bore catheter (12 Fr) was used in both groups. The sclerosant agent used for the purpose of pleurodesis was OT (35 mg/kg of body weight) in both groups. The total dose of OT instilled in the pleural cavity was identical in both groups.

For the purpose of analgesia, prilocine; 1%, 20 cc (intrapleural, only single dose administration) and naproxen sodium 550 mg, tablet 2×1 (per os at least for the initial two or three days) were given to all of the patients included. This analgesia protocol sufficiently provided the required pain control.

Patients in group 1 had catheter drainage until radiological evidence of lung re-expansion was obtained and the total amount of fluid drained was less than 150 ml/day, before OT was instilled. The catheter was clamped for 6 h and then opened to free drainage. It was removed when the amount of fluid drained after instillation of OT was less than 150 ml/day.

Patients in group 2 also had small-bore catheter drainage, but the OT was instilled in a fractionated-dose manner following aspirations of the effusion at 6 h intervals. In average, 383,61±113,60 ml of fluid per aspiration was removed every 6 h before each instillation of OT. All the fluid was aspirated at 6 h intervals either until the negative suction was achieved or before patients' comfort level was compromised. The first dose was the half of the total calculated dose. And, the rest was instilled dividing into three equal amounts of doses after every aspiration. The catheter was clamped and left in place after administering each calculated doses of OT till the following aspiration step. The catheter was removed when the amount of fluid drained after completing the instillation of OT was totally less than 150 ml/last three aspirations.

2.2. Evaluation of response

Before pleurodesis, the size of the pleural effusion in a posteroanterior chest radiograph was catalogued as moderate, when extending from the diaphragm to the pulmonary hilum, and massive, when exceeding the hilar region. Patients were followed up with chest radiographs at 1, 3 and 6 months after pleurodesis. Responses were classified as:

(1) Complete (no clinical or radiological recurrence of pleural effusion); (2) partial (small amount of fluid reaccumulation in the chest radiograph, but no symptoms); (3) failure (reaccumulation of fluid causing symptoms or needing thoracentesis) [4].

2.3. Statistical analysis

Both study groups were compared with respect to demographic and disease characteristics, and site of primary tumour. The *t*-test for independent samples was used for continuous variables and the Chi-squared or Fischer's exact tests for comparison of proportions at each group. Response rates between the two treatment methods were compared at each evaluation (1, 3 and 6 months) using Chi-squared test. Time to recurrence and survival distributions was analysed using the Kaplan–Meier Survival Analysis and Log Rank test. All statistical comparisons between the two groups were carried out at the significance level of 0.05.

Table 1
Characteristics of patient in both treatment groups

	Group 1 ($n=12$)	Group 2 ($n=15$)	*P*-value
Age (yrs)[a]	(56.83±12.59) (33-71)	(51.93±10.22) (38-71)	NS
Male/Female	4/8	4/11	NS
Primary site (*n*)			
Breast	4 (33.3)	5 (33.3)	
Lung	1 (8.3)	2 (13.3)	
Unknown	2 (16.7)	0	
Mesothelioma	1 (8.3)	2 (13.3)	
Others	4 (33.3)	6 (40.0)	
Follow-up[a]	(5.5±3.03) (1 mo-9 mo)	(6.4±2.2) (2 mo-9 mo)	NS
Mortality[b]	6 (50)	5 (33)	NS

Values are expressed as absolute number of patients, and percentage in parenthesis.
[a] Mean±SD (range); NS: Non-significant ($P>0.05$).
[b] Mortality within 6 months after treatment.

3. Results

Demographic and primary disease characteristics are summarized in Table 1. The majority of patients had breast cancer, lung cancer, and mesothelioma. Nearly 25% had received prior systemic chemotherapy and 20–33% underwent surgery for primary tumour. There were no significant differences between the two groups with regard to demographic characteristics, primary disease and prior treatment.

Clinical and radiographic features were similar and in addition, morbidity of both procedures was statistically non-significant in both study groups.

Table 2
Response to both procedures

	Group 1 *n* (%)	Group 2 *n* (%)	*P*-value[a]
1 month evaluation			
NE	2	0	NS
CR	6 (60)	10 (66)	
PR	3 (30)	5 (33)	
Failure	1 (10)	0	
3 month evaluation			
NE	4	3	NS
CR	4 (50)	10 (83)	
PR	2 (25)	2 (17)	
Failure	2 (25)	0	
6 month evaluation			
NE	6	5	NS
CR	3 (50)	8 (80)	
PR	2 (33)	1 (10)	
Failure	1 (17)	1 (10)	

NE: not evaluable (death); CR: complete response, PR: partial response. NS: Non-significant ($P>0.05$).
[a] For comparison of CR with PR and Failure combined.

Table 3
Procedure-related aspects

	Group 1	Group 2	*P*-value
Days of drainage[a]	7.00±3.04	1.867±4.85	$P<0.001$
Total drainage (ml)[b]	3310.83±3712.24 (2325)	3048.93±1028.56 (2700)	$P>0.05$
Days of hospitalisation[a]	8.33±4.85	2.33±0.62	$P<0.001$
Cost-effectiveness ($)[b]	860±496.38 (740)	245±71.50 (200)	$P<0.001$

[a] Mean±SD.
[b] Mean±SD (median).

A trend for higher complete response rate was noted in the second group. Nevertheless, it was not statistically significant at 1, 3 and 6 months after pleurodesis (Table 2).

