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Small-bore *versus* large-bore catheters for talc pleurodesis of malignant pleural effusion: a tertiary hospital experience.

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Abstract

Background: Malignant Pleural Effusion (MPE) is a complication of advanced malignancy occurring commonly in patients with lung cancer, lymphoma and breast cancer. Pleurodesis is often used to prevent re-accumulation of fluid and to help respiratory status. The size of the catheter (small *versus* large) to be used for pleurodesis, however, continues to be debated.

Objective: To describe a tertiary hospital experience in patients requiring pleurodesis for malignant pleural effusion, with a comparison of small-bore catheter and large-bore catheter outcomes.

Methods: Retrospective chart abstraction study of patients who received chemical pleurodesis with talc *via* catheter for malignant pleural effusions between 1 January 2012 and 31 December 2014 in our hospital. Small-bore (8-10 F) *versus* large-bore (28-32 F) catheter outcomes of interest were length of stay (LOS) post-catheterization and total LOS.

Results: A total of 185 patients were included in the study, of whom 67 (36.2%) received a small-bore catheter and 118 (63.8%) a large-bore catheter groups, respectively. Lung cancer was the most common primary malignancy. Using propensity-score matched analyses, post-catheterization LOS was shown to be significantly shorter in the small-bore catheter group (1.8 d; p<0.001), however, total LOS was not different between the two groups (p=0.89).

The pain VAS score was significantly lower in small bore catheter group than in large bore catheter group (p<0.001). The success rates were similar in the two groups (p=0.68).

Conclusion: In our study post-procedure length of hospital stay is shorter when talc pleurodesis is conducted *via* small-bore catheter as compared to large-bore catheter. The success rates of pleurodesis were found to be similar regardless of the type of tube inserted. In addition, the pain VAS score was significantly lower in small bore catheter group than the large one.

Keywords: Talc pleurodesis, Malignant pleural effusion, Small-bore catheter.

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Introduction

Malignant pleural effusion is a complication of advanced malignancy, occurring commonly in patients with lung cancer, lymphoma and breast cancer, and is associated with a poor prognosis [1,2]. Malignant pleural effusion causes progressive dyspnoea, chronic cough, chest pain, and reduces physical activity, all of which significantly impact patient Quality of Life (QoL) [3,4]. To prevent re-accumulation, to improve respiratory status and to improve QoL, chemical pleurodesis is often performed in patients with malignant pleural effusion. This procedure employs chemical sclerosant agents such as talc, povidone-iodine, tetracycline derivatives, or bleomycin or physical abrasion of pleural surfaces [5-7]. Talc is preferred as it is associated with less malignant pleural effusion recurrence and a low risk of complications (e.g., acute respiratory failure, pneumonia, treatment-related death) [2,8].

Currently, both large and small-bore catheters are used in pleurodesis followed by pleural drainage. The main reason for using a large-bore catheter is the improved flow rate with more viscous effusions. However, large-bore catheters are uncomfortable and require a larger incision and tissue dissection. Previous studies support the hypothesis that small-bore catheters are as effective as large-bore catheters, and they have the advantages of being safe and well tolerated [9,10]. In

this study, we describe clinical characteristics of patients receiving talc pleurodesis for malignant effusion at a tertiary referral hospital and further evaluate the length of hospital stay associated with small-bore *versus* large-bore catheters.

Material and Methods

Study design and study population: We conducted a retrospective chart abstraction-based study of patients receiving chemical pleurodesis with talc *via* catheter. The inclusion criteria were adult patients over 18 y old with malignant pleural effusion that underwent pleurodesis *via* catheter in the Süreyyapaşa Chest and Thoracic Surgery Education and Research Hospital between 1 January 2012 and 31 December 2014. Malignant pleural effusions were proven pathologically by pleural fluid cytology and/or pleural biopsy. Patients whom performed pleurodesis in this study didn't have re-expansion problem after pleural fluid drainage. Each patient was verified for re-expansion by postero anterior chest X-ray graphy after pleural drainage. We excluded patients who received chemical pleurodesis for etiologies other than malignancy, and additionally patients who were requiring recurrent pleurodesis.

