Pleural manometry during thoracocentesis in patients with malignant pleural effusion: A randomized controlled trial

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Research Article

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Abstract

Background

Large volume therapeutic thoracentesis may be associated with re-expansion pulmonary edema RPE. Without the use of pleural manometry, this limits the amount of fluid drained. We investigated whether monitoring of pleural pressure with manometry during thoracentesis would avoid RPE or allow larger volume drainage.

Research Question

We wanted to see if using manometry to measure pleural pressure during thoracentesis may help minimize RPE or allow for more volume drainage.

Patients and Methods

We did a randomized controlled trial involving 110 patients with large malignant pleural effusions. Patients were randomly allocated to obtain thoracentesis with or without pleural manometry. The primary outcome was overall chest discomfort symptoms, the amount of fluid aspirated, and pleural pressures. This trial is listed on ClinicalTrials.gov as NCT04420663

Results

The mean amount of total paracentesis fluid withdrawn from the control group was 945.4 ± 78.9(ml) and 1690.9 ± 681.0(ml) from the cases group ($p < 0.001$). clinical signs of RPE appeared in (n = 20) (36.3%) of patients of cases group while no signs of RPE appeared in controls (p-value < 0.001). opening pleural pressure was 13.4 ± 12.7 cm H2O in non-REP cluster vs 23.5 ± 5.7 cm H2O in REP cluster (p-value = 0.002). The difference between opening and closing pressures between the non-REP and REP cluster was (32.8 ± 15.6 vs 42.2 ± 13) respectively. (p-value = 0.02). Total fluid withdrawn from non-REP was 1828.5 ± 505ml in comparison to 1450 ± 875ml in the REP cluster (p-value = 0.04)

Interpretation

Pleural manometry is useful in malignant pleural effusion to increase the amount of fluid withdrawn But has no role in preventing RPE. The drop of pleural pressure of more than 17cm H2O should be avoided. Our findings do not support the routine use of this approach.

1 Introduction

Pleural effusion is detected in over 1.5 million patients in the United States each year, making therapeutic thoracocentesis one of the most prevalent medical operations.[1]

The activity of the respiratory muscles causes cyclic variations in pleural pressure, which are directly responsible for both inspiration and expiration.[1] Throughout the breathing cycle, pleural pressure stays lower than air pressure under normal physiological circumstances. Normal, cyclic fluctuations in pleural pressure (between 3 and 5 cmH2O and 6 to 8 cmH2O) are important in respiratory physiology. [1 2]

Both pneumothorax and pleural effusion are important pleural diseases that frequently result in increased pleural pressure, which may be accompanied with clinical symptoms and a restricted ventilatory pattern. Pneumothorax aspiration and large volume therapeutic thoracentesis, on the other hand, may be accompanied with a considerable drop in pleural pressure. [2] Despite this, certain data does not support its usual usage during thoracocentesis. [3]It has been proposed that an uncontrolled reduction in pleural pressure is one of the mechanisms implicated in the development of several significant thoracentesis consequences, such as re-expansion pulmonary edema (RPE[2]

The prevalence of RPE is mainly unclear, although has been found to range between 0.2 and 14 percent 4. Because the majority of RPE patients are asymptomatic or have relatively minor symptoms, the real incidence is likely underreported. [5]. It should be noted that previous data indicate that the mortality risk related with RPE might be as high as 20% in extreme situations. The symptoms, which include a persistent cough, chest pain, tachycardia, dyspnea, and hemodynamic instability, generally appear within 24 hours of pleural fluid or air removal. [4]

Large amounts of pleural effusion can be safely evacuated if the pleural pressure does not fall below 20 cmH2O; however, the risk of RPE formation appeared to be related to the degree of the pleural pressure decrease rather than the volume of pleural fluid drained. However, because pleural manometry was not generally accessible, the authors advised that the volume of Respiratory removed pleural effusion not exceed 1000mL unless pleural pressure was assessed. [6] To minimize extremely negative pleural pressure, the British Thoracic Society recommends limiting drainage to 1.5 L of fluid. [7]

Because changes in pleural pressure cannot be anticipated using clinical or radiological data, direct, real-time monitoring of pleural pressure during therapeutic pleural operations is the only option to limit the risk of RPE. [2]

We wanted to see if monitoring pleural pressure with manometry during thoracentesis would prevent RPE or allow for bigger volume drainage.

