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Efficacy and safety of autologous blood pleurodesis versus talc pleurodesis in symptomatic pleural effusions: A randomized trial

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Abstract:

PURPOSE: This study aimed to compare the efficacy and safety of autologous blood pleurodesis with talc pleurodesis in patients with symptomatic pleural effusion.

METHODS: This is a prospective, randomized, noninferiority trial. The smallest sample size was determined as 26 for each group by power analyses. For pleurodesis, 5 g of talc and 2 ml/kg blood were administered through the chest catheter. The success rate and complication were recorded in the 1st month after the procedures. The effect of the procedure on the successful pleurodesis was analyzed by univariate and then multivariate logistic regression analysis.

RESULTS: A total of 60 patients were randomized. After randomization, 6 patients withdrew from the study. The overall success rate of pleurodesis was 72.0% in the autologous blood group and 69.0% in the talc group (P = 0.903). The most common complications were fever and pain, and both were higher in the talc group (P = 0.030 and *P* = 0.001, respectively). For successful pleurodesis, complete lung expansion and catheter duration (<7 days) were important factors in the talc group and in the autologous blood group, respectively (P = 0.001 and *P* = 0.034). The effect of the procedure on pleurodesis success was not significant (odds ratio [95% confidence interval): 1.51 [0.40–5.77]; *P* = 0.548) after adjustment for lung expansion and catheter duration.

CONCLUSION: Autologous blood pleurodesis is a simple, inexpensive, effective procedure and no related to significant adverse events for patients with recurrent symptomatic pleural effusion. Especially, it can be preferred in patients with incomplete lung expansion. Further studies are required to confirm the results of this study.

Keywords:

Autologous pleurodesis, recurrent pleural effusion, talc pleurodesis

Introduction

Pleurodesis is one of the current interventions for palliative treatment of uncontrolled symptomatic pleural effusions, primarily in malignant pleural effusions and to a lesser extent benign pleural effusion. To date, many pleurodesis agents have been tried, some of which are in use, and some have failed to enter clinical practice because

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they are not sufficiently effective and safe.[1] Among these, the main agent is talc powder. Talc is a well-established and widely used agent. Talc is the most effective pleurodesis agent known, and the risk of side effects is acceptable when sterile talc is used.[1,2] There is no advantageous agent than talc in terms of efficiency, safety, availability, and cost, especially in malignant pleural effusions so far. However, it has acute respiratory distress syndrome (ARDS) risk which is rarely seen but serious side effects, and its use is questionable and not available in some clinics.[3-7] Besides, a long-term problem of the talc pleurodesis, especially in benign patients, is a carcinogenic effect of talc.[8,9]

Autologous blood pleurodesis is used by the physicians to control prolonged air leakage in patients who had pneumothorax or underwent surgery.[10-13] In the practice of autologous blood pleurodesis, the patient's blood is given to the pleural cavity, causing direct clot formation or pleural irritation and inflammation and subsequent adherence of the pleural sheets, thus ensuring the removal of the pleural cavity. The success rate of autologous blood pleurodesis has been reported about 85% in patients with prolonged air leakage.[10] If this is achieved in symptomatic pleural effusions, re-accumulation of pleural fluid and thus shortness of breath will be avoided. However, there are limited studies about the use of autologous blood for pleurodesis in symptomatic pleural fluids.[14,15] This study aimed to compare the efficacy and safety of autologous blood pleurodesis with talc pleurodesis, which has high efficacy for pleurodesis, in patients with symptomatic pleural effusion. We also aimed to discuss the clinical and pleural fluid laboratory parameters on the success of pleurodesis.

Methods

Study design

This is a prospective, randomized, noninferiority trial comparing the efficacy and safety of autologous blood pleurodesis with talc pleurodesis. The study was carried out in the Chest Diseases Clinic of Eskisehir Osmangazi University Medical Faculty. The Ethical Committee of Eskişehir Osman Gazi University approved the study (No: 278/2012).

Patients

The patients with recurrent, symptomatic pleural effusion with a life expectancy longer than 3 months, whose symptoms relieved after thoracentesis, and over 18 years of age were included in the study. Patients with any contraindications for both procedures, <18 years or > 85 years of age, who did not give written informed consent or withdrew from the study were excluded from the study. Patients who agreed to participate in the study were informed about pleurodesis methods, expected benefit, possible complications, research, and randomization. Written informed consent was obtained for both the procedures and the study.

