2022

Comparing the Success Rate of Pleurodesis with Thoracoscopic Talc Poudrage Combined with Indwelling Pleural Catheter versus Thoracoscopic Talc Poudrage in Patient with Malignant Pleural Effusion, A Randomized, Non-inferiority Clinical Trial

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Medicine
Department of Medicine
FACULTY OF MEDICINE
Chulalongkorn University
Academic Year 2022

การศึกษาทางคลินิกแบบสุ่มและไม่ด้อยกว่าเปรียบเทียบอัตราความสำเร็จของการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดร่วมกับการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนังกับการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดในผู้ป่วยที่มีน้ำในช่องเยื่อหุ้มปอดจากภาวะมะเร็งแพร่กระจาย

น.ส.จิตรอนงค์ สูตรเลข

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาอายุรศาสตร์ ภาควิชาอายุรศาสตร์
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2565

Thesis Title	Comparing the Success Rate of Pleurodesis with Thoracoscopic Talc Poudrage Combined with Indwelling Pleural Catheter versus Thoracoscopic Talc Poudrage in Patient with Malignant Pleural Effusion, A Randomized, Non-inferiority Clinical Trial
By	Miss Jitanong Sootlek
Field of Study	Medicine
Thesis Advisor	Vorawut Thanthitaweewat, M.D.

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

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หลักการและเหตุผล: ภาวะน้ำในช่องเยื่อหุ้มปอดจากมะเร็งแพร่กระจายสามารถทำให้ผู้ป่วยมีอาการเหนื่อยและกระทบต่อคุณภาพชีวิต โดยสามารถรักษาด้วยการเชื่อมเยื่อหุ้มปอดด้วยผงทัลค์ หรือการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนัง เพื่อป้องกันการกลับเป็นซ้ำของน้ำในช่องเยื่อหุ้มปอด ลดอาการเหนื่อยและช่วยเพิ่มคุณภาพชีวิตให้กับผู้ป่วย การรักษาด้วยการเชื่อมเยื่อหุ้มปอดด้วยผงทัลค์จะต้องใช้เวลานอนโรงพยาบาลหลายวัน ในขณะที่การใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนังมีอัตราความสำเร็จของการเชื่อมเยื่อหุ้มปอดต่ำกว่า เนื่องด้วยข้อจำกัดเรื่องอัตราการครองเตียงในโรงพยาบาล ผู้วิจัยจึงพัฒนาวิธีการรักษาภาวะน้ำในช่องเยื่อหุ้มปอดจากภาวะมะเร็งแพร่กระจายโดยใช้วิธีการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์ร่วมกับการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนัง

วัตถุประสงค์ของการวิจัย: เพื่อประเมินประสิทธิภาพของการรักษาภาวะน้ำในช่องเยื่อหุ้มปอดจากมะเร็งแพร่กระจายโดยใช้วิธีการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์ร่วมกับการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนังเปรียบเทียบกับการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์แบบวิธีปกติ

วิธีการดำเนินการวิจัย: การศึกษาได้ดำเนินการเป็นการทดสอบความไม่ด้อยกว่าแบบสุ่ม ผู้ป่วยได้ถูกสุ่มแบ่งเป็นสองกลุ่มเพื่อเข้ารับการรักษาด้วยวิธีการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์ร่วมกับการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนัง หรือการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์แบบวิธีปกติ การศึกษาได้รวบรวมข้อมูลเกี่ยวกับคุณลักษณะประชากร, ระยะเวลานอนโรงพยาบาล, อาการและอัตราสำเร็จของการเชื่อมเยื่อหุ้มปอด ผลลัพธ์หลักของการศึกษาคืออัตราสำเร็จของการเชื่อมเยื่อหุ้มปอดที่ 12 สัปดาห์หลังการทำหัตถการ

ผลการวิจัย: ผลการวิเคราะห์ข้อมูลเบื้องต้นจากผู้ป่วย 26 ราย มีอายุเฉลี่ย 61 ปี พบว่าลักษณะพื้นฐานของผู้ป่วยในทั้งสองกลุ่มไม่แตกต่างกัน ยกเว้นคะแนนความเหนื่อยเฉลี่ยเริ่มต้นที่สูงกว่าในกลุ่มทดลอง พบอัตราความสำเร็จของการเชื่อมเยื่อหุ้มปอดในกลุ่มทดลองร้อยละ 88.89 และกลุ่มควบคุมร้อยละ 64.29% โดยมีความแตกต่าง 24.6% [95% CI, -7.83% to 57.03%] นอกจากนี้กลุ่มที่ใช้สองวิธีร่วมกัน ยังพบว่ามีการลดลงของคะแนนความเหนื่อยที่มากกว่า มีอาการเจ็บหลังทำหัตถการน้อยกว่ารวมถึงใช้ยาแก้ปวดน้อยกว่า ระยะเวลาในการรักษาในโรงพยาบาลสั้นกว่า และคุณภาพชีวิตโดยรวมของผู้ป่วยดีขึ้นอย่างมีนัยสำคัญ นอกจากนี้ ไม่มีความแตกต่างในอัตราการเกิดภาวะแทรกซ้อนระหว่างกลุ่มการรักษาสองกลุ่มนี้

สรุป: การรักษาด้วยการเชื่อมเยื่อหุ้มปอดผ่านการส่องกล้องช่องเยื่อหุ้มปอดและพ่นผงทัลค์ร่วมกับการใส่สายระบายทรวงอกชนิดฝังใต้ผิวหนังมีประสิทธิภาพและมีความปลอดภัยในการรักษาผู้ป่วยที่มีอาการเหนื่อยจากภาวะน้ำในช่องเยื่อหุ้มปอดจากมะเร็งแพร่กระจาย

สาขาวิชา	อายุรศาสตร์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2565	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

6470091530 : MAJOR MEDICINE
KEYWORD: Malignant pleural effusion Indwelling pleural catheter Pleurodesis Thoracoscopic talc poudrage

Jitanong Sootlek : Comparing the Success Rate of Pleurodesis with Thoracoscopic Talc Poudrage Combined with Indwelling Pleural Catheter versus Thoracoscopic Talc Poudrage in Patient with Malignant Pleural Effusion, A Randomized, Non-inferiority Clinical Trial. Advisor: Vorawut Thanthitaweewat, M.D.

Background: Malignant pleural effusion (MPE) can cause dyspnea symptoms that greatly impact a patient's quality of life. Talc pleurodesis or indwelling pleural catheter (IPC) insertion are two treatment options that can prevent recurrent MPE, alleviate dyspnea, and improve quality of life. However, talc pleurodesis requires a lengthy hospital stay, while IPC insertion is associated with lower pleurodesis success rates. Due to limited hospital bed capacity, we have devised a practical approach to managing MPE by combining TTP and IPC.

Objective: This study aims to evaluate the efficacy of combined Thoracoscopic talc poudrage (TTP) and IPC compared to TTP alone in patients with symptomatic MPE.

Methods: The study was conducted as a randomized non-inferiority trial at a single center. Patients were randomly allocated to receive either TTP and IPC or TTP alone. The study collected demographic data, hospital length of stay (LOS), symptoms, and pleurodesis success rates. The primary outcome of the study was the success rate of pleurodesis at 12 weeks post-procedure.

