Pleurodesis or Indwelling Pleural Catheter for Management of Malignant Pleural Effusion: Evidence Based Case Report

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ABSTRACT

Pleural effusion is a condition when there is an accumulation of fluid in pleural space. The condition may manifest in breathing impairment by limiting lung expansion space. Pleural effusion is suffered by more than 1.5 million people per year in America. A study held in Persahabatan Hospital between 2010-2011 found 119 cases of pleural effusion, 42,8% was malignant pleural effusion. Pleural malignancy is the most common indication for thoracocentesis, thus must be considered in massive pleural effusion (MPE). Therapy for MPE is palliative with the goal being relief of dyspnea. Treatment options for MPE are detemined by several factors: symptoms and performance status of the patient, the primary tumor type and its response to systemic therapy, and degree of lung re-expansion following pleural fluid removal. In this case, we will present a case of malignant pleural effusion as an illustration in searching of evidence in comparing between pleurodesis and indwelling pleural catheter in management of malignant pleural effusion.

Keywords: *Pleural catheter, pleurodesis, malignant pleural effusion.*

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INTRODUCTION

Pleural effusion is a condition when there is an accumulation of fluid in pleural space. The condition may manifest in breathing impairment by limiting lung expansion space. Pleural effusion is suffered by more than 1.5 million people per year in America.[1] A study held in Persahabatan Hospital between 2010-2011 found 119 cases of pleural effusion, 42,8% was malignant pleural effusion.[2]

Depends on the type of the fluid, generally pleural effusion can be classified into transudate and exudate pleural effusion. Most common etiologies of exudate pleural effusion by the incidence are pleural-related malignancies, parapleural infections, and lung embolism.[1] In parapleural infections cases, the volume of the effusion is usually small and rarery massive. Pleural malignancy is the most common indication for thoracocentesis, thus must be considered in massive pleural effusion.[1]

The incidence of malignant pleural effusion (MPE) in population is around 200,000 people per year and it became a common cause of morbidity among cancer patients.[3] It has been associated with reduced life expectancy ranged from 3 months to 12 months depends on the type of primary malignancy, histological type, and stage.[4] In most series, lung cancer is the leading cause of malignant pleural effusion in men (50%) and it has been observed to have the shortest survival time, while breast cancer is the leading cause in women (40%).[4] At least 50% of patients with lung cancer develop pleural effusion regardless of the cell types, but most frequent with adenocarcinoma, while small cell types have a lower incidence.[1]

Therapy for MPE is palliative with the goal is relief of dyspnea.[3] The initial step of managing patients with MPE is to identify the primary lesion of malignancy, so it can be decided whether systemic chemotherapy is indicated.[1] In conditions where the primary malignancy is not responsive to chemotherapy or where chemotherapy cannot improve clinical condition, the removal of pleural

fluid can be considered by a least invasive procedure with minimal morbidity within limited survival period of the patients.[4] There are two primary methods to remove pleural fluid, the insertion of indwelling pleural catheter and the creation of pleurodesis.[1]

Treatment options for MPE are detemined by several factors: symptoms and performance status of the patient, the primary tumor type and its response to systemic therapy, and degree of lung re-expansion following pleural fluid removal. Patients with prognosis less than 1 month can be treated by aspiration alone to relieve symptoms. British Thoracic Society recommends small bore chest tubes followed by pleurodesis in patients other than very short life expectancy. Once effusion drainage and lung re-expansion have been radiographically confirmed, pleurodesis should not be delayed.[5]

Insertion of indwelling pleural catheter (IPC) is indicated in patients whose dyspnea symptom can be relieved after pleural fluid removal and also have good family support to control pleural fluid drainage periodically.[1] Indwelling plural catheter is recommended in condition where pleural apposition is lacking (trapped lung).[5] Otherwise, pleurodesis must be considered.[1]

Pleurodesis is the process by which the pleural space is obliterated by inflammation induced through chemical or mechanical means, to achieve definitive and long standing pleural apposition with fibrosis.[4] Irritative agent recommended for pleurodesis is talc (slurry or insuflated). Some agents can also be used such as tetracylin derivatives (doxycyclin or minocyclin), antineoplastics (bleomycin or mitoxantrone), or povidone iodine. Most physicians considered an expected survival beyond 2-3 months necessary to justify the risk, discomforts, and cost of pleurodesis.[4]

In this case, we will present a case of malignant pleural effusion as an illustration in searching of evidence in comparing between indwelling pleural catheter and pleurodesis in management of malignant pleural effusion.