Randomization

After informed consent was obtained, the patients underwent known preprocedure preparation and evaluation before the thoracic catheter. Patients who met the inclusion criteria were randomized after insertion of the catheter. The randomization was performed in accordance with the Consolidated Standards of Reporting Trials statement recommendations. Block randomization with a sequence of 6 was used. The patients in arm A underwent talc pleurodesis and the patients in arm B underwent autologous blood pleurodesis.

Procedures

A small (<24F) or large size catheter (≥24F) was inserted under local anesthesia in the thorax endoscopy suit. Pleurodesis was performed in patients whose daily drainage was <150 ml. Talc pleurodesis was performed as follows: following the administration of 10 ml 2% prilocaine, 5 g of asbestos-free sterile talc was diluted in 100 ml saline under sterile conditions and administered through the chest catheter. Morphine was applied to the required patients. Nonsteroidal anti-inflammatory drugs were not used. Autologous blood pleurodesis was performed as follows: 2 ml/kg blood obtained from the patient's brachial vein under sterile conditions was immediately administered through the chest catheter without waiting. After both procedures, 50 ml of saline was given to prevent catheter occlusion. The chest catheter of all patients was clamped for 2 h, and the patients underwent rotation. The chest catheter was removed after 24-h tube drainage fell below 100 ml. The success rate and complication were recorded in the 1st month after the procedures. Patients were followed up till the end of life.

Two blinded researchers evaluated the efficacy of pleurodesis by chest radiography in the 1st month after the procedure.[16]

1. Complete response: No pleural fluid detected on chest radiography
2. Partial response: Minimal pleural accumulation that does not require drainage on chest radiography
3. Unsuccessful: Recurrence of pleural fluid which needs repeat thoracentesis or pleurodesis.

Statistical analysis

Power analysis was performed using G-Power Software (G Power Version 3.1.9.2, Germany). Type I error (α = 5%), Type II error ($1-\beta$ = 95%), and the effect size of the study were calculated to be 0.30, and the smallest sample size was determined as 26 for each group. The power of the study ($1-\beta$) was found to be 0.803 when *post hoc* power analysis was performed at the end of the

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study. Analyzes were performed by G*Power 3.1 (Demo program) statistics program.

The study data were analyzed by SPSS (version 15.0, IBM Corp., Armonk, NY, USA). Shapiro–Wilk W-test was used to determine whether the quantitative data showed normal distribution. The data did not show a normal distribution. Quantitative data were presented with median and minimum–maximum values. Mann–Whitney U-test was used to compare the data. For comparison of qualitative data, the Chi-square test, Fisher's exact test, or Monte Carlo exact Chi-square test was used when necessary.

Some clinical and laboratory parameters including age, gender, Karnofsky Performance Status (KPS), diagnosis, lung expansion, pleural fluid amount, catheter size, catheter duration, hemorrhagic pleural fluid, pleural fluid pH, protein, albumin, cholesterol, and lactate dehydrogenase (LDH) levels were analyzed in univariate logistic regression model. Moderate pleural effusion meant pleural effusion occupying up to 50% of hemithorax; large pleural effusion meant occupying more than 75% of hemithorax. The median values of pH, protein, albumin, cholesterol, and LDH of the pleural fluid were used. Adjustment for significant variables in univariate analysis ($P \leq 0.10$) was performed by multivariate logistic regression analysis to demonstrate the effect of the procedure on the success of pleurodesis. Survival time was accepted from pleurodesis to death. Survival times were calculated using the Kaplan–Meier method and compared with the log-rank test.

Results

A total of 60 patients were randomized. After catheter placement and fluid drainage, 1 patient in the talc group and 5 patients in the autologous blood group opted out of the study because they withdraw from the study. In this study, talc pleurodesis was performed in 29 patients and autologous blood pleurodesis in 25 patients. Most of them had malignant pleural effusion except two patients. There was no difference between the two groups in terms of mean age, gender, primary diagnosis, KPS, pleural fluid amount, catheter size, catheter duration, hemorrhagic pleural fluid, and pleural fluid pH, protein, albumin, cholesterol, and LDH [Table 1].

The overall success rate of pleurodesis (complete and partial response) in the 1st month was 72.0% in the autologous blood group and 69.0% in the talc group. There was no statistically significant difference between the two groups in terms of the efficacy of pleurodesis ($P = 0.903$).