Results: Preliminary data analysis from 26 patients with a mean age of 61 years showed that the baseline characteristics were similar between the two groups, except for the baseline mean VAS dyspnea score, which was significantly higher in the TTP+IPC group. Successful pleurodesis at 12 weeks was achieved in 88.89% of the TTP+IPC group and 64.29% of the TTP alone group, with a difference of 24.6% [95% CI, -7.83% to 57.03%]. Additionally, the TTP+IPC group showed a greater reduction in dyspnea, less pain following the procedure, and less analgesic medication use. The hospital LOS was also shorter, and the overall quality of life was significantly better. Furthermore, there was no difference in the incidence of complications between the two groups.

Conclusion: Combining thoracoscopic talc pleurodesis and IPC is both effective and safe for treating symptomatic MPE patients.

Field of Study:	Medicine	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....

ACKNOWLEDGEMENTS

This research was successfully completed with Dr.Vorawut Thanthitaweewat, our primary advisor, who provided invaluable guidance and support at every stage of the research process. The researchers wish to express their heartfelt gratitude to him.

We would like to express our sincere appreciation to the nurses and staff of the respiratory and critical care unit of King Chulalongkorn Memorial Hospital, for their outstanding assistance and cooperation in data collection for this study.

Finally, we would like to extend our deepest thanks to all the patients and their caregivers who graciously contributed their time and efforts to participate in this project. We also wish to acknowledge our parents for their unwavering support and encouragement throughout.

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Introduction

Background and rationale

Malignant pleural effusion represents a common and significant complication in the context of metastatic cancer. Epidemiological estimates suggest that this condition affects a considerable number of patients annually, with over 750,000 cases of cancer-related pleural effusion reported worldwide. Notably, in the United States and Europe, there has been an observed increase in the incidence of malignant pleural effusion over the years.[1, 2] The presence of pleural effusion from metastatic cancer is commonly found in patients with lung cancer, breast cancer, and malignant lymphoma. Approximately 15% of lung cancer patients have pleural effusion at the time of diagnosis, while 50% have pleural effusion throughout the course of their illness. Patients with pleural effusion from metastatic cancer have a poor prognosis with a short life expectancy, with a median survival of 4-7 months from the time of diagnosis[3, 4]. Even though the amount of pleural effusion may be small, the survival rate is lower compared to those without pleural effusion[5]. The survival rate depends on the type of cancer. Regarding lung cancer and gastrointestinal cancer, they have the lowest survival rates, with an average of only 2-3 months of expected survival time from the date of diagnosis[6]

In general, more than 50% of patients with malignant pleural effusion experience dyspnea[7], resulting in a deterioration of their performance status and overall quality of life. Treating malignant pleural effusion is a palliative approach aimed at improving the patient's quality of life, reducing dyspnea, and minimizing hospital admission[8]. While treatment of malignant pleural effusion cannot provide a complete cure, it can prevent its recurrence and combined with cancer treatment.

There are several methods available for treating malignant pleural effusion, each with its own advantages and disadvantages. These include:

Thoracentesis, which involves draining the fluid from the pleural space to provide temporary relief. This is a palliative treatment, and the patient may experience recurrence of symptoms after the procedure. The duration between procedures depends on the rate of fluid accumulation, making it more suitable for patients with slower fluid accumulation rates or those with shorter life expectancies (less than 1 month)[9].

Medical pleurodesis is a procedure that involves introducing medication or substances into the pleural cavity to stimulate inflammation and adhesion of the parietal and visceral pleura. Commonly used substances for pleurodesis include talc, tetracycline, and doxycycline. Among these, talc has been found to be the most effective substance for pleurodesis[10]. There are two methods for performing talc pleurodesis:

The first method is talc poudrage, which involves the direct application of talc powder onto the parietal and visceral pleura through thoracoscopy. This method has the advantage of allowing for precise and comprehensive application of talc powder and can be performed in conjunction with pleural biopsy for further diagnosis.

The second method is talc slurry, which involves the instillation of talc solution into the pleural cavity through a chest drain[11].

Both methods require hospitalization for a period of 4-13 days[12], during which the success rate of pleurodesis ranges from 60-90%. Prior to performing medical pleurodesis, it is necessary to assess the likelihood of success of the procedure. This can be done by measuring pleural elastance during thoracentesis, with a measured value of no more than -14.5 cmH2O/L indicating a high chance of successful pleurodesis. After pleurodesis, the patient should be monitored for treatment outcomes. If there is a recurrence of pleural effusion and the patient experiences dyspnea, additional treatment may be necessary, such as periodic thoracentesis or placement of a subcutaneous chest drain (indwelling pleural catheter) for long-term fluid drainage.[13]

Indwelling pleural catheter (IPC) is a type of chest drain that can be left in place for a long time. The catheter is a small, flexible tube made of silicone, with one end inserted into the pleural space, and a series of perforations for fluid drainage. The catheter is anchored to the skin to prevent displacement and infection, and the other end is attached to a one-way valve and a drainage bag. Patients or caregivers can drain the fluid themselves at home, which is safe and effective. IPCs are suitable for patients with poor lung expansion due to various causes, especially in those with malignant pleural effusion.

Over the past decades, IPCs have gained popularity as an alternative to talc pleurodesis in the management of malignant pleural effusion, because of its ease of insertion and ability to provide palliation in outpatients. IPCs have been reported to provide symptom relief in up to 96% of patients, and spontaneous pleurodesis occurs in up to 65% of patients[13, 14]. Additionally, daily drainage has been found to increase the likelihood of spontaneous pleurodesis compared to intermittent drainage[15].

The use of IPCs is not significantly different from pleurodesis achieved through talc pleurodesis. However, it does not require hospitalization or have a shorter hospital stay than talc pleurodesis[3, 16, 17]. The potential complications that may occur include catheter-related infections, which occur at a rate of 1-9.6%[18], and low mortality rates (0.29%)[14].

King Chulalongkorn Memorial Hospital has the ability to provide effective treatment for malignant pleural effusions through various methods. However, there are limitations on the number of patients who can receive treatment. Thoracoscopic talc poudrage, which is only performed on patients with scheduled procedures, can accommodate only 4-6 patients per month. This capacity is insufficient to treat the number of patients requiring treatment, which can be as high as 10 patients per month. Consequently, patients must receive temporary treatment through thoracentesis, which necessitates frequent travel and missed work for patients and their relatives. In addition, frequent thoracentesis can lead to complications such as pneumothorax and increased fibrosis which is linked to the outcome of pleurodesis[19]. Furthermore, during the COVID-19 pandemic, hospital wards were closed to allocate healthcare personnel to other areas, resulting in a significant decrease in the number of available beds for the patients. As a result, the number of patients who can undergo pleurodesis also decreased due to insufficient hospital beds available for patients.

The researchers have identified the aforementioned issues and have devised a practical approach to manage malignant pleural effusion by combining the benefits of both thoracoscopic talc poudrage and indwelling pleural catheter. We will conduct a study to evaluate the success rate of the new procedure and compare it to the conventional pleurodesis technique. If the new treatment is found to be equally effective, efficient, and safe, with no significant complications, it can be implemented to improve the hospital's capacity to support the increasing number of cancer patients in the future.

Research questions

Primary research question:

Does the combination of indwelling pleural catheter and thoracoscopic talc poudrage for pleurodesis have a success rate that is non-inferior, with a margin of 20%, to conventional thoracoscopic talc poudrage alone in the treatment of malignant pleural effusion?