CASE ILLUSTRATION

Mr. DSN, male, 35 years old patient came to Cipto Mangunkusumo Hospital with chief complain of progressive dyspnea since one day before admission accompanied with throbbing left chest pain and non-productive cough. Patient felt comfortable lying on his left side. Dyspnea initially felt since one month before admission. He went to a hospital and went into some examination. It was said by the doctor that there was fluid accumulation in his left chest. He went through pleural fluid aspiration and an amount of 600 ml reddish fluid was removed. He got chest CT scan examination and was being said that he had a tumor on his left lung.

Patient has no history of chronic cough before. Patient has family history of lung cancer on his uncle and grandmother, also thyroid cancer on his sister. He denied history of smoking, chemical, and asbestoses exposure. On physical examination, there was asymmetrical movement of the chest. On the left lung, there was decrease in vocal fremitus and vesicular sound, also dullness on percussion.

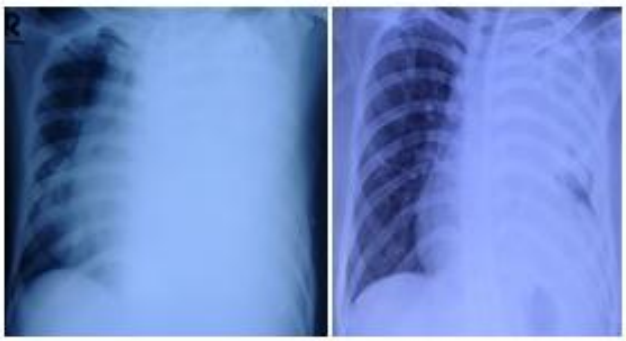


Figure 1. Patient's chest X-ray

Chest X-ray on the admission showed massive left side pleural effusion that pushed trachea and mediastinum to the right side of the chest (left). Chest X-ray after installation of chest tube (right) showed improvement of the effusion and mediastinal shifting.

Chest x-ray showed massive left pleural effusion that pushed mediastinum and trachea to the right side of the chest. Thorax CT scan showed effusion and a mass on upper to lower part of left lung with paracarinal lymphadenopathy, and lytic lesion on T11-T12 spine. Pleural fluid analysis showed serohemorrhagic fluid with exudate characteristic. Transthoracal biopsy result concluded lung adenocarcinoma.

Chest tube was applied to the patient with daily production of pleural fluid around 500 ml per day via water seal drainage. Pleurodesis was performed on patient using bleomycin when the fluid production was less than 200 ml per day which was on 20th day of treatment. After the procedure, chest tube was clamped for 2 days. The fluid production after the clamp was released was less than 200 ml per day. A week after the procedure, patient decided to discharged from

the hospital with his own consent. Chest tube was released, and pleural catheter wasn't installed.

CLINICAL QUESTION

Does the use of pleurodesis improve the symptom of dyspnea on patient with malignant pleural effusion more than indwelling pleural catheter?

Problem : Patients with malignant pleural effusions
Intervention : Pleurodesis
Comparison : Indwelling pleural catheter (IPC)
Outcome : Improvement of dyspnea

METHODS

A search was performed on December, 1st 2015 on PubMed, Cochrane Library, Proquest database using keywords: "malignant pleural effusion" AND "indwelling pleural catheter" AND "pleurodesis" AND "dyspnea". The flowchart is shown in Figure 1. Based on these search strategy, we found 34 articles from PubMed and 11 articles from Cochrane. The inclusion criteria were clinical trial, english language, human subjects, and publication within the past 5 years. After filtered them based on inclusion criteria, we found 18 articles from PubMed and 9 articles from Cochrane. There was no meta-analysis nor systematic review found that directly compared the using of IPC and pleurodesis in which are suitable for our clinical question. After screening abstract, we found 2 clinical trials from both search engine. After filtering double articles, we got 2 clinical trial articles.