Pleurodesis technique

After malignant pleural effusion was proven pathologically, pleural drainage was performed *via* small or large bore catheters by the thoracic surgeons. The thoracic surgeons decided the catheter type and replaced these catheters. After local anesthesia with lidocaine, a large-bore (size 28-32 F) or small-bore catheter (size 8F-10 F) was inserted into the mid-axillary line through the fifth or sixth intercostal space. The catheter was connected to a drainage system to completely drain the effusion and facilitate lung re-expansion. Total lung re-expansion was radiographically verified and pleurodesis was performed when drainage decreased to <200 mL/d. Patients were first sedated with 10 mg diazepam administered parenterally. Normal saline solution (50 mL) containing 2 mg/kg lidocaine was infused through the catheter as a local anaesthetic. After 15-20 min, 5 g sterile, asbestos-free talc (Steritalc® F2; Novatech, France) in 50 mL normal saline was instilled through the chest drain. After asbestos free talc slurry was instilled through the catheter, 50 ml normal saline was pushed afterward. Then catheter was clamped for 6 h after talc instillation. The catheter was withdrawn when<200 mL of fluid was drained per day.

Variables

Patients were classified into two groups according to whether they underwent pleurodesis with a small-bore (8-10 F) or large-bore (28-32 F) catheter. The primary outcome was LOS post-catheterization, and the secondary outcome was the total LOS. The pain Visual Analogue Scale (VAS) score was recorded. Chest x-rays following pleurodesis within 12 weeks were evaluated to detect efficacy of the procedure. We defined complete response as symptomatic improvement of dyspnoea with complete radiographic resolution of the effusion and partial response as symptomatic improvement of dyspnoea that did not require additional thoracentesis and fluid level below prepleurodesis level at the end of the 12 weeks follow up period. Total response rate was defined as the sum of both complete and partial response.

Confounders were determined as age, gender, previous chemotherapy, type of primary cancer, comorbidities and pleural fluid parameters. Patients' demographic variables were recorded from their medical records. All laboratory results were collected from our hospital online database (HIS: Hospital Information System). Pleural fluid parameters included levels of adenosine de-aminase (ADA), lactate dehydrogenase (LDH), total protein, albumin, and glucose. Malignancy type, comorbidities, chemotherapy, in-hospital death, the pain VAS score, response rates, complication rates, total LOS, and post-catheterization LOS were recorded.

Ethical approvals

The study was approved by the local Ethics Committee of the Health Science University, Süreyyapasa Chest Disease and Thoracic Surgery Education and Research Hospital and conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were defined as frequencies and percentages, or mean values and standard deviations (SDs). Chi-square tests were performed for group comparisons of categorical variables. We performed t-tests for normally distributed continuous variables and non-parametric Mann-Whitney U tests for variables with non-normal distributions. Based on associated factors with catheter type selection (i.e., age, gender, hypertension, cardiac failure, and other types of cancers), propensity scores were calculated to control for potentially confounding variables and minimize the effect of selection bias on patient allocation. These groups were matched with regard to age, sex, pleural fluid parameters, comorbidities, hypertension, cardiac failure and other types of cancer. In this propensity analysis, 50 matched pairs were identified. Linear regression analysis adjusted to propensity scores was used for multivariate analyses. A p value<0.05 was considered significant. All statistical analyses were carried out using SPSS software (version: 16.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 221 patients who received catheter for pleurodesis were identified during the study period. Of these, 185 had malignant pleural effusion and met inclusion and exclusion criteria, with 67 (36.2%) and 118 (63.8%) patients in the small and large-bore catheter groups, respectively (Figure 1). Patient demographics and clinical characteristics according to catheter type are shown in Table 1. Lung cancer was the most common primary malignancy leading to malignant effusions (61.6%),

with adenocarcinoma being the most prevalent among lung cancers (27.6%).