There were no life-threatening events that occurred in both the groups. The most commonly reported complications were fever and pain, and both were higher

Table 1: Comparison of talc and autologous blood pleurodesis groups in terms of demographic and clinical features

Variables	Talc group (*n*=29)	Autologous blood group (*n*=25)	*P*
Age (years), X±SD (minimum-maximum)	63.0±14.4 (34-85)	64.1±9.0 (46-85)	0.738
Gender (male/female), *n*	16/13	14/11	0.951
Diagnosis, *n* (%)			
Malignant mesothelioma	12 (41.4)	11 (44.0)	0.977[a]
Lung cancer	10 (34.5)	8 (32.0)	
Others	7 (24.1)	6 (24.0)	
KPS, X±SD (minimum-maximum)	81.03±8.17 (70-100)	81.20±6.00 (70-90)	0.934
Pleural fluid amount, *n* (%)			
Moderate	9 (31.0)	7 (28.0)	0.808
Large	20 (69.0)	18 (72.0)	
Catheter size, *n* (%)			
<24	2 (6.9)	3 (12.0)	0.653[b]
≥24	27 (93.1)	22 (88.0)	
Catheter duration (day), median (minimum-maximum)	6 (2-16)	6 (2-35)	0.944
Hemorrhagic pleural fluid, *n* (%)			
No	23 (82.1)	24 (96.0)	0.196[b]
Yes	5 (17.9)	1 (4.0)	
Pleural fluid characteristics, median (minimum-maximum)			
pH	7.37 (7.08-7.49)	7.41 (7.28-7.56)	0.117
Protein (g/dl)	4.50 (3.68-5.60)	4.70 (0.90-5.70)	0.920
Albumin (g/dl)	3.00 (1.50-3.70)	3.00 (0.60-3.30)	0.355
Cholesterol (mg/dl)	88.00 (44.00-306.00)	89.00 (9.00-160.00)	0.812
LDH (IU/l)	560.50 (13.00-2474.00)	488.00 (118.00-4327.00)	0.841

[a]Monte Carlo exact Chi-square test, [b]Fisher's exact test. SD: Standard Deviation, KPS: Karnofsky Performance Status, LDH: Lactate dehydrogenase

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in the talc group (for fever 37.9% and 12.0%, $P = 0.030$; for pain 34.5% and 0%, $P = 0.001$, respectively). The rest of the complications were empyema in two patients in the talc pleurodesis group, entry site infection in one patient in the talc pleurodesis group and two patients in the autologous blood group, and hypotension in one patient in the talc pleurodesis group [Table 2].

Table 3 presents the effect of various factors on successful pleurodesis in both the groups. The complete lung expansion was an important factor for successful pleurodesis in the talc group but not in the autologous blood group (P = 0.001 and $P = 0.673$, respectively). The catheter duration of fewer than 7 days was an important factor for successful pleurodesis in the autologous blood group but not in the talc group ($P = 0.034$ and $P = 0.675$, respectively).

The effect of the procedure on the successful pleurodesis after adjustment for lung expansion and catheter duration was evaluated by multivariate logistic regression analysis. The effect of the procedure on pleurodesis success was not found to be significant (odds ratio [95% confidence interval (CI)]: 1.51 [0.40–5.77]; $P = 0.548$).

There was no significant difference between the groups in terms of survival times (median survival times ± standard error [95% CI] were 10.0 ± 1.56 [6.95–13.05] and 9.0 ± 1.68 [5.72–12.28] months for the talc and autologous blood groups, respectively) (log-rank: 0.057; $P = 0.811$) [Figure 1].

Discussion

This study has compared the efficacy and safety of the autologous blood pleurodesis with the talc pleurodesis in patients with recurrent symptomatic pleural effusion and showed that the autologous blood pleurodesis to be as effective and safe as the talc pleurodesis. However, although there was no life treating complications in both the groups, fever and pain after the talc pleurodesis were higher than in the autologous blood pleurodesis. The lung expansion was an important factor for successful pleurodesis in the talc group, whereas the catheter duration was an important factor in the autologous blood group. The procedure was not a significant factor on the success of pleurodesis. The survival between the two groups was also similar.

Talc is an effective, easily accessible, and inexpensive agent that has been used for many years as a pleurodesis agent. Since it is an old and well-known agent, the effect of other agents is evaluated by comparing it with talc in pleurodesis studies.[1,2] However, it has been the subject of discussions about its safety for many years.[2,4] The reason for the debate is that it causes ARDS and cancer, especially in benign patients over the years.[3,7,8] A procedure which has these advantages and does not show the disadvantages of talc would be the ideal pleurodesis method. From this point of view, we thought that the autologous blood pleurodesis procedure, which has been used to end the prolonged airway, could respond to these expectations.