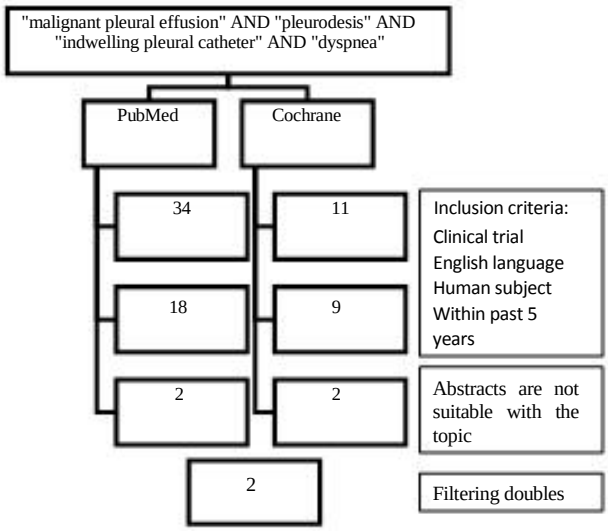


Figure 2. Flowchart of selecting articles used in EBCR

RESULTS

We found two trial articles that compared the improvement of dyspnea in patients with MPE treated with IPC and pleurodesis. The first trial article, Second Therapeutic Intervention in Malignant Effusion Trial (TIME2) was published in 2012 by Davies HE, et al.[5] It was the first randomized controlled trial to compare indwelling catheter and talc pleurodesis on patients with MPE on 106 people in England. Adult with clinically confident diagnosis of symptomatic malignant pleural effusion requiring pleurodesis was enrolled. Exclusion citeria were age younger than 18 years, expected survival of less than 3 months, cylothorax, previous

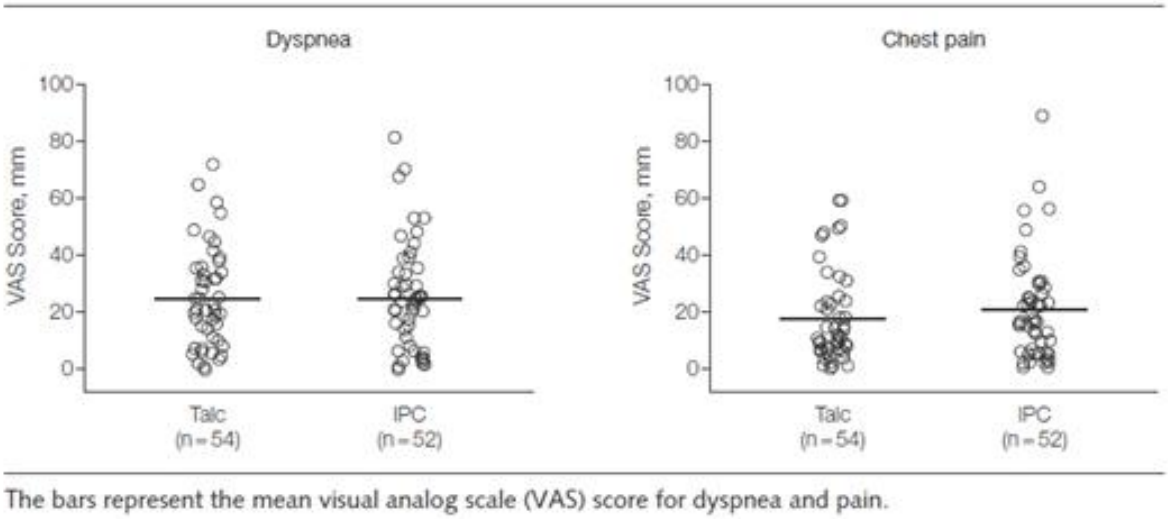


Figure 3. Comparison of dyspnea and chest pain among patients treated with IPC vs patients treated with chest tube and talc slurry pleurodesis.[6]

lobectomy or pneumonectomy, previous attempt of pleurodesis, pleural infection, hypercapnic ventilatory failure, pregnancy, lactating mother, irreversible bleeding diathesis, and irreversible visual impairment.[6]