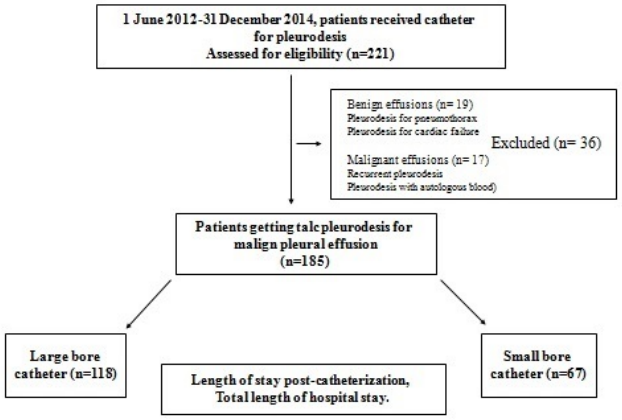

Figure 1. *Study flow chart.*

Table 1. *Patient's demographic and clinical characteristics.*

	Small bore catheter group n: 67	Large bore catheter group n : 118	P value
Age	62 ± 13	65 ± 13	0.1
Gender(male)	33 (48.5)	68 (57.6)	0.29
Presence of comorbidity	29 (43.3)	55 (46.6)	0.36
Prior systemic therapy	40 (59.7)	62 (52.5)	0.39
Lung cancer			
Adenocarsinoma	22 (32.8)	29 (24.6)	0.75
Non-small cell carcinoma	15 (22.4)	25 (21.2)	
Small cell carcinoma	8 (11.9)	15 (12.7)	
Mesothelioma	9 (13.4)	18 (15.3)	
Extrapulmonary malignancy			
Breast cancer	8 (11.9)	14 (11.9)	-
Ovarian cancer	2 (2.9)	5 (4.2)	
Lymphoma	2 (2.9)	3 (2.5)	
Colon cancer	1 (1.4)	4 (3.4)	
Gastric cancer	0 (0.0)	2 (1.7)	
Renal cancer	1 (1.4)	0 (0.0)	
Osteosarcoma	0 (0.0)	1 (0.8)	
Pancreas cancer	0 (0.0)	1 (0.8)	
Pleurla LDH	635 ± 1937	619 ± 1124	0.93
Pleural glucose	99 ± 48	119 ± 53	0.032
Pleural albumin	4 ± 9	2 ± 1	0.92
Pleural protein	4 ± 1	4 ± 1	0.7
Length of post-catheterization hospital stay(d)	3.6 ± 2.2	5.3 ± 3.5	<0.001
Total length of hospital stay (d)	6.5 ± 4.6	6.7 ± 4.5	0.89
In-hospital death	9 (13.4)	15 (12.7)	0.88

In unadjusted analyses, post-catheterization LOS was significantly shorter in the small-bore catheter group ($p<0.001$), total LOS was not different between the small- and large-bore groups ($p=0.89$, Figures 2A and 2B).

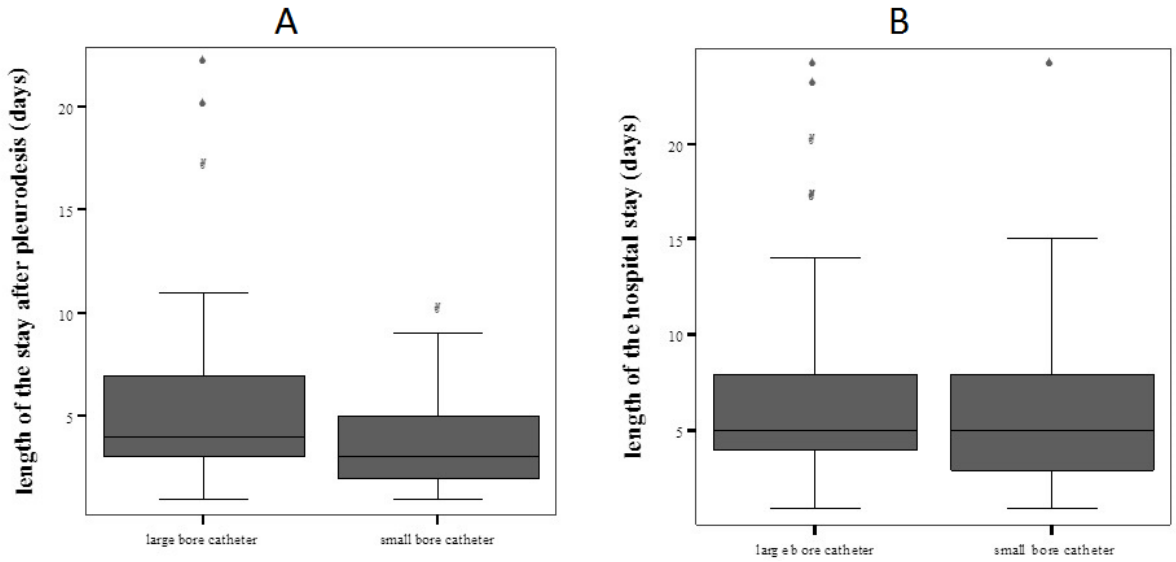

Figure 2. *(A) Length of hospital stay post catheterization; (B) Length of total hospital stay.*