Cochrane meta-analysis showed that talc poudrage ranked highly compared with other agents.[1] The success rate of talc pleurodesis is about 80%.[17] In our study, the success rate appears to be slightly lower than in literature. Intact mesothelial cells and cytokines play a crucial role in the initiation and maintenance of pleural inflammation and pleural space obliteration.[18] Therefore, the lungs should be expanded and pleural layers must be confronted for successful pleurodesis. The rate of patients with complete lung expansion was higher among the patients with successful pleurodesis in the talc group in the present study. If lung expansion does not occur, an indwelling pleural catheter is recommended instead of pleurodesis.[19,20] Consistent with the literature, approximately one-third of the

Table 2: Comparison of study groups in terms of expansion of lung and pleurodesis success

Variables	Talc group (*n*=29)	Autologous blood group (*n*=25)	*P*
Lung expansion, *n* (%)			
Incomplete	9 (31.0)	9 (36.0)	0.700
Complete	20 (69.0)	16 (64.0)	
Pleurodesis success, *n* (%)			
Unsuccessful	9 (31.0)	7 (28.0)	0.903[a]
Partial response	9 (31.0)	7 (28.0)	
Complete response	11 (38.0)	11 (44.0)	
Complication, *n* (%)			
Pain	10 (34.5)	-	0.001[b]
Fever	11 (37.9)	3 (12)	0.030[b]
Empyema	2	-	
Entry site infection	1	2	
Hypotension	1	-	

[a]Monte Carlo Exact Chi-square test, [b]Fisher's exact test

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Table 3: The effect of various factors on successful pleurodesis in talc and autologous blood groups

Variables	Successful pleurodesis in the talc group, *n* (%)	*P*	Successful pleurodesis in the autologous blood group, *n* (%)	*P*
Age				
<65	9 (64.3)	0.700	10 (83.3)	0.378
≥65	11 (73.3)		8 (61.5)	
Diagnosis				
Malignant mesothelioma	9 (75.0)	0.223[a]	8 (72.7)	0.302[a]
Lung cancer	3 (42.9		3 (50.0)	
Others	8 (80.0)		7 (87.5)	
Gender				
Male	10 (62.5)	0.454	10 (71.4)	1.000
Female	10 (76.9)		8 (72.7)	
KPS				
<80	15 (68.2)	1.000	16 (72.7)	1.000[b]
≥80	5 (71.4)		2 (66.7)	
Lung expansion				
Incomplete	2 (22.2)	0.001[b]	6 (66.7	0.673
Complete	18 (90.0)		12 (75.0))	
Pleural fluid amount				
Moderate	7 (77.8)	0.675	6 (85.7)	0.626
Large	13 (65.0)		12 (66.7)	
Catheter size				
<24	2 (100.0)	1.000[b]	1 (33.3)	0.180[b]
≥24	18 (66.7)		17 (77.3)	
Catheter duration (day)				
<7	15 (71.4)	0.675	14 (87.5)	0.034[b]
≥7	5 (62.5)		4 (44.4)	
Hemorrhagic pleural fluid				
No	15 (65.2)	0.281	17 (70.8)	1.000[b]
Yes	5 (100.0)		1 (100.0)	

[a]Monte Carlo Exact Chi-square test, [b]Fisher's exact test. KPS: Karnofsky Performance Status

