COMPARISON OF EARLY PLEURODESIS PRACTICE WITH CONVENTIONAL (LATE) PLEURODESIS PRACTICE IN PATIENTS WITH RADIOLOGICALLY EXPANDED LUNG HAVING EXUDATIVE PLEURAL EFFUSION

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ABSTRACT

Introduction: Malignant pleural effusion is commonest cause of exudative pleural effusions. Chemical pleurodesis, using an intrapleural sclerosing agent, is a good palliative measure to obliterate the pleural space, prevent fluid accumulation and improve breathing.

Objective: To compare early pleurodesis practice with late pleurodesis practice in with patients with radiologically expanded lung in term of pleurodesis success, post pleurodesis drainage, and hospital stay.

Study Design, Place and Duration: It was a randomized clinical trial conducted in Pulmonology Department, Post Graduate Medical Institute, Lady Reading Hospital, Peshawar, from 26th March 2009 to 25th March 2010.

Materials and Methods: Patients with malignant pleural effusion were randomly assigned to early pleurodesis group (Group I) and late pleurodesis group (Group II). Tetracycline was used as sclerosing agent for pleurodesis in both groups. Group I comprises those patients in whom lung was expanded radiologically while daily drainage was still more than 100ml. Group II includes those patients in whom lung was expanded as well as daily drainage was less 100ml. pleurodesis was considered successful if post pleurodesis drainage was less than 150ml in 24 hours and failed if drainage was more than 150 ml per day for 3 days. Total hospitay stay was counted from the date of intubation to the date of extubation.

Results: Out of 234 patients 122 (51.1%) were males and 112 (47.9%) were females. In Group I age range was 17 to 110 years with mean of 58 + 15 SD, while in Group II, age range was 13 to 90 years with mean of 54+14 SD. In Group I and Group II the pleurodesis success rate was 89.3% and 94% respectively (p 0.260). Mean post pleurodesis drainage in successful Group I and Group II was 164 ml $\pm$ 341 and 99+138 (P-value 0.95). Mean hospital stay in Group I was 6.16 days $\pm$ 5 while In Group II mean hospital stay was 7.88 days $\pm$ 4 with a P-value of 0.017.(Mean hospital stay in successful Group I was 5.19 days $\pm$ 3.5 while In Group II mean hospital stay was 7.6 days $\pm$ 4.15 with a p value of 0.000). Comparison of the early versus late pleurodesis in term of hospital stay showed significant difference (P-value <0.05).

Conclusion: Early pleurodesis is not inferior and as better as late pleurodesis in patients with pleural effusion when lung is expanded radiologically irrespective of the excessive daily drainage.

Key Words: Malignant Pleural effusion; Early pleurodesis; late pleurodesis

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INTRODUCTION

Diseases of pleura are common, difficult to diagnose, and problematic to manage[1]. Effusion is one of the common pleural diseases both in developed and developing countries. It can either be exudative or transudative[2]. Common causes of exudative pelural effusion are malignancy, infection and connective tissue disorders. Massive symptomatic exudative pleural effusions are difficult to treat and the management is usually palliative. Several palliative treatment options are available[3]. pleurodesis (sclerotherapy) is defined as a procedure aimed at making adhesions between the visceral and parietal pleura, obliterating the potential pleural space. pleurodesis can be chemical (medical) or surgical[4]. Chemical pleurodesis, using an intrapleural sclerosing agent, is a good palliative measure to obliterate the pleural space prevents fluid accumulation and improves breathing. Different types of sclerosing agents are used[5,6,7]. Talc, Bleomycin and tetracycline are considered the primary sclerosing agents[9-11]. The advantages of tetracycline are its reasonable efficacy, excellent safety profile, ease of administration and low cost[8,12].

The most important requirements for successful pleurodesis is satisfactory apposition of the parietal and visceral pleura confirmed radiologically[8,13]. It is a common practice to wait for pleurodesis till post intubation per day drain become less than 100ml[12,13]. One study of similar nature (Irain less than 100ml/24 hours) was performed in department of chest diseases, Osmangazi Unive3rsity Medical Faculty, Eskisehir, and Turkey14. However British Thoracic Society (BTS) guidelines and other studies on pleural diseases recommended that pleurodesis should be done as early as possible when lung is radiologically expanded even if drain is more than 100ml per day[8,12]. The use of early pleurodesis technique could substantially shorten the patient's hospital stay or could be done on an outpatient basis, minimizing cost. BTS guidelines also recommended that this early pleurodesis practice is one of the potential areas for future research[8].