Secondary research questions:

1. Does the use of combined thoracoscopic talc poudrage (TTP) and indwelling pleural catheter (IPC) result in a statistically significant difference in the duration of hospitalization compared to pleurodesis through TTP alone?
2. Is there a statistically significant difference in the length of hospital stay due to any cause in patients who have undergone pleurodesis through TTP combined with IPC compared to those who have undergone pleurodesis through TTP alone, within 12 weeks of the procedure?
3. Is there a statistically significant difference in the length of hospital stay due to pleural effusion-related causes in patients who have undergone pleurodesis through TTP combined with IPC compared to those who have undergone pleurodesis through TTP alone, within 12 weeks of the procedure?
4. Do patients undergoing TTP combined with IPC have a statistically significant difference in dyspnea and breathlessness scores compared to those undergoing TTP alone?
5. Is there a statistically significant difference in the overall quality of life between patients undergoing TTP combined with IPC and those undergoing TTP alone?
6. Are there statistically significant differences in the incidence of complications and side effects between patients who have undergone pleurodesis through TTP combined with IPC and those who have undergone pleurodesis through TTP alone?

Objectives of research

Primary research objectives

To compare the success rate of pleurodesis through thoracoscopic talc poudrage (TTP) in combination with indwelling pleural catheter (IPC) to pleurodesis through TTP alone in the treatment of malignant pleural effusion, with a non-inferiority margin of 20%.

Secondary research objectives

1. To determine whether there is a statistically significant difference in the duration of hospitalization between patients undergoing pleurodesis through TTP combined with IPC and those undergoing pleurodesis through TTP alone.
2. To assess whether there is a statistically significant difference in the length of hospital stay due to any cause between patients who have undergone pleurodesis through TTP combined with IPC and those who have undergone pleurodesis through TTP alone, within 12 weeks of the procedure.
3. To determine if there is a statistically significant difference in the length of hospital stay due to pleural effusion-related causes in patients who have undergone pleurodesis through TTP combined with IPC compared to those who have undergone pleurodesis through TTP alone, within 12 weeks of the procedure.
4. To compare dyspnea and breathlessness scores between patients undergoing pleurodesis through TTP combined with IPC and those undergoing pleurodesis through TTP alone.
5. To evaluate whether there is a statistically significant difference in the overall quality of life between patients undergoing pleurodesis through TTP combined with IPC and those undergoing pleurodesis through TTP alone.
6. To compare the incidence of complications and side effects between patients who have undergone pleurodesis through TTP combined with IPC and those who have undergone pleurodesis through TTP alone.

Hypothesis

Null hypothesis:

The success rate of pleurodesis through thoracoscopic talc poudrage (TTP) combined with indwelling pleural catheter (IPC) for malignant pleural effusion is inferior to pleurodesis through TTP alone, with a difference exceeding the clinically meaningful difference of 20% (non-inferior margin of 20).

Alternative hypothesis:

The success rate of pleurodesis through TTP combined with IPC for malignant pleural effusion is non inferior to pleurodesis through TTP alone, with the difference not exceeding the clinically meaningful difference of 20 percent.

Assumption

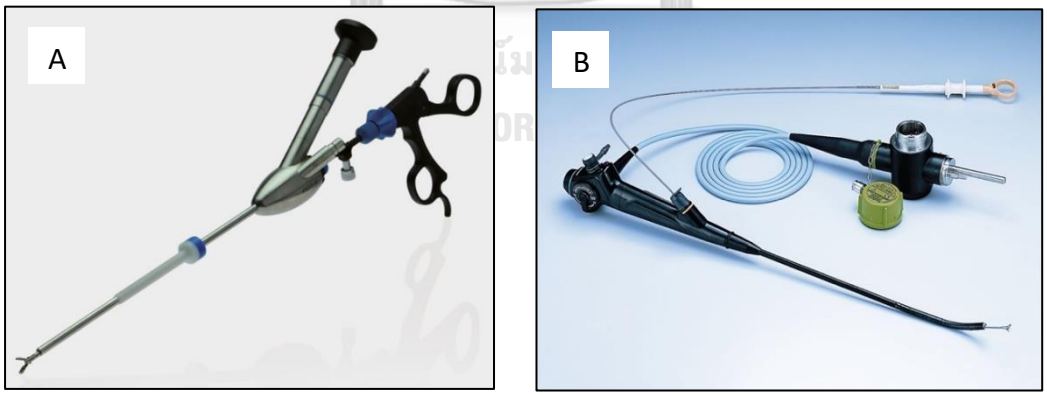
1. The patients who are expected to participate in the study are those with pleural effusion caused by metastatic cancer. These patients are required to have a life expectancy of at least three months, which will be evaluated using the LENT score (as presented in Table 1), and they should not have received pleurodesis in the affected lung.

Table 1 LENT scores in assessing the survival period of patients with malignant pleural effusion

	Variables		Score
L	**L**DH in pleural effusion (IU/L)	<1500 >1500	0 1
E	**E**COG Performance status	0 1 2 3 to 4	0 1 2 3
N	Blood **n**eutrophil to lymphocyte ratio	<9 >9	0 1
T	**T**umor type Low risk tumor type Moderate risk tumor type High risk tumor type	 Mesothelioma, Hematologic malignancy Breast, Renal cell, Gynecological malignancy Lung cancer, other tumor types	 0 1 2

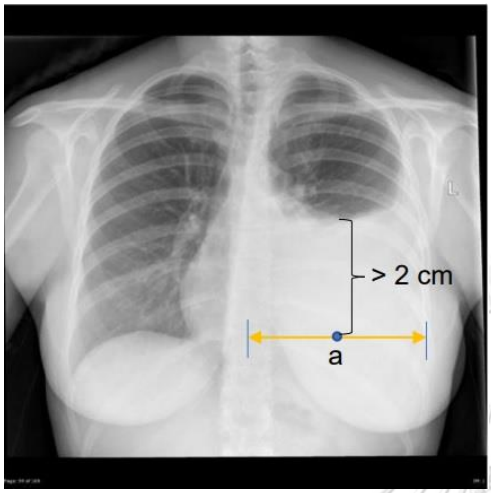
2. The assessment of pleurodesis through TTP combined with IPC and pleurodesis through TTP alone will be conducted using a rigid or semi-rigid thoracoscope manufactured by Olympus, model LFT-160. This is a commonly used instrument for patients of pulmonary disease and pulmonary critical care unit at King Chulalongkorn Memorial Hospital. (*Figure 1*)

Figure 1 Rigid pleuroscope (A) and Semi-rigid pleuroscope (B)



3. The medical professional who will conduct the thoracoscopy procedures must be either an interventional pulmonologist or a fellow in pulmonary disease and pulmonary critical care with a minimum of three previous thoracoscopy procedures performed. The procedures will be closely supervised by Dr.Vorawut Thanthitaweewat, who is an interventional pulmonologist. Patients who undergo the procedure by the researcher will not be included in this study.