Indwelling Pleural catheter was installed in 52 patients, and 54 patients received pleurodesis. Patients followed up for 12 months. The observed outcomes were improvement dyspnea, improvement in chest pain, hospital length of stay, mortality, quality of life, and adverse events. The primary outcome was the mean daily dyspnea over 42 days after enrollment as measured by 100 mm visual analog scale (VAS) measured by 2 independent researchers. The secondary outcomes were the proportion of patients achieving clinically significant decrease in mean VAS dyspnea over first 42 days (10 mm); mean VAS dyspnea at 6 weeks, 3 months, and 6 months; mean daily chest pain at 6 weeks, 3 months, and 6 months; night spent in hospital from randomized to discharged; all cause mortality up to 1 year; self reported global quality of life assessed by EORTC-QLQ 30 as percentage; and frequency of serious and nonserious adverse events.[6]

This trial found clinically significant decrease in dyspnea within first 42 days in IPC group on 86% of patients, and 74% in pleurodesis group (OR 0.9; 95% CI 0.18-4.43; p=0.9) (Figure 1). The decrease of dyspnea VAS in first 42 days was around 24,7 mm on IPC group compared to 24,4 mm on pleurodesis group. The difference was considered clinically and statistically insignificant (0.16; 95% CI (-6.82)-(7.15); P=0.96). However after 6 months of follow up, the difference of dyspnea improvement in the IPC group compared with pleurodesis group became clinically and statistically significant (-14mm; 0,95% CI (-25.2)-(-2.8); P=0.01). (Figure 2)[6]

In this trial, there was no significant difference between IPC and pleurodesis in the improvement of chest pain with VAS over 42 days of 8,2 mm (95% CI 0.3-16.2) in IPC group and 4.4 mm (95% CI 3.8-12.6) in pleurodesis group; mortality (-0.8 months 95% CI (-2.4)-8; P=0.32) (Figure 4), or changes in patient's quality of life that was assessed with EORT QLQ-30 (4.8; 95% CI (-1.6)-11.2; p=0.14). Patient's length of stay in IPC group was significantly shorter than who got pleurodesis (-3.5 days; 95% CI (-4.8)-(-1.5); P<0.001). Nevertheless, the incidence of adverse event was significantly higher in IPC group than in pleurodesis group (OR 4.7; 95% CI 1.75-12.6; P=0.002) (Table 1).[6]

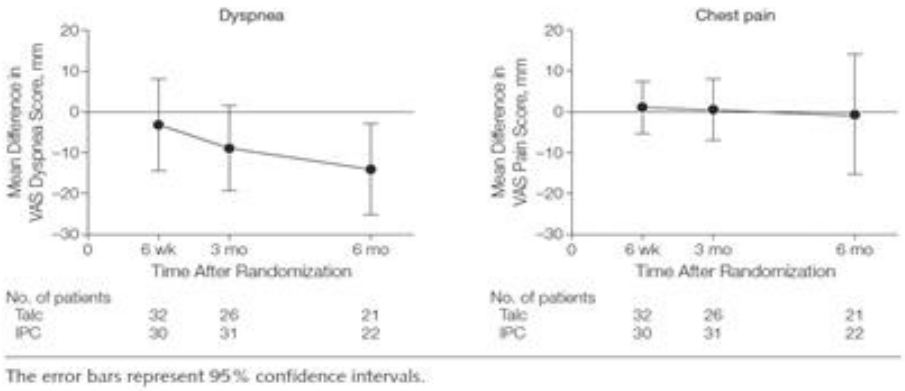


Figure 4. Mean difference in visual analog scale for dyspnea and chest pain[6]