Given concerns about confounding by indication, we developed a propensity score using age, gender, hypertension, cardiac failure and other types of cancers besides lung were chosen as propensity score calculation variables. The overlap range of propensity scores was found to be acceptable between the two groups. These groups were matched with regard to age,

sex, pleural fluid parameters, comorbidities, hypertension, cardiac failure and other types of cancer. In this propensity analysis, 50 matched pairs were identified. The clinical and demographic characteristics of propensity score matched patients are shown in Table 2.

Table 2. *Propensity score matched patient's clinical and demographic characteristics.*

	Small-bore catheter group n:50	Large-bore catheter group n:50	P value
Age	63 ± 14	64 ± 14	0.64
Gender (male)	21	30	0.05
Comorbidity (n)	20	19	0.5
Previous chemotherapy (n)	30	28	0.42
Lung carcinoma (n)	32	32	0.91
Adeno carcinoma	16	15	
Small cell carcinoma	11	12	0.81
Non-small cell carcinoma	6	4	
Mesotelioma	7	8	0.9
Breast carcinoma	7	6	
Lymphoma	1	1	
Kolon carcinoma	2	2	
Osteosarcoma	0	1	
Pancreas carcinoma	1	0	
Pleural LDH	649 ± 952	877 ± 1520	0.37
Pleural glucose	99 ± 48	102 ± 52	0.79
Pleural albumin	3.6 ± 9.8	2.2 ± 0.7	0.33
Pleural protein	3.9 ± 1.1	4.1 ± 0.9	0.68
Pleural ADA	13 ± 11	16 ± 12	0.44

Propensity score-adjusted linear regression analysis revealed that post-catheterization LOS was 1.8 d shorter in the small-bore catheter group (95% confidence interval: -0.9 to 2.8, $p<0.001$). The pain VAS score was significantly lower in small bore catheter group than in large bore catheter group ($p<0.001$, Table 3). Considering each group, pleurodesis as successful in 56 cases (83.6%) in small bore catheter group and in 103 cases (87.3%) in large bore catheter group. The total response rate was similar between the small-bore and large-bore catheter group and the success rates did not show a statistically significant difference (p: 0.68, Table 3).

Table 3. *Comparison of response rate, pain VAS score and length of hospital stay between propensity score matched catheter groups.*

	Small bore catheter group N: 50	Large bore catheter group N: 50	P value
Pain VAS score (cm)	3.9 ± 0.8	7.0 ± 0.8	<0.001
Post-catheterization LOS	3.5 ± 2.2	5.4 ± 3.6	<0.001
Total LOS	6.3 ± 4.5	7.6 ± 6.4	0.07
Complete and partial response rate	0.836	0.873	0.068

VAS: Visual Analog Scale; LOS: Length of Hospital Stay.

Discussion

In this study, we have shown that talc pleurodesis for malignant pleural effusion through a small-bore catheter resulted in a significantly shorter post-catheterization LOS as compared to those who received a large-bore catheter. Whereas the post-procedure LOS was 1.8 d shorter for small-bore catheter receiving patients, there was no difference between the two groups for total length of stay. This finding suggests that for small bore catheters receiving patients, there was a delay from time of hospitalization to time of procedure. The reasons for this are not clear, but may relate to the amount of effusion at time of admission. Nonetheless, the fact that post-procedure LOS was reduced is an important finding that supports the use of small-bore catheters, and ideally sooner during hospitalization. Although hospital stay cost data was not available in our study, the reduction in post-catheterization LOS and earlier discharge in the small-bore catheter group implies lower hospitalization costs, and additionally benefit to patients who often receive pleurodesis as a component of palliation care. In addition the mean pain VAS score was lower in small-bore catheter group than the large-bore catheter group. There is no statistically significant difference in total response between two groups. The response rates were similar.