2 Methods

2.1 Patients:

The study's goal was to quantify pleural pressure during thoracocentesis in patients with malignant pleural effusion and assess the use of those data in both diagnostic and treatment choices. The primary result was the quantity of total fluid aspirated during thoracocentesis and the overall chest pain sensations of RPE from before to after the surgery.

We conducted a randomized controlled trial guided by the CONSORT statement[8] during the months of August 2019 and December 2021-as the sample size reached- We enrolled 110 patients with significant volume malignant pleural effusion who were referred to our Cardiothoracic Department at Ain Shams University for therapeutic thoracentesis. Patients were assigned at random to have thoracentesis guided just by symptoms (control) or symptoms with pleural manometry. The randomization schedule was developed by a computer. To determine the quantity of pleural effusion, we employed a simple erect posteroanterior chest X-ray.[9] The extent of the effusion was evaluated using the well-known method of counting intercostal spaces (ICS) from the costophrenic angle (mild-localized to 1 ICS, moderate 2–3 ICS, severe 4 ICS). [10] We split the patients into two groups at random: 1/ Cases: thoracocentesis with pleural manometry; 2/ Controls: thoracocentesis without pleural manometry. During therapeutic thoracentesis, all patients provided informed permission for pleural pressure monitoring.

There were specified inclusion requirements, which were as follows: (1) age between 18 and 85 years, (2) moderate to severe pleural effusion occupying at least one-third of the ipsilateral hemithorax in P-A chest radiograph (CXR), (3) no contraindications for therapeutic thoracentesis, (4) general health condition allowing prolonged therapeutic thoracentesis procedure, and (5) patients with malignant pleural effusion proven by pleural cytology or radiological criteria for malignancy.[11] Patients with non-malignant effusion, patients with very small amounts of pleural effusion, patients on mechanical ventilation, patients on anticoagulant therapy, non-free-flowing effusions, inability to maintain a seated position for the procedure, and patients refusing to be subjected to thoracocentesis were excluded from the study. The institutional review boards and the ethics committee both authorized the study. This randomized clinical study was listed on 09/06/2020 on ClinicalTrials.gov as NCT04420663.

2.2 Randomization:

We randomly allocated patients to either thoracentesis guided just by symptoms (control) or thoracentesis guided by symptoms plus manometry. The group assignment sequence was produced by a machine. A study assistant created sealed opaque envelopes with treatment allocations.

2.3 Methods of procedure:

In a sitting position, therapeutic thoracentesis was conducted. Betadine antiseptic solution was used to clean the skin. Pleural aspiration was performed in a sterile environment utilizing full aseptic methods. As a local anesthetic, 5–10 cc Lidocaine 2 percent was injected into the puncture site. Using a wide-bore catheter (central venous line 7 Fr with 3 ports) as a pleural catheter, a wide-bore catheter was introduced into the pleural cavity - using the Seldinger method - in the dependant region blindly defined by

auscultation (usually one intercostal space above the diaphragm). The 3-way adapter connects a basic water manometer to the pleural catheter. Figure 1.jpg

The system (IV tubing) purged air with normal saline, and the vertical reference point for a pressure of zero was established at the level of catheter insertion into the chest. The CVP line is moved forward until fluid is aspirated. The cable was then removed, and the CVP biggest port line was connected to a 3-way adaptor. The infusion line is attached to one side port of the 3-way adapter, which drains into the drainage collection bag, and the other side port of the 3-way adapter is connected to a 50 cm plastic syringe for suctioning the pleural fluid under negative pressure. The other CVP port line was pre-flushed with normal saline and attached to an infusion line, after which a 500 ml bag of normal saline was hung down to 40 cm below the puncture site and then elevated (creating a "U") with the ascending arm connected to the IV stand. Figure 2.jpg

Prior to the start of pleural fluid extraction, baseline pleural pressure was measured. After that, the pleural fluid was aspirated. When one of the following events happened, the pleural fluid removal was terminated: Thoracocentesis completion is defined as no more fluid in the pleural cavity, whereas thoracocentesis incompletion is described as poor procedure tolerance, i.e., the development or exacerbation of symptoms (e.g., severe dyspnea, coughing, chest pain, tachycardia). A closing pleural pressure of -30 cm water in the manometry group or a fluid withdrawal of 1000 ml in the control group were additional signs that the operation should be stopped. Pleural pressure was measured during silent tidal breathing after each 200 ml of pleural fluid withdrawal until the fluid withdrawal was stopped. The closure pressure was determined by using the most recently measured pressure. All patients' demographics, initial and subsequent pleural pressures, closure pressure, total fluid volume extracted, complaints with the original diagnosis, amount of effusion in pre- and post-procedural CXR, pre- and post-procedural SO2, and symptoms of REP, if any, were noted.