The success rate of late pleurodesis, when the drainage fell below 100ml/24 hours and the lung is expanded completely) was 80 – 82% in different studies[14]. While success rate of rapid or early pleurodesis (when the lung is fully expanded but the drainage per day is more than 100ml) was ranged from 81% to 88.4% in few international studies.[15, 16] To our knowledge there is no reported study from Pakistan using the early pleurodesis technique.

The rationale behind this study is to explore the role of the early pleurodesis practice when lung is fully expanded but the drainage per day is more than 100 ml. Once it is proven that pleurodesis can be done is patients with post intubation radiologically expanded lung in spite of daily drainage more than 100 ml, early pleurodesis can be adopted in routine for patients with exudative pleural effusion thus reducing patient's hospital stay, and post pleurodesis complications related to prolonged chest intubation. The main objective of the study was to "Compare early pleurodesis practice with Conventional (late) pleurodesis practice in patients with radiologically expanded lung having exudative pleural effusion".

HYPOTHESIS: Success rate of early pleurodesis technique is better than conventional pleurodesis in patients of pleural effusion with post intubation radiologicaly expanded lung.

METHODOLOGY

This was a radomized clinical trial conducted in Pulmonology Department Postgraduate Medical Institute, Lady Reading Hospital, Peshawar. Study duration was Minimum 6 months. (from April 01, 2007 to October 02, 2007). Sample size was 234 as calculated by using 95% confidence co-efficient 80% success rate of late pleurodesis[14] and 88.4% success rate of early pleuodesis[15,16], 80% power of test, under WHO formula for sample size determination . Consecutive purposive (non-probability) sampling technique was used.

After getting the permission to conduct the study from Hospital ethical committee, a total of 234 consecutive patients with pleural effusion presenting to the Outpatient department / emergency department of Pulmonology unit, Postgraduate Medical Institute, Lady Reading Hospital Peshawar were admitted in the Pulmonology unit during the selected study duration and patients fulfilling inclusion criteria were enrolled in this study and were subjected to pelurodesis according to defined operational guidelines, after taking informed consent. Patient were briefed about the treatment plans of groups 1 and group 2 informed written consent was taken from patients from inclusion in the study and merits and demerits of the both treatment were also discussed with the patients. A total of 234 patients were divided randomly into two groups of 117 patients in each group by closed envelop method in which we prepared 117 chits with the name of group 1 procedure and other 117 with name of group 2 procedure. Patients were assigned group 1 or 2 on lottery method by taking envelopes from the box .Group 1 comprised of those patients in whom rapid pleurodesis was done and Group II comprised of those patients in whom conventional

(late) pleurodesis done. In all patients 1gm of tetracycline diluted in 50 ml normal saline was introduced through chest tube into the pleural space and tube were clamped for 2 hours. After 2 hours clamp were released. X-ray chest were done after 24 hours and post pleurodesis per day drainage were noted. If drainage was less than 150ml, and lung was expanded, chest tube was removed. If post pleurodesis per 24 hours drain was more than 150mol for 3 consecutive days then pelurodesis was considered fail and repleurodesis done. Exclusion criteria were followed to control confounders and bias in the study results. Comparison between the two the groups was done in term of rate of success of pleurodesis, post pleurodesis drain per 24 hours and total hospital stay. Early or rapid pleurodesis is defined when pleurodesis is performed in patients with radiologically expanded lung even if chest drain is more than 100ml per day. Conventional (late) pleurodesis is defined when chest drain is less than 100 ml per day in radiologically expended lung then pleurodesis is performed. Patient with empyema and those having tuberculous pleural effusions were excluded from study.