4. Patients who participate in the study must have clear indications of pleurodesis, including repeated instances of symptomatic pleural effusion resulting from metastatic cancer, as well as sufficient pleural effusion to permit the performance of a medical thoracoscopy procedure as shown in *Figure 2*

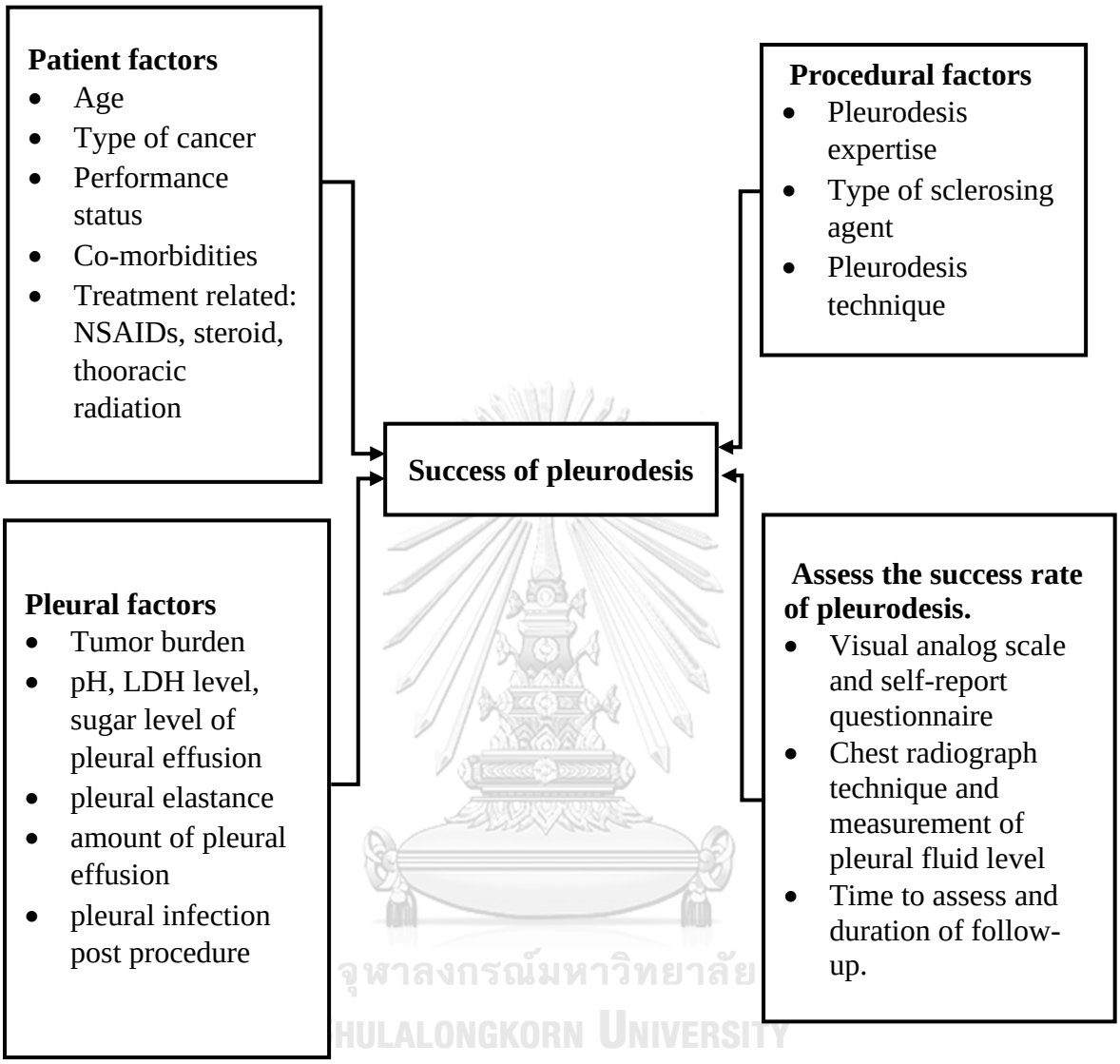


The point "a" is defined as the midpoint between the inner edges of the thoracic spine and the midpoint of the thoracic spine. In order to perform pleuroscope, it is necessary for "a" to be at least 2 centimeters to be considered sufficient.

Figure 2 Measurement of pleural effusion on chest X-ray

5. The sclerosing agent employed in this study for pleurodesis is graded talc, specifically STERITALC® from Novatech, which is packed in 4-gram vials. The quantity administered is contingent upon the size of the patient's pleural cavity and the physician's clinical judgment to guarantee that the talc can be distributed uniformly across both the parietal and visceral pleura.
6. The present study utilized the Rocket® Indwelling pleural catheter as the subcutaneous pleural catheter, which was accompanied by a drainage bag.
7. The surgical instruments used in both groups were identical, except for the type of chest drainage catheter used: either a conventional chest drain or an indwelling pleural catheter used following pleurodesis through thoracoscopy.
8. Additional treatments, such as pain relief medication, antipyretics, or antibiotics, were administered at the discretion of the treating physician.
9. Self-reported thoracic pain, chest tightness, and dyspnea were measured using a visual analog scale (VAS) ranging from 0 to 10, where a score of 0 indicates the complete absence of symptoms and a score of 10 indicates the maximum possible level of symptoms.
10. The quality of life was measured using the EuroQol 5-dimension 5-level questionnaire, and the responses were converted into a utility score ranging from -0.42 to 1.00. Additionally, a score on the VAS ranging from 0 to 100 mm was obtained, with higher scores indicating better quality of life.[20, 21]

Conceptual framework



Operational definition

1. Malignant pleural effusion refers to the presence of fluid in the pleural cavity that has been found to contain cancer cells either through cytological examination of the fluid or histological examination of the pleural tissue.
2. The success of pleurodesis can be divided into three categories[22]:
    a. Complete success, which means that the patient has no symptoms related to pleural effusion and there is no recurrence of pleural effusion on chest radiography within 6 weeks after the procedure.
    b. Partial success, which means that the patient has no symptoms related to pleural effusion, although there is a recurrence of pleural effusion on chest radiography, but the amount of fluid is less than 50% of the initial chest radiograph, and there is no need for additional drainage within 6 weeks after the procedure.

   c. Failed pleurodesis, which means that the procedure did not meet the definition of successful pleurodesis as stated above.
3. According to the study, the success of pleurodesis was determined by counting both complete and partial pleurodesis as successful outcomes.
4. The procedural time was measured from the start of the skin incision and ended when the chest tube was sutured.
5. The hospital length of stay after the procedure is calculated as the number of nights the patient stays in the hospital from the day of the procedure until the day the patient is discharged.
6. The duration of hospitalization for various reasons, including chemotherapy, infections (excluding pleural infections), and radiotherapy, among others. Hospitalization duration was determined by counting the number of nights patients spent in the hospital, encompassing all the hospitals where they received treatment, excluding day care or outpatient visits. This calculation covered the entire 12-week study period and did not include hospital stays related to pleural conditions.
7. The duration of hospitalization due to causes related to pleural effusion, such as infection in the pleural cavity, shall be counted by the number of nights that patients stay in the hospital, including all hospitals where patients receive treatment for such causes, excluding day care or outpatient visits, throughout the 12-week study period.