2.4 Statistical analysis:

A two-sample t-test was used to determine that a sample size of 110 patients (55 in each group) would provide 80 percent power with a probability of a type I error set at = 0.05 based on the previously reported amount of pleural fluid withdrawn during thoracocentesis and pleural pressures measured by pleural manometry.

Data were statistically examined using the social science statistical software (SPSS). Means and standard deviations for continuous variables, percentages and frequencies for categorical variables, and an inquiry for outliers were all part of the descriptive statistics. For statistical analysis, we assumed normality and homoscedasticity. For quantitative data analysis, hypothesis student's "t" tests will be used, while qualitative data (ordinal, categorical) will be evaluated using the chi-square test (x2). For all statistical comparisons, a P-value of 0.05 is considered significant, while a P-value of 0.01 is regarded extremely significant.

We performed two predetermined main sub-analyses: a subgroup analysis of the outcomes between case and control groups. The second subanalysis was performed comparing the clusters that experienced re-expansion pulmonary edema and those that did not in order to determine the most important elements causing this pathophysiology.

3 Results

3.1 Patient and Effusion Characteristics

The current study examined 150 individuals, 110 of whom were randomly given thoracocentesis and were included in the final analysis (55 in each group).figure 3.jpg The control group had a mean age of 59.6 ± 7.4 years while the cases group had a mean age of 61.6 ± 9.2 years. The control group had 34 (61.8%) men, whereas the cases group included 37 (67.2%) males. Mesothelioma (n = 100) was the most frequent malignancy, with 10 individuals suffering from lung cancer. According to the occupied zones on Chest X-ray, 38 (69%) patients in the control group exhibited significant pleural effusion, compared to 42 (76.3%) in the cases group. All patients (n = 100) had dyspnea as their pre-procedural primary complaint. The mean pre-thoracocentesis oxygen saturation in the control group was 93.9 ± 3.8 against 94.1 ± 2.4 in the case group.

At baseline, there was no significant difference in age, sex, complaint (chest discomfort and dyspnea scores), pleural fluid appearance, amount of malignant pleural effusion in CXR, initial diagnosis, laterality of thoracentesis, or pre-thoracocentesis oxygen saturation between the manometry and non-manometry groups. (p-value > 0.05) Table 1

3.2 Therapeutic Thoracocentesis

In 55 of the 110 patients (50 percent) included in our research, we performed Therapeutic Thoracocentesis with the assistance of Pleural Manometry (cases group). The average quantity of fluid withdrawn from the controls was 945.4 ± 78.9 ml, compared to 1690.9 ± 681.0 ml from the cases group (p-value0.001).figure 4.jpg The proceedings came to a halt in (n = 20). 36.3 percent of the participants in the case group had clinical indications of RPE. (n = 10) Coughing was experienced by 18.1 percent of patients during drainage (n = 10). During the operation, 18.1 percent of patients suffered coughing and dyspnea, although controls showed no evidence of RPE (p-value0.001). The post-thoracocentesis oxygen saturation in the controls was 94.7 ± 33.4 against 92.3 ± 63.1 in the patients (p-value0.001). The completion of paracentesis was in 20 (36.4 percent) of the controls and 35 (63.6 percent) of the cases (p-value = 0.004). In compared to zero patients in controls, 40 (72.7 percent) of cases were assessed to have inflated lungs without (residual) pleural fluid following the intervention (p-value0.001). In the control group, 55 (100%) of post-procedural CXRs showed inadequate drainage with persisting malignant pleural effusion and a non-expanded lung, compared to 15 (27.3%) in the case group (p-value0.001). Table 1

Table 1
; the difference between cases and controls group in Age(year), Sex, Amount of effusion (degree), Oxygen Saturation% (pre), Total paracentesis fluid withdrew value (ml), Paracentesis completion, Symptoms of Re-expansion Pulmonary Edema, CXR (post), Oxygen Saturation% (post)