All the information like age, sex, pleural fluid routine examination and cytology, post intubation drain, date of chest intubation date of pelurodesis, date of extubation, post pelurodesis drain and total hospital stay were recorded on proforma specially designed for this purpose. All the qualitative variables like chest x-ray findings, investigation findings (pleural biopsy report, CT thorax report) of both groups were analyzed by calculating frequencies and relative percentages. Mean ± standard deviation were calculated for quantitative variable like age, post prluedesis drainage, and hospital stay. For gender, male to female ratio were calculated. The results are presented through tables, cross tabulation, graphs and charts. chi square test (string versus string data) and student t test (string vesus numeric data, numeric versus numeric data) were used where appropriate to compare the post pleurdesis parameters like success rate, post pleurodesis drainage and hospital stay will be used.

RESULTS

In this study, out of 234 patients 122 (51.1%) were males and 112 (47.9%) were females. In Group I there were 65 (55.6%) males and 52 (44.4%) females. While in Group II, 57 (48.7%) were males and 60 (51.3%) were females (Table 1).

In Group I, patients's age range was from 17 to 110 years. While in Group II, the age range was from 13 to 90 years. Mean age was 58.13±14.84 SD in Group I and 54.43±14.22 SD in Group II (Table 2).

Mean pre-pleurodesis fluid drainage in the last 24 hours drain when the lung fully expanded, and with successful pleurodesis was 195.72 ml ± 438 SD, while in patients with failed pleurodesis the pre-pleurodesis fluid drainage was 263.53 ml ± 398 SD. However the difference of prepleurodesis drainage in the successful and failed patients was not statistically significant (p 0.424) (Table 3).

In Group 1 the success rate of pleurodesis was 98/117 (83.8%) and the failure rate was 19/117 (16.2%). In Group II the success rate of pleurodesis was 106/117 (90.6%) while the failure rate was 11/117 (90.4%) (Table 4).

In 130 (55.6%) patients the pleural effusion was on the right side while in 104 (44.4%) it was on the left side. Mean pre-pleurodesis drainage in the first 24 hours in Group I was 133.42 milliliter ± 227.30 SD, while mean pre-pleurodesis drainage in the first 24 hours in Group II was 93.25 ml ± 130.77 SD (Table 5).

Mean total post pleurodesis fluid drainage in Group I was 250.09 ml ± 465.22 SD, while mean total post pleurodesis drainage in Group II was 158.59 ml ± 311.49 SD (Table 6).

Table 1: Crosstabulation for gender of patients in two groups (n-234)

		Gender of patient		Total
		Male	Female	
Group	Early Group	65	52	117
		55.6%	44.4%	100.0%
	LATE GROUP	57	60	117
		48.7%	51.3%	100.0%
Total		122	112	234
		52.1%	47.9%	100.0%

Table 2: Age-wise distribution of all patients (n=234)

Group	Gender of Patient	Mean	N	Std. Deviation	Minimum	Maximum
Early Group	Male	61.06	65	14.318	18	85
	Female	54.46	52	14.800	17	110
	Total	58.13	117	14.841	17	110
Late Group	Male	56.19	57	14.245	13	90
	Female	52.75	60	14.120	20	80
	Total	54.43	117	14.225	13	90
Total	Male	58.79	122	14.432	13	90
	Female	53.54	112	14.400	17	110
	Total	56.28	234	14.623	13	110

Table 3: Mean Pre pleurodesis drain in milliliters (n-234)

	pleurodesis outcome	n	Mean	Std. Deviation	p-value
Mean Pre-pleurodesis Drain In ml	**Successful**	204	195.72	± 438.30	0.424
	Failed	30	263.539	± 398.17	

Table 4: Cross Tabulation of success rate of pleurodesis in two groups (n-234)

		pleurodesis Success			p-value
		Successful	Failed	Total	
Group	**Early Group**	98	19	117	0.11
		83.8%	16.2%	100.0%	
	LATE GROUP	106	11	117	
		90.6%	9.4%	100.0%	
Total		204	30	234	
		87.2%	12.8%	100.0%	

Total hospital stay in Group I was 5.82 days ± 4.77 SD, while in Group II the total hospital stay was 7.70 days ± 4.22 SD (Table 6).

Chi square test was used to compare the success rate of pleurodesis the two Groups. Though the success rate in Group I was 83.8% and in Group II 90.6%, it was statistically not significant. (p 0.118) (Table 6).