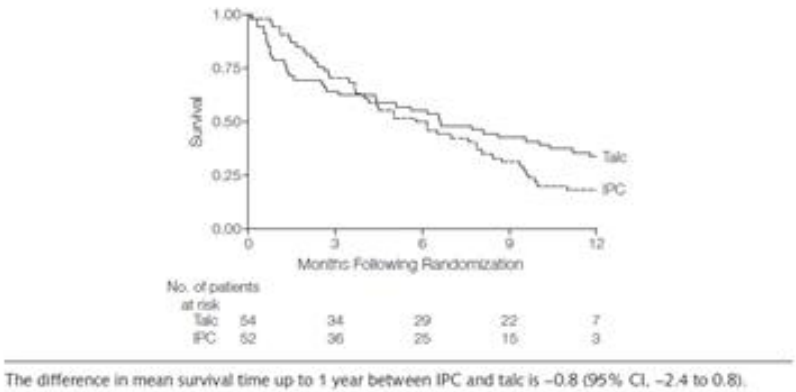


Figure 5. Survival estimates between patients treated with indwelling plural catheters vs. patients treated with chest tube and talc slurry pleurodesis.[6]

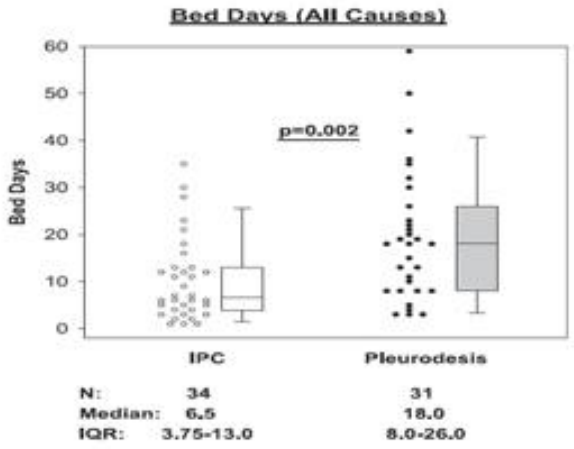
Table 1. Summary of adverse events by treatment group[6]

	IPC		Talc	
Type of Adverse Event	Serious	Nonserious	Serious	Nonserious
Pleural infection	5	2	1	0
Cellulitis	1	5	0	1
Symptomatic fluid loculation requiring fibrinolytics	1	2	1	0
Catheter site metastases	0	1	0	0
Catheter blockage	1	9	1	0
Other[b]	1	0	2	3
Total	9	19	5	4

Abbreviations: IPC, indwelling pleural catheter; talc, chest tube and talc slurry pleurodesis.
[a] This table represents the total number of adverse events. A single patient may have had more than 1 adverse event.
[b] The serious adverse events included in the "Other" category were chest pain requiring readmission (1 IPC), surgical emphysema (1 talc), persistent air leak (1 talc). The 3 nonserious adverse events in the talc group were all chest tube displacement prior to pleurodesis. The complications of symptomatic fluid loculation requiring fibrinolytics, cellulitis, and blocked catheter in the talc group were observed in 2 patients who had IPCs inserted following failure of pleurodesis.

The second trial by Fysh ETH, et al. in 2012, compared the length of stay of patients with MPE receiving IPC compared to pleurodesis.[7] The trial was a prospective multicenter study. The study was nonrandomized but governed by the choice of patients. Of 160 patients with MPE enrolled, 65 had symptomatic MPE, in which 34 patients elected to be treated with an IPC and 31 with pleurodesis. The chief endpoint of the trial was the length of stay due to admission of any causes. Other end points was the control of the effusion, short term quality of life, symptom measures, and major complications. The result of the study was that group treated with IPC had significantly shorter length of stay (median 6.5 days IQR 3.75-13) compared to pleurodesis (median 18 days IQR 8-26) (p=0.002). The differences in pleural effusion-related hospital bed days were even more pronounce with IPC group median 3.0 days (IQR 1.75-8.25) vs pleurodesis group 10.0 days (IQR 6.0-18.0) (<0.001) (Figure 5).[7]

Patients with IPC shown to have better effusion control and improvement of dyspnea compared to pleurodesis (86.5% vs 67.7%) and (93.3% vs 78.6%) but both of the differences was statistically insignificant (P=0.12) and (P-0.33). In patients with IPC, the improvement of short term quality of life was significantly higher than patients with pleurodesis (93.3% vs. 50%) (P=0.02) (Figure 6). Complication rates during study period was higher in pleurodesis group compared to IPC groups (45.2% vs. 18.9%) (P=0.04) (Table 3).[7]