		Controls(n = 55)	Cases(n = 55)	P-
Age(year)		59.6 ± 7.4	61.6 ± 9.2	NS
Sex	male	34(61.8%)	37(67.2%)	NS
Amount of effusion (degree)	moderate	17(30.9%)	13(23.6%)	NS
	severe	38(69%)	42(76.3%)	NS
Oxygen Saturation% (pre)		93.9 ± 3.8	94.1 ± 2.4	NS
Total paracentesis fluid withdrew value (ml)		945.4 ± 78.9	1690.9 ± 681.0	0.00
Paracentesis completion		20(36.4%)	35(63.6%)	0.004
Symptoms of Re-expansion Pulmonary Edema	No symptoms of REP	55(100.0%)	35(63.6%)	0.00
	Cough	0	10(18.1%)	
	Cough and Dyspnea	0	10(18.1%)	
CXR (post)	Lung Inflated	0	40(72.7%)	0.00
	Pleural Effusion	55(100%)	15(27.3%)	
Oxygen Saturation% (post)		94.73 ± 3.4	92.36 ± 3.1	0.00

3.3 Pleural Manometry (cases group)

The average quantity of Total paracentesis fluid extracted from the control group was 945.4 ± 78.9 (ml) and 1690.9 ± 681.0 (ml) from the case group (p-value0.001). Complete paracentesis was achieved in 20 (36.4%) of the control group patients versus 35 (63.6%) of the cases group patients (p-value = 0.004). In the post-procedural CXR, 40 (72.7 percent) of the cases group patients had full lung inflated, but none of the control group patients did (p-value0.001). Table 1

There was a significant difference in post-procedural oxygen saturation between the control and case groups (94.7 ± 33.4 vs 92.3 ± 63.1) (p-value0.001); this data is explained by the formation of RPE in a substantial percentage of manometry patients. Table 2

Table 2
; thoracocentesis parameters for cases group

Cases Group parameter	Mean ± SD
Oxygen Saturation (pre)	93.91 ± 3.8
Total paracentesis fluid withdrawn	1690.91 ± 681
Oxygen Saturation (post)	92.36 ± 3.1

3.4 Pleural Pressures in the cases group

The mean opening pleural pressure at baseline was (17 ± 11.7 cm H2O) while the mean closure pressure was (-19.1 ± 10.8 cm H2O). The average decrease in pleural pressure was (36.2 ± 15.3 cm H2O).figure 6.jpg Table 3

Table 3
; mean pleural pressures in cases group

Pleural Pressure	Mean ± SD
Opening pleural pressure	17.09 ± 11.7
Pleural pressure after withdrawal of 200ml	8.82 ± 7.78
Pleural pressure after withdrawal of 400ml	2.18 ± 12.04
Pleural pressure after withdrawal of 600ml	− .55 ± 12.15
Pleural pressure after withdrawal of 800ml	2.22 ± 8.01
Pleural pressure after withdrawal of 1000ml	− .44 ± 7.97
Pleural pressure after withdrawal of 1200ml	-3.25 ± 8.03
Pleural pressure after withdrawal of 1400ml	-6.00 ± 7.91
Pleural pressure after withdrawal of 1600ml	-11.29 ± 11.24
Pleural pressure after withdrawal of 1800ml	-11.67 ± 5
Pleural pressure after withdrawal of 2000ml	-15.80 ± 5.53
Pleural pressure after withdrawal of 2200ml	-21.80 ± 7.45
Pleural pressure after withdrawal of 2400ml	-19.00 ± 0
Pleural pressure after withdrawal of 2600ml	-20.00 ± 0
Pleural pressure after withdrawal of 2800ml	-21.00 ± 0
Pleural pressure after withdrawal of 3000ml	-21.00 ± 0
Closing pleural pressure	-19.18 ± 10.86

3.5 Re-expansion pulmonary edema in the cases group

Re-expansion pulmonary edema occurred in 20 patients (36.3 percent) in the cases group against zero cases in the control group (p-value0.001). The mean pre-procedural oxygen saturation in the no-REP group was 93.8 ± 3.7 percent vs 94 ± 4.1% in the REP group (p-value = 0.9). In the pre-procedural CXR, 25 (71.4%) patients in the no-REP cluster had a severe degree of malignant pleural effusion, compared to 15 (75%) patients in the REP cluster (p-value = 0.8). The opening pleural pressure in the non-REP cluster was 13.4 ± 12.7 cm H2O compared to 23.5 ± 5.7 cm H2O in the REP cluster (p-value = 0.002). While the non-REP cluster had a closing pleural pressure of -19.4 ± 12.3 cm H2O, the REP cluster had a closing pleural pressure of -18.7 ± 79 cm H2O (p-value = 0.8). The difference in opening and closing pressures (a reduction in pleural pressure) was statistically significant between the non-REP and REP clusters (32.8 ± 15.6 vs 42.2 ± 13). (p-value < 0.02).figure 5.jpg Table 4