Student t test was calculated to compare the fluid drainage in first 24 hours after pleurodesis in two Groups and was found to be statistically not significant, p value was more than 0.05 (Table 6).

Total hospital stay in the two Groups was compared by using Independent-samples T Test. Total hospital stay in Group I was 5.82 days, and Group II was 7.70 days with a p value of 0.002 which was statistically significant (Table 6).

Table 5: Pre pleurodesis comparison between two groups (n-234)

PARAMETERS		EARLY GROUP n- 117	LATE GROUP n- 117	p-value
Gender of patients (n)	Male	65	57	0.29
	Female	52	60	
Side of effusion (n)	Right	63	67	0.59
	Left	54	50	
Age of patients (mean)		58 years **14.841 ± SD**	54 years **14.225 ± SD**	0.05
Pre pleurodesis 24 hrs fluid drainage (mean)		370 ml **284.333 ± SD**	38 ml **51,65.4 ± SD**	0.00

Table 6: Post pleurodesis comparison between two groups (n-234)

Parameters	Early Group n-117	Late Group n- 117	p-value
pleurodesis success rate	98 (83.8%)	(106) 96.6%	0.11
Post pleurodesis first 24 hrs drainage (mean)	133.42 ml **± 227.309 SD**	92.25 ml **± 130.779 SD**	0.09
Total Post pleurodesis drainage (mean)	250 ml **± 465.22 SD**	158.59 ml **± 311.49 SD**	0.78
Hospital stay from date of intubation to date of extubation (mean)	5.82 days **± 4.770 SD**	7.70 days **± 4.229 SD**	0.00

DISCUSSION

Pleural Effusion is one of the most common clinical conditions that we come across in pulmonology clinics and in hospitals. Infectious as well as malignant pleural effusions are very common cause of exudative pleural effusion in this part of the country as opposed to developed countries where malignancy and noninfectious causes are more important.[17,18]

The neoplasms that more frequently determine pleural effusions are lung and breast cancer and pleural mesothelioma. Lymphomas, tumours of the genitourinary tract and gastrointestinal tract as a group account for a further 25%. [19]

It is most common in elderly people above 50 years of age. Malignant pleural effusion is a frequent condition with important prognostic repercussions on duration and quality of life.[19] In this study it was found that mean age was 58.13 in early pleurodesis Group and 54.43 in late pleurodesis Group respectively. In agreement with our results a study also reported mean age of 54 years with range of 42 to 66 years.[20] While in contrast to our results a study reported mean age of 64 years (range from 36 to 73 years).[21] This difference could be due to small sample size and inclusion criteria of the studies reported age incidence rates.

In our study females were presented to the hospital at slight younger age as compared to males and with male preponderance. In few international studies, male preponderance has also been reported with varying frequencies.[20-23] That may be due to fact that gynecological malignancies (breast, ovarian and utrine tumors) occur at slightly younger age as compared to male malignancies. The reason for male preponderance could be that in this part of the country due to some social, religious and local customs, females are usually home bound and they are not even allowed to seek medical treatment from male doctors. In contrast of these results a study reported that out of 45 patients, there were 19 men and 26 were women.[21]

Though repeated pleural aspirations are indicated in those patients that have lower expectations of life it is burdensome for patients with rapid re accumulation and longer life expectancy. The recurrence risk can be reduced with chemical pleurodesis. 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. Rapid pleurodesis methods should be improved in the light of effective palliation in these patients suffering from continuing challenges.[21]

Numerous chemical irritants have been used to induce pleurodesis. These include talc, tetracycline, minocycline, doxycycline, silver nitrate, iodopovidone, bleomycin, Corynebacterium parvum with parenteral methylprednisolone acetate, erythromycin, fluorouracil, interferon beta, mitomycin C, cisplatin, cytarabine, doxorubicin, etoposide, and

Streptococcus pyogenes A3.[22-25] The choice among these agents is determined by several factors, including local expertise, availability of individual agents, and the underlying process for which chemical pleurodesis is needed.