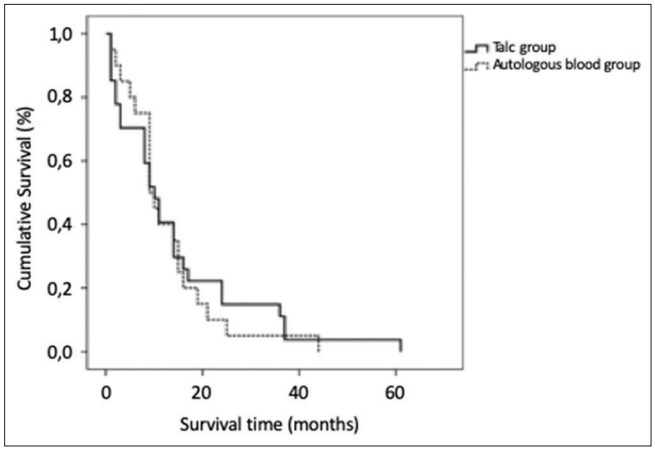


Figure 1: Comparison of study groups in terms of median survival times

patients have nonexpandable lung in our study.[17,21] The low success rate of pleurodesis may be due to the nonexpandable lung. In a recent randomized study, autologous blood pleurodesis was compared with talc.[14] They excluded trapped lung and found that the success rate of autologous blood pleurodesis was around 82%, comparable to talc (87%).[14] High rates may be due to pleurodesis only in case of a fully expanded lung. It is not yet clear how nonexpandable lung can be detected. One way to predict lung expansion could be the intrapleural pressure measurement.[19] The role of intrapleural pressure measurement in determining lung expansion is not clear. It is thought that large-volume thoracentesis may be helpful in determining both fluid-related dyspnea and lung expansion.[19] The main point of this study was that there was no difference in terms of lung expansion among the patients who have successful pleurodesis in the autologous blood group. Filling the cavity with blood and closing the gap may be important as much as inflammation for pleurodesis with autologous blood. Therefore, autologous blood pleurodesis may be a choice of an inexpensive and effective method in patients whose lungs do not expand and do not have the possibility of an indwelling pleural catheter.

Autologous blood pleurodesis has previously been used to control pleural fluid in a limited number of studies.[14,15] In these studies, autologous blood pleurodesis was compared with talc and tetracycline prospectively by the same authors. They excluded trapped lung and found that the success rate of autologous blood pleurodesis was around 80% in both studies.[14,15] In their studies,

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no difference was found between the autologous blood pleurodesis with other agents in terms of the success rate of pleurodesis similar to our study. All pleurodesis agents cause inflammation and fibrosis in the pleural space. Autologous blood pleurodesis is also effective as a blood patch filling the pleural space. In our study, we found that if autologous blood pleurodesis was not successful up to 7 days, it would not happen in the following period. Therefore, keeping the catheter longer may increase the risk of complications, so pleural fluid should be controlled with another method without waiting.

The most important early and late complications of talc pleurodesis are ARDS and malignant transformation, respectively. For many years, some authors recommended that talc should not be used due to the risk of ARDS.[4] It was emphasized that this effect was more pronounced with the high dose of small particle size talc.[5,6] In a recent study, older age and underlying interstitial abnormalities were stated as risk factors for developing ARDS after talc pleurodesis.[7] We see that the tight opposition to the use of talc in previous years, especially United States, has gradually loosened in recent years and has been replaced by modest recommendations.[22] Likewise, talc-induced malignant transformation has been a subject of debate for many years. It has been reported that asbestos-free talc may cause malignant transformation.[8] A recent assessment suggested that asbestos-free talc did not increase the risk of cancer.[9] Of course, this does not matter in malignant patients with limited survival. However, autologous blood pleurodesis should be kept in mind as an option in benign pleural effusion that cannot be controlled by medical treatments such as hepatic hydrothorax, nephrotic syndrome, and congestive heart failure. In our study, no life-threatening complication was reported in either group. However, empyema, which is a significant complication, was found to be higher in the talc group, contrary to expectations.[12] As mentioned above, if autologous blood pleurodesis is not successful within a week, another method should be considered. Otherwise, prolonged catheter duration may increase the risk of infection. As expected, pain and fever were more common in the talc group by following the literature.[14]

There is an association between achieving successful pleurodesis and survival in patients with malignant pleural effusion.[23] Several factors can influence survival in malignant patients. However, it has been suggested that talc prolongs survival time by inducing intrapleural immune response. This is presented as an argument, especially in malignant mesothelioma, a primary tumor of the pleura.[24,25] There is an ongoing clinical trial related to this topic in our clinic. There was no significant difference between the groups in terms of survival times in this study.

The study has some limitations. Although it is a prospective study, some patients withdrew from the study. This resulted in an unequal number of patients between the groups in a randomized trial.

Conclusion

Recurrent symptomatic pleural effusion remains an important issue for both patient and physician. The common option to manage pleural effusion is pleurodesis with different agents. Autologous blood pleurodesis is a simple, inexpensive, effective procedure and does not appear to be associated with a significant risk of adverse events for patients with recurrent symptomatic pleural effusion. Especially, it may be preferred in patients with incomplete lung expansion. Further studies are required to confirm the results of this study.

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Conflicts of interest
There are no conflicts of interest.

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