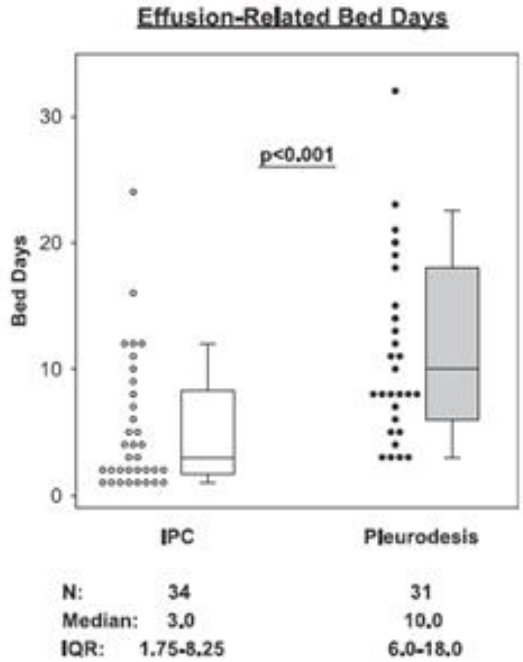


Figure 6. Total number of days in hospital throughout the follow up period from any cause of admission (left) and related to effusion (right)

Table 2. Short term QOL and dyspnea scores.[7]

Score Type	Significantly Improved	Unchanged or Deteriorated	*P* Value
QoL scores			.02
IPC (n = 15)	14 (93.3)	1 (6.7)	
Pleurodesis (n = 12)	6 (50)	6 (50)	
Dyspnea scores			.33
IPC (n = 15)	14 (93.3)	1 (6.7)	
Pleurodesis (n = 14)	11 (78.6)	3 (21.4)	

Table 3. Complication rates during study period.[7]

Complication	IPC (n = 37)	Pleurodesis (n = 31)	P Value
Pain postprocedure	2 (5.4)	4 (12.9)	.40
Symptomatic loculation/ failed pleurodesis	5 (13.5)	10 (32.3)	.12
Empyema	4 (10.8)	2 (6.4)	.68
Hemothorax	1 (2.7)	2 (6.5)	.59
Dislodgement of catheter	1 (2.7)	3 (9.7)	.32
No. of patients experienced a complication	7 (18.9)	14 (45.2)	.04

Data are presented as No. (%). See Table 1 legend for expansion of abbreviation.

The critical appraisal for both studies above had been done based on criteria by Centre of Evidence Medicine University of Oxford. It is presented in tables below.

Study	Validity						
	Study design	Number of patients	Randomization	Similarity treatment to control	Blinding	Comparable treatment	Intention to treat analysis
Davis HE, et al.	+	106	+	+	-	+	+
Fysh ETH, et al.	+	65	-	+	-	+	+

Study	Importance	
	How large the treatment effects?	How precise was the estimate of the treatment effect?
Davis HE, et al.	A	Not statistically significant
Fysh ETH, et al.	B	Not statistically significant

A. Clinically significant decrease in mean VAS dyspnea was observed in 42 of 49 patients (86%) in IPC group and in 35% of 47 patients (74%) in pleurodesis group. The ARR was 12% and the NNT was 8.3=9. This difference was not statistically significant (OR 0.9; 95%CI 0.18-4.43; P=0.9).

B. More patients in the IPC group recorded an improvement in dyspnea than in pleurodesis group (93% vs 78,6%). The difference was clinically significant, but did not reach statistically significant (P=0,33). The ARR was 14,4% and the NNT was 6,9=7.