The total fluid taken from the non-REP cluster was 1828.5 ± 505 ml compared to 1450 ± 875 ml in the REP cluster (p-value = 0.04), indicating that the volume of pleural fluid withdrawn does not correspond with the development of symptoms but that a change in pleural pressure is more relevant.figure 7.jpg
Table 4

Table 4
; the difference between REP and Non-REP clusters in Age(year), Sex, Group, Oxygen Saturation (pre)%, Amount of effusion(degree), Opening pleural pressure (cm H2O), Pleural pressure after withdrawal of 1000ml (cm H2O), Pleural pressure after withdrawal of 2000ml (cm H2O), Closing pleural pressure (cm H2O), Difference between opening and closing pressures, Total paracentesis fluid is withdrawn (ml), Paracentesis completion, Oxygen Saturation (post)%, CXR (post)

		Symptoms of Re-expansion pulmonary edema		P-value
		No REP(n = 35)	REP(n = 20)	
Age(year)		60.7 ± 10.9	63.2 ± 4.6	NS
Sex	male	20(57.1%)	15(75%)	NS
Group	Cases (manometry)	35(63.6%)	20(36.3%)	0.000
	Controls	55(100%)	0	
Oxygen Saturation (pre)%		93.8 ± 3.7	94 ± 4.1	NS
Amount of effusion(degree)	Moderate	10(28.5%)	5(25%)	0.04
	Severe	25(71.4%)	15(75%)	
Opening pleural pressure (cm H2O)		13.4 ± 12.7	23.5 ± 5.7	0.002
Pleural pressure after withdrawal of 1000ml (cm H2O)		-3 ± 7	8.5 ± 2.6	0.000
Pleural pressure after withdrawal of 2000ml (cm H2O)		-18.6 ± 5	-11.5 ± 2.6	0.000
Closing pleural pressure (cm H2O)		-19.4 ± 12.3	-18.7 ± 7.9	NS
Difference between opening and closing pressures		32.8 ± 15.6	42.2 ± 13	0.02
Total paracentesis fluid is withdrawn (ml)		1828.5 ± 505	1450 ± 875	0.04
Paracentesis completion	Incomplete Paracentesis	0	20(100%)	0.000
	Complete Paracentesis	35(100%)	0	
Oxygen Saturation (post)%		93.2 ± 3.2	90.7 ± 2.2	0.003
CXR (post)	Pleural Effusion	0	15(75%)	0.000
	Lung Inflated	35(100%)	5(25%)	

4 Discussion

In this randomized controlled experiment, we evaluated patient clinical outcomes as well as pleural pressure during therapeutic thoracentesis for large malignant pleural effusions. Our findings imply that routine use of manometry during thoracentesis did not minimize symptoms of re-expansion pulmonary edema, but our subgroup analysis suggests that RPE is preventable if fluid aspiration is halted before a pleural pressure drop of 17 cm H2O. Furthermore, we discovered that we can aspirate more fluid > 1000 ml while being directed by pleural pressure.

There has been very little published material on the use of pleural manometry in low-income countries. The explanation for this might be because many pulmonologists do not comprehend the physiological rationale for doing pleural manometry. The absence of pleural speciality training or fellowship programs, as well as the absence of pleural specialization clinics may also contribute to the former[12]

It is a straightforward and relatively safe method that may be included in standard pleural fluid thoracentesis operations. Furthermore, pleural manometry may be more useful in treating patients with malignant pleural effusion, particularly in low-resource settings.