Pleurodesis with large-bore (28 F to 36 F) or small-bore (7 F to 16 F) catheters is an important palliative procedure for recurrent pleural effusions due to malignant diseases. Usually, this procedure requires 5-7 d of hospitalization [11,12]. Once the drainage is decreased to 100-200 mL/d, a sclerosant agent is instilled. Talc is most often used due to its high success rate without relapse [4,13,14].

Boshuizen et al. described 381 patients with MPE who underwent pleurodesis. This cohort was largely comprised of females with breast cancer, and the median age was 61 y [15]. In another the study of chemical pleurodesis with iodopovidone, breast, lung, and ovary cancers were the most common malignancies with female dominance [10]. The mean age of our patients was similar to these two reports, but most of our patients were male, and lung cancer (adenocarcinoma) was the most common primary malignancy. These differences can be explained by the fact that our center is a pulmonary disease-specific hospital.

Patz et al. reported the first series of 19 patients with malignant effusions who underwent bleomycin pleurodesis using small-bore (10.3 F) catheters, and the length of catheterization was 2 to 11 d (mean 5.1 d) [16]. In a randomized controlled trial with talc pleurodesis, the mean LOS was 4.9 d in the chest tube group [17]. Fysh et al. reported longer pleural effusion-related

hospital LOS (median, 10 d; interquartile range, 6-18 d) than previous studies of talc pleurodesis [18]. In 32 patients with known primary malignancies who underwent small-bore catheter for talc pleurodesis, the catheters remained in place for 2-9 d (mean 4.9 d) [9]. Catheterization time for both catheter types was similar in some previous studies. In a prospective analysis comparing large- and small-bore catheters for iodopovidone pleurodesis, the total tube durations were 5.6 and 5.7 d, respectively [10]. Another group concluded that tube duration and total LOS were not different between small- and large-bore catheter groups of patients with MPE [19]. Conversely, we found that patients in the small-bore catheter group had nearly 2 d shorter post-catheterization LOS compared to those in the large-bore catheter group. Interestingly, the secondary outcome of total LOS was not different between the two groups. We suspect that poor performance status of patients, large size of effusion, and loculated effusion are variables that could explain these discrepant findings. Correspondingly, it was reported that mean tube duration was significantly longer in patients with loculated pleural effusions than those with non-loculated effusions (means of 7.6 and 4.4 d, respectively) [9].

The main factors determining LOS are prolonged fluid drainage before pleurodesis and delayed chest tube removal after pleurodesis [20]. Difficulties with tube occlusion have been described when using chest tubes smaller than 12 F [20]. Conversely, we observed a shorter post-catheterization LOS for the small-bore catheter group. This suggests that the smaller size did not cause drainage difficulties, but we were unable to confirm this with data about the amount of fluid drained.

In the literature, increasing evidence shows that small bore catheters induce less pain to large bore catheters in the management of malignant effusion and pneomothoraces [21-23].

In accordance with the literature, the mean pain VAS score was significantly lower in small bore catheter group than the large one in our study. In addition the response rates between two groups were similar in accordance with the literature [24,25].

Pleural fluid pH and ADA levels have been reported as independent predictors of talc pleurodesis outcome, but there are no studies regarding the relationship between LOS and pleural fluid parameters [26]. The present investigation did not reveal any significant difference between the groups for pleural fluid ADA or LDH level.

Our study has limitations. Given its retrospective design, there is the potential for selection bias as the patients were not randomized; resulting in confounding by indication. We accounted for these shortcomings by using a well-established propensity score method to control for confounding and to minimize the effect of selection bias. Nonetheless, we did not have reliable data on fluid loculation, original pleural fluid amount, which may have impacted catheter selection and LOS.

Conclusion

Pleurodesis with talc *via* small-bore catheter in malignant pleural effusion appears to result in a shorter post procedure length of hospital stay as compared to large-bore catheters, thus potentially reducing hospitalization costs. The success rates of pleurodesis were found to be similar regardless of the type of tube inserted. Pleurodesis *via* small-bore catheter seems to be less painful than the large-bore catheters.

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