Among these several agents, talc is still the most popular because of its efficacy and availability, but is associated with more adverse effects, including infection, systemic embolization and respiratory failure.[26-29] The advantages of tetracycline are its reasonable efficacy, excellent safety profile, ease of administration and low cost.[30] We have used only tetracycline, because majority of our population was poor and tetracycline is of low cost. Also to reduce bias, we used only one sclerosing agent tetracycline.

In preparation for pleurodesis there should be no fluid in pleural cavity and lung should be expanded. The pleural space is usually drained by tube thoracostomy. Once the lung is expanded it is common practice to delay pleurodesis until daily chest tube drainage is less than 150 mL because of the fear of pleurodesis failure. In our study although the success rate of late pleurodes (pleurodesis delayed until chest tube drainage was less than 150 mL) was slightly higher than the early group (pleurodesis done irrespective of drainage once lung expanded), it was statistically not significant (83.8% versus 90.6%). These results of our study are also supported by two small randomized trials and a case series.[31-33] For example in study of Villanueva AG et al response to tetracycline sclerotherapy in the two groups was the same (80%) but the duration of chest tube drainage was significantly shorter for patients in group II. However his study consisted of only 25 patients with malignant pleural effusions (15 patients in group I and 10 in patients group II).[31]

In our study we achieved success rate of 83.8% and 90.6% in early and late groups respectively. This was slightly higher than reprted by Villanueva AG in his small randomized clinical trial. In his study pleurodesis was successful in 80 percent of patients in both groups. A much lower success rate (48%) was reported by Spiegler PA et al in his study. However his method was a bit different from our study. [33] In this study following radiographic confirmation of complete fluid evacuation, a sclerosing agent (ie, talc slurry or bleomycin) was instilled into the pleural space within 2 h of chest tube insertion. After clamping the tube for 90 min, the pleural space was drained for 2 h, after which the chest tube was removed and moreover patients were assessed at 4 weeks. [33]

In our study the mean hospital stay in early and late group was 5 and 7 days respectively. The hospital stay was significantly shorter in early pleurodesis than late group (p 0.002). In the study of Villanueva AG the mean hospital stay in early and late pleurodesis group was 2 and 7 days respectively. The shorter hospital stay in early pleurodesis Group in his study was due to early removal of chest drain (next 24 hours) after postpleurodesis irrespective of the postlpleurodesis drainage.[7831] While we followed the traditional approach in both the groups for removal of chest drain after pleurodesis. But even with approach the hospital stay was shorter in the early pleurodesis group.

The traditional approach is to leave the chest tube in place until drainage is less than approximately 150 mL per 24 hours, in our study we followed this approach although there are no scientific data to support this approach. The rationale is that ongoing pleural drainage helps to maintain apposition of the pleural surfaces and the chest tube is in place should repeat pleurodesis be needed. For example, if drainage is greater than 150 mL over 24 hours, repeat pleurodesis may be considered after 48 to 72 hours. Alternatively, some clinicians remove the chest tube within 24 hours after the instillation of talc or doxycycline, based on two small randomized trials showing no difference between the two approaches.[78,8131,34] The largest trial randomly assigned 41 patients with a malignant pleural effusion to have their chest tube removed either 24 hours or 72 hours after talc pleurodesis; there was no difference in the success rate between the two groups.[8134] Based on the results of these studies and the potential benefits of late removal of chest drain we also suggest leaving the chest tube in place until the rate of drainage of pleural fluid is <150 ml/day. In spite of this late approach the hospital stay is still significantly shorter than the late pleurodesis and this is of immense importance in the health care resource utilization and total cost of hospital stay.

CONCLUSIONS

From the results of this study it is concluded that both early and late pleurodesis practices are equally effective in term of success rate but the hospital stay is significantly shorter in early pleurodesis practice and is thus more superior and cost-effectiveness than the late conventional pleurodesis practice. So in the management of patients with malignant and non maliganat refractory pleural effusion the single most important thing, before sclerotherapy is the radiographic evidence of fluid evacuation and lung re-expansion. pleurodesis should not be delayed and performed once the lung is expanded irrespective of the amount of daily fluid drained. Shortening the duration of drainage will reduce the length of hospital stay without sacrificing the efficacy of pleurodesis. This new pleurodesis method provided shorter

hospital stay resulting in superior cost-effectiveness and palliation without sacrificing the efficacy of pleurodesis.

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