There are several uses for employing pleural manometry during thoracocentesis. A therapeutic thoracentesis can provide superior alleviation of dyspnea in individuals with malignant quickly increasing pleural effusion. In the absence of pleural manometry, it is impossible to determine how much pleural fluid may be safely evacuated in a single session. In such a case, many sessions of "limited" volume thoracentesis will be necessary, resulting in recurrent expenditures and multiple hospital trips for the same procedure. [13]

Furthermore, in the case of a significant pleural effusion, we may need to do a CT scan of the chest or an ultrasound-guided biopsy. If the CT scan or ultrasound-guided biopsy is performed without thoroughly emptying the pleural fluid, the procedure may be technically more difficult. Using pleural manometry to guide a therapeutic thoracentesis may help remove as much fluid as possible, increasing the possibility of information from the CT scan and making ultrasound-guided biopsy simpler. [13]

Water manometers and electrical devices that are simple. Both approaches have advantages and downsides. Water manometers are theoretically simple, inexpensive, and user-friendly, but they lack the capacity to measure and record genuine instantaneous pleural pressure. This is due to continual oscillations of the water column during respiration, as well as the system's relatively high inertia and flow resistance when water is utilized as an indication. As a result, basic water manometers can only estimate the mean values of pleural pressure. Furthermore, abrupt pressure fluctuations, such as those seen when coughing, can considerably falsify the result. [14]

Several studies have been conducted to examine varied patient outcomes when doing pleural manometry. The amount of pleural fluid evacuated has no relation to patient complaints such as chest discomfort or coughing. The onset of chest discomfort, rather than coughing, was related with lower

closure pleural pressures and should be regarded as an indication to discontinue continued thoracentesis.[15]

Similar studies found no significant difference in the number of patients who suffered chest pain or dyspnea after therapeutic thoracentesis when the treatment was performed with manometry vs when the procedure was performed without manometry.[316]

Our research found a link between the degree of pleural pressure decrease, the difference between opening and closure pressure, and re-expansion pulmonary edema after pleural fluid withdrawal. Except for one research, practically all investigations demonstrate a link between pleural pressure measures (opening and closing). Lentz and colleagues,[3] who advises avoiding exceeding 10 cm H2O during thoracocentesis. Based on the mean difference between opening and closure pressure in the no-REP cluster minus the standard deviation, our findings indicate that the degree of pleural pressure decrease during therapeutic thoracentesis should not exceed 17 cm H2O.

Due to the limited number of studies, the classic belief of a drop in pleural fluid pressure below 20 cmH2O to -30 cm H2O should not be an absolute indication for terminating pleural fluid withdrawal to prevent re-expansion pulmonary edema, but the degree of the drop in pleural pressure should be the major determinant of continuing thoracocentesis to prevent RPE.

There are various limitations to this study. For starters, it was not intended to detect re-expansion pulmonary edema, which is the most clinically significant pressure-related consequence after thoracentesis. However, because re-expansion pulmonary edema is uncommon, we opted to construct the research to measure symptoms such as chest tightness, pain, coughing, and dyspnea. We chose a modest closure pressure to end the operation since a larger pressure might have resulted in fewer RPE instances in the manometry group. Second, pleural pressure could only be reliably measured after fluid aspiration had stopped using a water manometer. Using continuous digital pleural manometry during fluid aspiration, operators may be able to detect rapid changes in pleural pressure. However, instruments that provide continuous pleural manometry are not widely accessible for normal clinical usage, thus we relied on the typical basic water manometer. Future comparison research with continuous manometry might be beneficial.

5 Recommendations

Pleural manometry can be used to increase the volume of fluid removed on each occasion in patients with malignant pleural effusion. In our study, manometry has no advantage over traditional thoracocentesis in terms of avoiding RPE. We believe that a reduction in pleural pressure of more than 17 cm H2O should be avoided in order to avoid re-expansion pulmonary edema. Our data do not support the adoption of this method on a regular basis.

Declarations

All Authors confirm that reporting all experiments were performed in accordance with relevant guidelines and regulations under "Ethics approval and consent to participate"

All Authors confirm that all methods were carried out in accordance with relevant guidelines and regulations.

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Figures

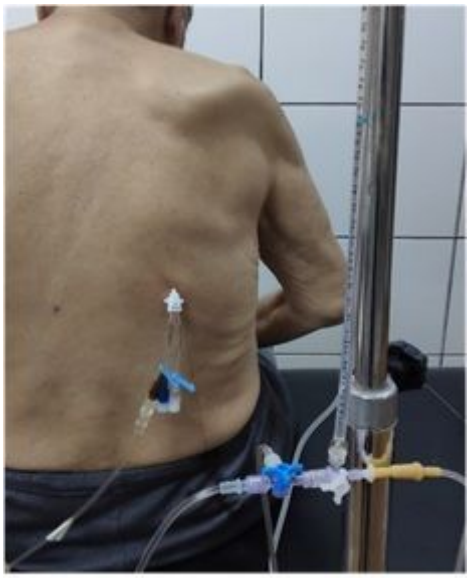

Figure 1

Figure 1

Legend not included with this version.