Expected benefits and applications

Once successfully completed, this study could provide valuable insights into the success rates of pleurodesis using thoracoscopic talc pleurodesis combined with indwelling pleural catheter compared to the traditional method. In the event that no statistically significant differences in success rates are found between the two methods, the data from this study could be used to support physicians in choosing the method that is more comfortable for the patient, which may reduce hospitalization and waiting times for the procedure. Additionally, this could enable the thoracoscopic procedure to be performed on an outpatient basis. Furthermore, the study goes beyond the success rate of pleurodesis and provides information on other factors such as dyspnea, patient quality of life, and postoperative complications for both methods.

Obstacles and strategies to solve the problem.

As this study is conducted on cancer patients with symptoms of pleural effusion caused by metastatic cancer, a large number of participants are necessary to achieve meaningful results. Additionally, follow-up treatment for 12 weeks may make it difficult to find the required number of patients, and patients may be lost to various factors such as worsening symptoms or death from cancer. Some patients may request a change in treatment plan or may transfer to a hospital closer to their home. There may also be a lack of communication during the study, which could result in some participants dropping out.

To address these potential obstacles, the study team has developed preliminary plans. First, it is essential to evaluate suitable participants who are in good health and able to participate. Establishing a good relationship with the participants is also important. Follow-up and assessment of symptoms will be done through telephone consultations to ensure that participants are confident and willing to cooperate in receiving continuous treatment and follow-up.

Chapter 2
Review of related literature

Malignant pleural effusion

The pleura, a thin, dual-layered membrane, envelops the lungs and chest cavity, with the visceral pleura lining the lungs and the parietal pleura lining the chest wall and diaphragm. The space between the two layers, called the pleural space, contains a small volume of fluid that lubricates the movement between the two layers during breathing. Pleural effusion refers to the pathological accumulation of excess fluid within the pleural space, resulting from various underlying causes, including cardiac failure, infections, and cancer[23].

Malignant pleural effusion (MPE) is a common complication of advanced cancer that impacts the pleural space, affecting approximately 15% of patients with cancer, and is the second most frequent cause of pleural exudate fluid[1, 2]. The accumulation of fluid in the pleural space is caused by the spread of malignant cells from the primary tumor site to the pleura. The presence of MPE generally indicates an advanced stage or metastatic cancer, leading to a poor prognosis, with a mean life expectancy of 3-12 months depending on the tumor type and comorbidities[3]. The leading causes of MPE are lung cancer, breast cancer, lymphoma, gynecological malignancies, and malignant mesothelioma.

The diagnosis of MPE usually involves a combination of clinical findings, imaging studies, and cytological analysis of pleural fluid. However, the sensitivity and specificity of these tests can vary depending on factors such as the underlying cancer, the volume of fluid, and the clinician's experience[24, 25]. Patients with MPE often experience severe dyspnea and other distressing symptoms that can significantly affect their quality of life.

Several treatments are available for managing MPE, which primarily focus on relieving symptoms and enhancing patients' quality of life. Customizing therapy for individual patients is essential, considering factors such as their preferences, life expectancy, affordability, presence of trapped lungs, available resources, and the treatment team's experience. Commonly used procedures for the management of MPE include thoracentesis, pleural drainage, and pleurodesis. Nonetheless, managing MPE remains a challenging endeavor.

Management of malignant pleural effusion

A small proportion of patients with malignant pleural effusion (MPE) is asymptomatic and can be managed through observation alone. However, for those who present with symptoms, the primary objective is to alleviate dyspnea and improve their quality of life through minimally invasive procedures.

Thoracentesis

Thoracentesis is the initial step in managing symptomatic MPE. Thoracentesis can be safely performed on an outpatient or inpatient basis. Pleural manometry and ultrasound guidance can be employed for assessing patient response to fluid removal during large volume thoracentesis. This procedure can also assist in identifying patients with trapped lung, which requires additional definitive intervention.

Trapped lung is characterized by a non-expanding lung, caused by the formation of a fibrous layer along the visceral pleural surface due to local pleural pathology.

In patients with recurrent MPE who experience dyspnea relief following thoracentesis, there are several options available, including repeated thoracentesis, drainage with pleurodesis, insertion of an indwelling pleural catheter (IPC), and surgery. Our institution follows the current ATS guidelines for managing MPE[2] *(Table 2)* and has developed a practice algorithm *(Figure3)* that is included in this document. The treatment decision should be based on the patient's preferences, affordability, quality of life, expected life expectancy, underlying tumor type, presence or absence of trapped lung, and local practices. Tools such as the LENT score, which is based on pleural fluid LDH, ECOG performance scale, neutrophil/lymphocyte ratio, and tumor type, can be used to assess the risk of mortality and aid in treatment selection[6].

Table 2 Summary of Current recommendations of ATS/STS/STR

PICO [1]	**RECOMMENDATIONS**
1. In patients with known or suspected MPE should thoracic USG be used to guide pleural interventions?	Yes
2.In patients with known or suspected MPE, who are asymptomatic, should pleural drainage be performed?	No
3.Should the management of symptomatic known or suspected MPE guided by large volume thoracentesis and pleural manometry?	Yes. Manometry if pleurodesis is contemplated to assess for lung re-expansion
4.In patients with known or suspected symptomatic MPE, with expandable lung and no prior definitive treatment, should IPC or chemical pleurodesis be used as first line intervention?	Yes
5.In patients with known or suspected MPE, undergoing talc pleurodesis, should talc slurry or talc poudrage be used?	Yes, there is no difference in the efficacy between the two
6.In patients with symptomatic MPE with non-expandable lung, failed pleurodesis or loculated effusion, should IPC or chemical pleurodesis be used?	IPC is the preferred method of choice over chemical pleurodesis
7.In IPC associated infection, is catheter removal required?	Not unless infection does not improve

[1]PICO : population, intervention, comparator, outcome format.