Pleural fluid pH and pleural fluid glucose levels were measured in group 1 and group 2 patients: 7.30±0.124 vs. 7.27±0.111 ($P=0.57$) and 65.33±13.47 mg/dl vs. 65.00±10.18 mg/dl, ($P=0.94$), respectively. The results were statistically non-significant between both study groups.

The mean volume of pleural fluid drained during the procedures was not significantly different in both groups. In contrast, the mean day of drainage [7.00±3.04 vs. 1.867±4.85] and hospitalisation [8.33±4.85 vs. 2.33±0.62] were significantly lower in the second group. The results showed that the new proposed method was more cost-effective since patients spent less time at the hospital (Table 3).

Six patients died in the first arm and five in the second one, with a mean follow-up time of 5.5–6.4 months. There was no significant difference in median survival period between the two treatment groups, 6.00 vs. 7.27 months, respectively.

Although not statistically significant, relapse occurred later in group 2 patients at a median time interval of 8.8 months vs. 7.56 months.

4. Discussion

Malignant pleural effusions are associated with significant morbidity. Prompt clinical evaluation followed by aggressive treatment often results in successful palliation [4]. Treatment response for malignant pleural effusion is highly variable [5].

We have developed a new method of rapid pleurodesis, which worked effectively in patients with short survival expectations.

The selection of pleurodesing agents stays debatable. Talc is more effective, but is allied with more unfavourable effects. Talc pleurodesis is followed by systemic and pulmonary inflammation [6]. We considered OT to use in the current study due to three main reasons. First, it was cheaper than sterile talc. Second, it was impossible to find talc out of asbestos in Turkey, also more expensive. Lastly, OT was known to be well tolerated by the patients without major side effects [7].

For a pleurodesis to be effective, firstly the lung must be fully expanded [2,8] so that the parietal and visceral pleural surfaces are in apposition. Secondly, there must be good dispersion of the sclerosing agent throughout the pleuzral space. Moreover, the pleural spaces must be kept in close apposition after instillation of the agent for the chemical pleuritis to progress to pleural symphysis [8,9].

In the present clinical trial, the pleural fluid was aspirated manually at 6 h intervals to keep both pleurae in close apposition before instillation of OT. The main purpose was to increase the contact duration and surface area of both pleurae for increasing the chemical pleuritis in the shortest possible interval.

The aspiration periods of the pleural effusion were immediately followed by administration of OT. The total dose of OT to be administered was calculated as 35 mg/kg of body weight [7]. The first fractionated dose, which was half of the total, was administered intrapleurally immediately after the first aspiration. The rest was divided into three equal amounts and given consecutively after the sequential aspirations. These dosages are arbitrary, but seem to work well. The intra pleural dose of OT should be kept at a certain level to induce inflammatory and fibrogenic effect on the pleurae [3,9] as the drug is being partially absorbed by the pleura and decreasing the drug levels intrapleurally [10].

In conclusion, the findings of the current study showed that the new recommended method of 6 h aspiration intervals with fractionated doses of OT resulted in reduced days of drainage and hospitalisation days rendering no more morbidity than the standard procedure.

Further clinical studies need to be undertaken with larger groups with a view to compare the efficacy of the OT with the other sclerosing agents using this novel pleurodesis method.

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Appendix A. Conference discussion

Dr S. Elia (*Rome, Italy*): What was the basic pathology? The survival changes even concerning the type of disease. If we're talking about lung cancer, it's one matter. If we're talking about breast cancer, it's another point. So the survival end results of your study have this type of bias, I think. What can you say concerning that?

Dr Yildirim: You mean the pathological types?

Dr Elia: The basic disease, right.

Dr Yildirim: The basic disease was the breast cancer and the second was lung cancer.

Dr Elia: And there was no difference between the two?

Dr Yildirim: Yes. Of course, this study included a small group of patients and the study was going on at the moment, and we raised it to 40 patients, and again the results are the same.

Dr Elia: I think that you should try to have a more homogeneous group of patients, like breast cancer patients and lung cancer patients, separately. That probably would help in understanding the results better.

Dr Yildirim: Yes, you might be right.

Dr G. Cardillo (*Rome, Italy*): Have you considered in your group of patients the condition of the lung before pleurodesis? I mean a free lung i.e. a lung that is able to expand after thoracentesis, usually shows a good result in terms of pleurodesis. A trapped lung gives very bad results. So I think that the main point we have to consider in talking about pleurodesis and the type of pleurodesis, is if the lung we are going to treat is a free lung or is it a trapped lung.

Dr Yildirim: We had only 2 patients with entrapped lung in the first group and one patient in the second. As I've said, this is a small group of patients. These patients indeed did not benefit from this procedure and we had to perform thoracentesis and tube thoracostomy. You are right.

Dr P.L. Filosso (*Torino, Italy*): We usually use talc for the pleurodesis in this kind of patient. We have a large clinical experience using talc for pleurodesis in patients with malignant pleural effusions. Did you observe adverse side effects in using the tetracycline?

Dr Yildirim: We just had pleuritic pain, not any other side effects, and we could manage it by instilling prilocine 1% intrapleurally before the procedures in both groups.

Dr W. Klepetko (*Vienna, Austria*): Where precisely did you insert the catheter, and how did you make sure there was an equal distribution of the tetracycline within the thoracic cavity?

Dr Yildirim: Before the procedure we tried to find the best place by using serial thoracentesis, by puncture needle, and then we inserted the catheter, and before the insertion, we prepared the solution at the calculated dose and then instilled it.