Study	Applicability		
	Similarity with the patient?	Is the treatment is feasible in the patient's setting?	Will the potential benefits of this treatment outweigh the potential harms for this patient?
Davis HE, et al.	+	+	+
Fysh ETH, et al.	+	+	+

DISCUSSION

Recent guideline from British Thoracic Society recommends that graded talc slurry be used as the sclerosing agent of choice delivered via an intercostal tube as first-line management for patients with malignant pleural effusion while indwelling pleural catheter (IPC), or tunneled pleural catheter, insertion is recommended for a select subgroup.[5]

Pleurodesis approach will have the advantage of a time-limited course of treatment and high pleurodesis rate.[8] However, pleurodesis are not always successful and sometimes even contraindicated. Also, patients need to visit the hospital regularly or have to stay hospitalised for several days.[9] Not to mention higher initial hospital bed-day costs are incurred with patients who went through pleurodesis especially in patients with less than 14 weeks of survival.[10] Complications of pleurodesis from some previous studies including risk of pleural infection associated with pleurodesis technique of 0.4%-4%, and also ARDS as high as 9%.[11]

The IPC has acquired widely used especially in patients with malignant pleural effusion and trapped lung, those who had failed pleurodesis and have been shown to have 45% rates of spontaneous pleurodesis.[12] A chronic IPC could provide a simple, completely outpatient way to provide respiratory relief and improvement in quality of life in patients with malignant pleural effusions, the cost of long term need for catheter drainage and care.[9] One of major initial concerns about IPCs was the possibility that they may lead to pleural infection with reported pleural infection rates of 2.8% with typical time to infection around 2 months after insertion.[13] Other complications including pleural malfunction with rate of 9%.[11]

There were some trials comparing both methods in achieving better palliative care for patients with MPE. Two of them compared directly both methods for a better dyspnea improvement. In the first trial, among patients with MPE, there was no significant difference between IPCs and talc pleurodesis in relieving patient-reported dyspnea. Indwelling pleural catheters reduce time in hospital but are associated with an excess of adverse events.[5] In the second trial, it was found that IPC treatment is safe and significantly avoids additional pleural procedures for fluid management with significantly less time in hospital compared with those who received pleurodesis. The quality of life improvement was in favor for the use of IPC, while

there were no significant differences in dyspnea improvement and complication rates for both IPC and pleurodesis.[7]

Randomization was performed in both studies, but blinding could not be performed. The demographic of both groups in both trial was comparable with no significant differences and analyzed in intention-to-treat analysis. Both of the trials had showed that IPC clinically gave dyspnea improvement in bigger proportion than pleurodesis with NNT of 7 and 9 in our current evidence. Even though the results was statistically insignificant. The secondary outcome of length of stay and quality of life was in favor for IPC in both studies. While the incidence of adverse events was different between studies.

In this case report, the patient was still in the inclusion criteria from both study. A 33 years of man with symptomatic left MPE caused by lung adenocarcinoma. The improvement of symptom and radiological imaging after removal of the fluid indicated no trapped lung, so the pleurodesis was indicated as in the previous guideline for management of MPE. Even though, the based on using of IPC was giving NNT of 7-9

The presence of MPE portends a poor prognosis with overall median survival rates are in 4-6 month range, with variation with different type of tumor cell types. Mesothelioma has median survival rates of 6-10 months, breast cancer has 9-11 months, and lung cancer has only 4 months.[8] In our our patient's case, with limited expectancy of survival rate, the preferred choice of paliative care is crucial.

Based on recent evidence we found that dyspnea improvement can be achieved in both pleurodesis and IPC, so the primary palliative method in pleural fluid removal must be chosen in other consideration such as the prognosis of the primary malignancy, the quality of life, length of hospital stay, and the possibility of adverse events.

CONCLUSION

Malignant pleural effusion is a common manifestation in patient with advanced malignancy especially lung cancer. The main goals are directed to palliative therapies with symptom control and quality of life improvement rather than to cure the disease. Recent guideline recommends pleurodesis as first-line management for patients with malignant pleural effusion. However, pleurodesis are not always successful and associated with higher cost, long hospital stay, and some adverse events.

Insertion of an IPC is a useful palliative option for the management of recurrent malignant pleural effusion. It is simple technique that enables fast symptom control and outpatient management. From recent evidence, there are no statistically significant differences between both methods in relieving dyspnea. Therefore the prognosis of the primary malignancy, the quality of life, length of hospital stay, and the possibility of adverse events must be considered in choosing the preferred method for patients. Since IPC and pleurodesis approaches have their own strengths and weaknesses, the possibilities of combining both methods to create an optimal approach to MPE need to be investigated.

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