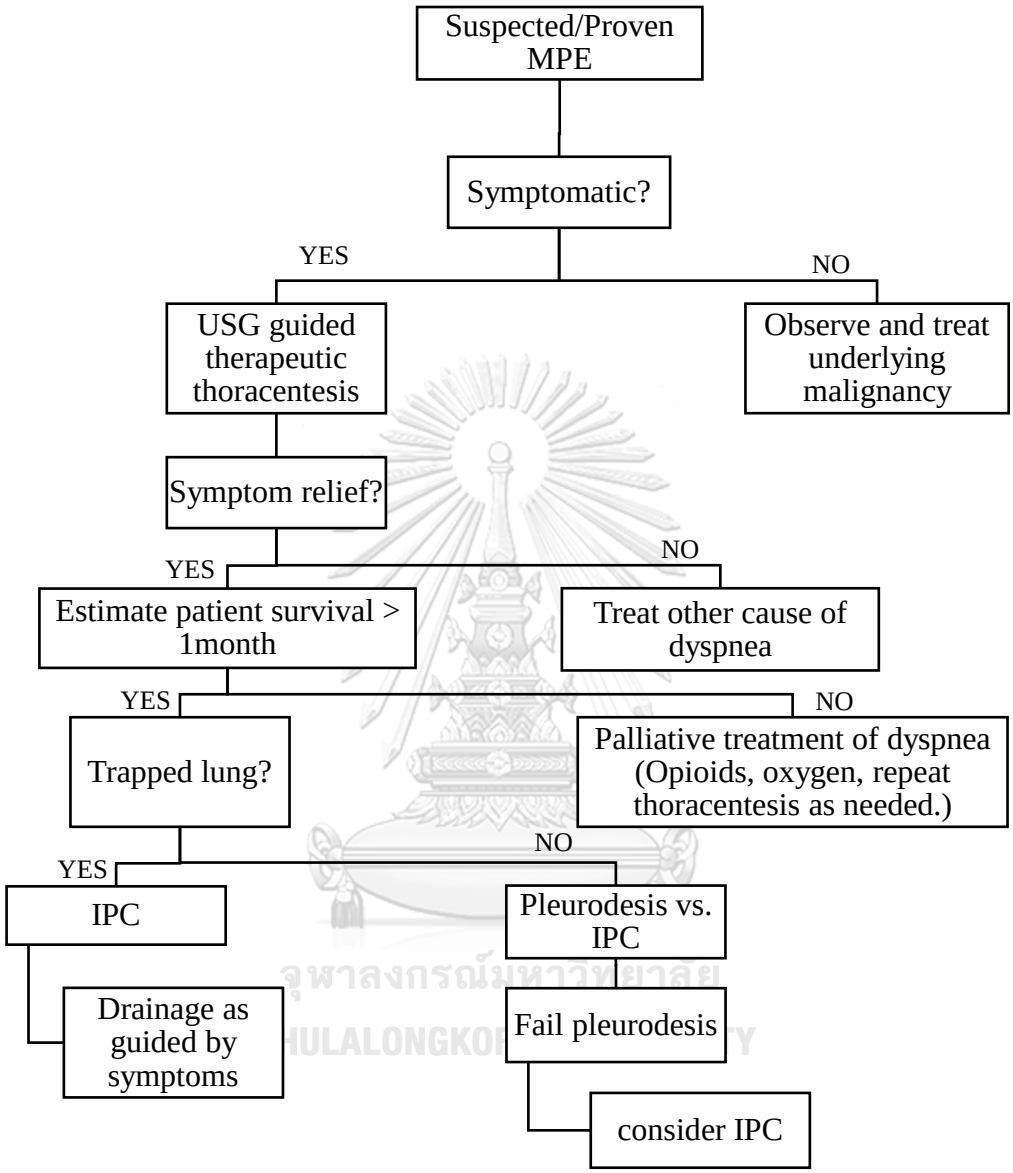


Figure 3 Algorithm suggested for the management of suspected/proven recurrent malignant pleural effusion .

Pleurodesis

Pleurodesis is a medical procedure that aims to prevent the reoccurrence of pleural effusions or treat persistent pneumothorax by filling or obliterating the pleural space. The procedure can be performed using mechanical or chemical methods. Chemical pleurodesis involves injecting a sclerosing agent, such as talc, doxycycline, or bleomycin, into the pleural space. This causes an inflammatory response, resulting in adhesion formation between the two pleural membranes, and preventing the accumulation of fluid or air in the pleural cavity. On the other hand, mechanical or surgical pleurodesis can be carried out using different techniques such as medical thoracoscopy, video-assisted thoracoscopy (VATS), or open thoracotomy. These methods employ mechanical abrasion techniques, such as scraping or talc powder application, to create friction between the pleural layers. The resulting scar tissue formation creates adhesions that bind the two pleural membranes together, reducing the chance of further fluid or air accumulation[26, 27].

There are several sclerosing agents used in chemical pleurodesis. Talc is the most commonly used sclerosing agent in chemical pleurodesis. Several studies have shown that talc is highly effective in achieving pleurodesis in patients with recurrent pleural effusions. A meta-analysis of 15 randomized controlled trials involving a total of 1,145 patients found that talc was significantly more effective than other sclerosing agents in achieving complete or partial pleurodesis (RR=1.35, 95% CI=1.19-1.53)[28]. Another meta-analysis of 19 randomized controlled trials involving a total of 1,459 patients also found that talc was more effective than other sclerosing agents in achieving pleurodesis (RR=1.22, 95% CI=1.09-1.38)[29].

There are two methods of talc administration: talc poudrage (TP), which involves the instillation of dry talc powder through thoracoscope, and talc slurry (TS), which involves the instillation of talc mixed with a fluid through chest tube.

Talc poudrage (TP) is a technique that involves spraying talc directly onto the pleura using pleuroscopy. This approach allows for visualization of the pathological features within the pleural cavity and facilitates biopsy to assist in diagnosis. Talc poudrage has been shown to be effective in achieving pleurodesis in up to 95% of cases[30].

Pleuroscope, also known as a thoracoscope, was initially used for diagnosing pleural diseases in 1865 and has since undergone modifications to its current design. There are currently two types of pleuroscopes available: a rigid pleuroscope with a solid metal tube and a semi-rigid pleuroscope that features a camera body comprising both a rigid tubular part and a twistable part at the tip. (*Figure1).* The rigid pleuroscope and semi-rigid pleuroscope have distinct advantages as depicted in *Table 3* (both of these devices are available at King Chulalongkorn Memorial Hospital). Previous research has indicated that these two pleuroscopes lead to varying diagnostic outcomes, with larger tissue samples obtained from the rigid pleuroscope as compared to the semi-rigid pleuroscope[31].

Table 3 A comparison of the advantages of rigid pleuroscopes and semi-rigid pleuroscopes

Rigid Pleuroscopy	Semi-rigid Pleuroscopy
Trocar with multifunction valve	More familiar to chest physician
Larger biopsy specimen	Compatible with existing light source and processor
Easily to biopsy from dense lesion	Allows better view
Suitable for complicated case	Flexible tip facilitates homogeneous insufflation of talc
Robust, less expensive and less maintenance cost	

Talc slurry (TS) can be administered via a chest tube, which may be either a large bore (size >20 Fr) or a small bore (≤14 Fr) chest tube. Recently, there has been a growing preference for the use of small-bore chest tubes for talc pleurodesis due to their ease of insertion, lower pain scores, and lower incidence of complications. The British Thoracic Society guideline recommends the use of smaller tubes for drainage and pleurodesis in patients with MPE[1]. According to the results of meta-analyses and systematic reviews, some studies have indicated that small bore chest tubes may be as effective as large bore tubes in achieving pleurodesis, with no significant differences in success rates observed between the two. Furthermore, small bore tubes were found to be more comfortable for patients than large bore tubes[32, 33].

Prior to performing talc pleurodesis, it is essential to assess the effectiveness of pleurodesis. A commonly used method is to determine pleural elastance by measuring changes in pleural pressure during drainage within the pleural cavity. This can be calculated using the following formula:

$$Pleural\ elastanc = \frac{\Delta\ \text{Pleural pressure (cmH2O)}}{\text{Volume of pleural effusion(L)}}$$

In patients who experience limited pulmonary expansion after thoracentesis, pleural elastance values often exceed 14.5 cmH_2O/L[34]. Research indicates that patients with pleural elastance values exceeding 18 cmH_2O/L have a high likelihood of experiencing pleurodesis failure[35].

There have been several studies comparing the effectiveness of talc poudrage (TP) and talc slurry (TS) in treating MPE, and the results have been mixed. Some studies have shown that talc poudrage is more effective than talc slurry, while others have found no significant difference between the two techniques.