Figure 2

Figure 2

Legend not included with this version.

Figure 3

Figure 3

Legend not included with this version.

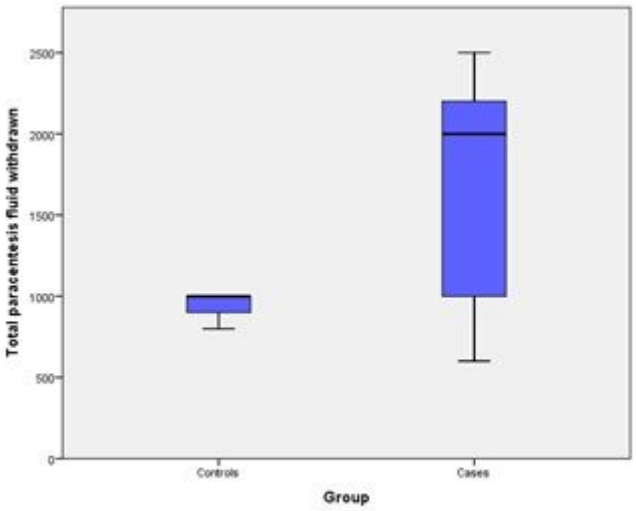

Figure 4

Figure 4

Legend not included with this version.

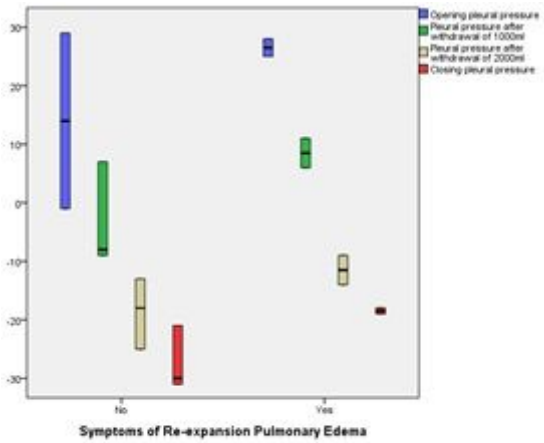

Figure 5

Figure 5

Legend not included with this version.

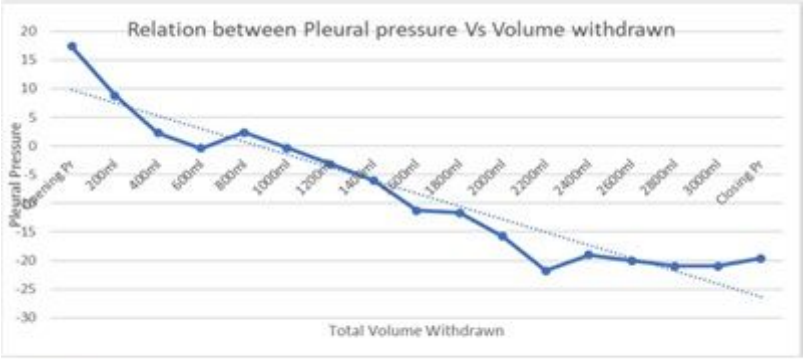

Figure 6

Figure 6

Legend not included with this version.

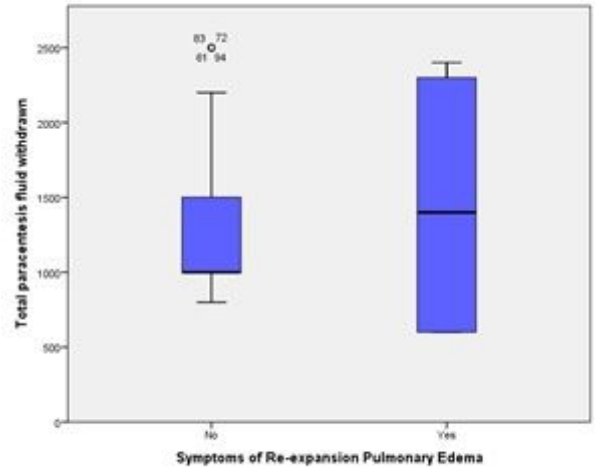

Figure 7

Figure 7

Legend not included with this version.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistMSWord.doc
- clinicaltrials.gov.pdf