In their prospective non-randomized study, Stefani et al. investigated the efficacy of TP and TS on 109 patients. The results showed that TP was significantly more effective than TS. Specifically, the TP group had a higher immediate successful pleurodesis rate of 87.5%, compared to 73% in the TS group ($p = 0.049$). Furthermore, after 90 days, 88.3% of patients in the TP group and 69.6% in the TS group had a successful pleurodesis. In the long-term, 81.9% of patients in the TP group and 62.2% in the TS group had a life-long pleurodesis ($p = 0.023$). Notably, there were no significant adverse effects observed between the two groups.[36]

In a retrospective cohort study, it was found that TP had a higher success rate compared to TS after one month (85% vs 68%, p=0.01). However, there was no significant difference in success rates between the two procedures after three months (77% vs 88%, p=0.21). The study suggests that TP may be more effective than TS after one month, particularly for patients with good performance status and non-thoracic related malignant pleural effusion[37].

Dresler et al. conducted randomized studies to compare the efficacy of pleurodesis using talc poudrage versus talc slurry in patients suffering from malignant pleural effusion. The study enrolled 501 patients, and the success of pleurodesis was measured by assessing chest radiographs at 30 days. The findings revealed that there were no significant differences in the success rates of pleural pleurodesis in both groups at 30 days. Talc poudrage demonstrated a success rate of 78%, whereas the talc slurry group showed a success rate of 71%t. However, subgroup analysis indicated a significantly higher success rate with talc poudrage in lung cancer and breast cancer patients, with rates of 82% and 67%, respectively. Patients reported a better quality of life and improved comfort levels after pleurodesis, although no significant differences were observed[38].

Bhatnagar et al. conducted a randomized controlled trial (RCT) at 17 hospitals in the UK, which included 330 participants. The primary outcome of the study was pleurodesis failure up to 90 days after randomization. After 90 days, the pleurodesis failure rate was 22% in the TP group and 24% in the TS group. The adjusted odds ratio was 0.91 (95% CI, 0.54-1.55) with a p-value of 0.74 and a difference of -1.8% (95% CI, -10.7% to 7.2%). These findings suggest that there was no significant difference in pleurodesis failure rates between the two groups[39].

Both methods of talc pleurodesis require hospitalization, with the length of stay ranging from 4 to 13 days[12]. The success rate of talc pleurodesis has been reported to be between 60% and 90%[13]. In cases where pleurodesis fails and patients experience recurrent symptoms, additional treatment such as intermittent thoracentesis or the insertion of an indwelling pleural catheter for long-term drainage may be necessary[35].

Indwelling pleural catheter (IPC)

The indwelling pleural catheter is a type of chest drain that can be left in place for a long time. The catheter is a small, flexible tube made of silicone, with one end inserted into the pleural space, and a series of perforations for fluid drainage. The catheter is anchored to the skin to prevent displacement and infection, and the other end is attached to a one-way valve and a drainage bag which regulates the discharge of pleural effusion in one direction. Patients or caregivers can drain the fluid themselves at home, which is safe and effective. IPCs are suitable for patients with poor lung expansion due to various causes, especially in those with malignant pleural effusion.

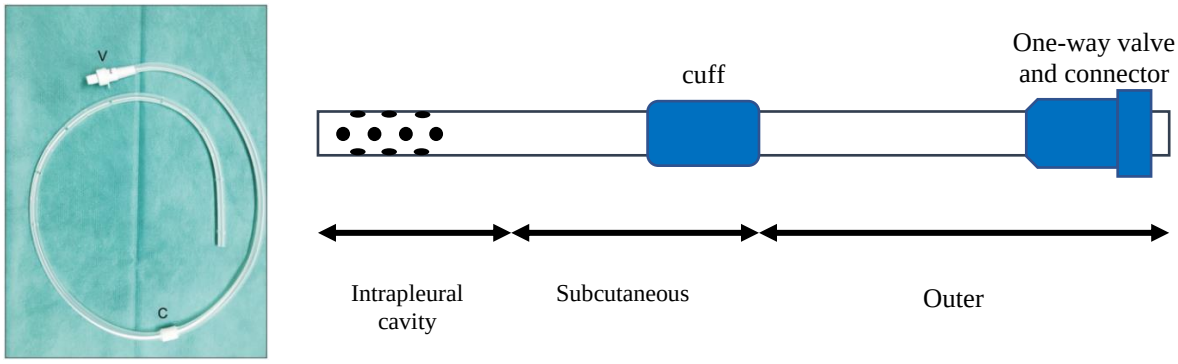


Figure 4 Indwelling pleural catheter

IPC placement is generally considered a safe procedure with a low rate of serious complications. A prospective study of 100 patients who underwent IPC placement reported a 3% rate of serious complications, including bleeding, infection, and catheter malposition. However, the majority of complications were minor, such as local skin irritation or pain. The overall complication rate was lower than that reported for other pleural procedures, such as pleurodesis[40].

The use of IPC has been applied to treat patients with MPE, specifically those who have pleural elastance unsuitable for pleurodesis or have a low success rate of pleurodesis (trapped lung). Davies et al. conducted a randomized controlled trial that compared the efficacy of IPC to talc slurry in 106 patients with MPE. The study found no significant difference between the two methods in managing dyspnea. However, there was a tendency indicating that IPC may be more effective in managing dyspnea after 6 months. Additionally, statistically significant results showed that patients who received IPC had shorter hospital stays than those who received talc slurry (0 days versus 4 days)[17].

The study conducted by Dr. Wahidi and his colleagues on patients with IPC demonstrated that a statistically significant increase occurred in the incidence of spontaneous pleurodesis, or self-adhesion of pleura, in the group of patients who released drainage fluid every day, as compared to the group who released it every other day. The increase was noted over a 12-week follow-up period. Specifically, the daily drainage group had a 47% incidence of spontaneous pleurodesis compared to the control group that followed standard every-other-day drainage, which had a 24% incidence. Moreover, the occurrence of spontaneous pleurodesis was faster in the daily drainage group (54 days) compared to the control group (90 days), with no significant difference in the incidence of complications[15].

The study conducted by Dr. Thomas and his colleagues revealed that the use of IPC is more effective in reducing hospital length of stay when compared to talc slurry. The study demonstrated statistically significant reductions in hospital length of stay for both reasons related to the pleural effusion (1 day versus 4 days) and other reasons (10 days versus 12 days) when IPC was employed[41].

Combined thoracoscopic talc poudrage (TTP) and indwelling pleural catheter (IPC)

Talc poudrage is known to be highly effective in treating malignant pleural effusion, but it necessitates the patient's hospitalization for several days. Conversely, the insertion of IPCs is a common day-case procedure, but it is associated with a notably lower rate of pleurodesis.

In response to the increasing number of patients with MPE seen at our institution and the challenges with hospital bed, we developed a pragmatic management approach by combining TTP and insertion of IPC in the same procedure. We take advantage of both management strategies while minimizing their disadvantages.

The combined TTP with IPC placement has previously been demonstrated in a first pilot study conducted by Reddy et al. in patient with symptomatic malignant pleural effusion. The objective was to assess the efficacy and safety of rapid pleurodesis in hopes of reducing hospital length of stay, minimizing the need for IPC insertion, and improving patient quality of life. In this study, patients received pleuroscopy, IPC insertion, and 5 grams of talc pleurodesis. It was observed that patients experienced no dyspnea and were able to have their IPC removed. The success rate of pleurodesis at 6 months was 92%, and IPC were removed within 1-2 weeks, with a mean of 7.54 days. All patients showed improvement in performance status, but the study lacked a comparison group and was not a randomized controlled trial[42].

A subsequent retrospective review of an additional 26 patients who underwent the same rapid pleurodesis protocol after the initial trial ended recorded a median hospital length of stay of two days and a successful pleurodesis rate of 79%[43].

Dr. Boujaoude et al. conducted a small prospective study that utilized both TTP and IPC insertion to evaluate their combined efficacy compared to the use of TTP alone, as observed in past data. The results showed that the success rate of pleurodesis after one month in the combined group was 92%, and 82% rate for TTP alone, although the difference was not statistically significant. Additionally, the combined approach was associated with a median hospital stay of 3 days and an improvement in dyspnea scores. However, it should be noted that the study's reliability is limited by its historical comparison design, as there were no direct comparative studies[44]

According to the latest retrospective study conducted by Foo et al., which included forty-five patients who received ambulatory combined TTP and IPC insertion, the success rate of pleurodesis at six months was 77.8%, and the majority of patients were discharged on the same day of the procedure[45].

There have been only four other studies that have investigated combination strategies similar to ours. However, these studies did not include a comparison group and were not randomized controlled trials. Therefore, further randomized controlled trials are needed to validate our conclusions regarding the safety and efficacy of combined TTP and IPC insertion.

Chapter 3
Research methodology

Study design

Experimental study with open label randomized, non-inferiority trial.

Population and sample

Inclusion criteria

1. The patients are aged 18 years or older.
2. The patients have received a verified diagnosis of malignant pleural effusion, which has been confirmed through either pathological or cytological examination or through the presence of recurrent exudative lymphocytic pleural effusion with no identifiable cause.
3. The patient's dyspnea symptoms have shown improvement of at least 50% subsequent to the drainage of pleural effusion, as evaluated using a visual analog scale.
4. The patients have an expected survival of at least 3 months, with a LENT score of less than 5
5. The patients are in good physical condition, as evaluated using Eastern Cooperative Oncology Group (ECOG) score 0-2.
6. The pleural elastance must remain below 14.5 centimeters of water..
7. No history of previous pleurodesis on that side of hemithorax.
8. The patients have an ample amount of pleural effusion for the pleuroscopy procedure, as determined by a chest X-ray measurement of the pleural effusion level exceeding 2 centimeters in a straight position. This measurement was taken at the midpoint between the inner edge of the rib cage and the midpoint of the thoracic vertebrae at the diaphragm level *(Figure2)*.
9. The patients are able to comply with the research protocol and conduct continuous follow-up as scheduled.
10. The patients must sign a consent form to participate in the research.

Exclusion criteria

1. Patients who are pregnant.
2. Patients who have a known allergy to talc.
3. Patients with unresolved or untreatable coagulopathy, as defined by a platelet count below 50,000/mm3 and/or an INR above 1.5.
4. Patients with unstable hemodynamic status, indicated by a systolic blood pressure greater than 180 mmHg or a diastolic blood pressure below 90 mmHg.
5. Patients with an inappropriate procedure location, such as an infected skin area.
6. Patients with acute heart failure and pulmonary edema.
7. Patients who have experienced myocardial ischemia within 6 weeks prior to the procedure.

8. Patients with blood oxygen values below 90% that cannot be corrected by oxygen supplementation.
9. Patients with severe fibrosis in the pleural cavity or a pleural cavity area that is too small to permit endoscopy, as evaluated by performing bedside ultrasound.

Sample technique

Target Population : Patients in Thailand with symptomatic malignant pleural effusion or those suspected to have malignant pleural effusion.

Sample Population: Patients with symptomatic malignant pleural effusion or those suspected to have malignant pleural effusion pleural effusion who were admitted to the King Chulalongkorn Memorial Hospital, selected using quota sampling.

To ensure random allocation of participants, a block randomization technique using computer-generated randomization is employed. The randomization is stratified by age (below or above 60 years old) and type of cancer (specifically, lung cancer and non-lung cancer) to minimize the effects of confounding variables. The randomized sequences are then recorded in a sealed envelope to ensure blinding, and the envelope is kept in a secure location.

Sample size determination

To determine the required sample size for a randomized, non-inferiority trial comparing the success of pleurodesis using combined TTP and IPC insertion with TTP alone, where the outcome is a dichotomous variable (pleurodesis success or failure), use the formula provided below.

First, we determine the requirements.

- Determine the expected success rate of pleurodesis from previous studies.
- Determine type of clinical trial : parallel
- Allocation ratio between the experimental and control group = 1
- Determine the desired power of the study = 80%
- Determine the significance level (alpha) = 5%
- Determine the non-inferiority margin. = 20%

$$n_c = \left(\frac{z_{1-\alpha} + z_{1-\beta}}{d+\delta}\right)^2 \left[\frac{p_T(1-p_T)}{k} + p_C(1-p_C)\right]; n_T = kn_C$$

when

n_c	=	sample size for one group.
$Z_{1-\alpha} + Z_{1-\beta}$	=	cumulative distribution function of a standardized normal deviated, based on the α (type I error) and the β (type II error)
α	=	one-sided significant level (type I error)
β	=	power trial = 1- β (type II error)
p_C	=	success proportion of standard treatment
pT	=	success proportion of new treatment
δ	=	non-inferiority margin
d	=	difference of proportion between new treatment group and the standardized care group. ($d = p_T - p_C$)

As per the findings of Boujaoude et al.'s research[44] the effectiveness of pleurodesis using a combination of thoracoscopic talc poudrage (TTP) and indwelling pleural catheter (IPC) insertion is 92%, whereas using TTP alone yields a success rate of 82%.

To achieve a statistically significant sample size, the study enrolled 32 patients per group. However, to account for potential loss to follow-up during the 12-week treatment period, a dropout rate of 20% was factored in, resulting in an increased sample size of 38 patients.

Observation and measurement

The independent variable being studied is pleurodesis technique, which can be accomplished through the use of either thoracoscopic talc poudrage (TTP) in combination with indwelling pleural catheter (IPC) insertion or TTP alone

The dependent variable is the success rate of pleurodesis.

The control variables are other equipment utilized during the procedure, such as talc and low-pressure suction, etc.

Data was collected and measured using various methods, including the utilization of a data record form. The visual analog scale was employed to assess symptoms such as patient dyspnea, chest tightness, and pain. The EQ 5D-5L questionnaire was utilized to ascertain the overall quality of life of the patients. Additionally, self-report questionnaires and physical examinations were conducted to evaluate post-procedure complications. Chest radiographs were employed to determine the effectiveness of pleurodesis, and laboratory results were taken into account as well.

Steps to conduct research

1. The research objectives and the steps involved in the study were explained, along with the benefits that the patients would receive and the potential side effects that could occur. The patients who participated in the study were informed, and their consent was obtained.
2. Medical history was collected, a physical examination was performed, and dyspnea, chest tightness, and pain symptoms were evaluated using a visual analog scale. The overall quality of life was assessed using the Thai version of the EQ 5D-5L questionnaire. The results were recorded in the data record form.
3. All patients underwent blood sampling to detect thrombocytopenia and coagulopathy, which were contraindications for the procedure.
4. Chest radiography was performed on all patients to assess the amount of pleural effusion.
5. The study participants were categorized into two distinct groups through the implementation of a stratified randomization technique based on age (below or above 60 years old) and cancer type (specifically, lung cancer and non-lung cancer). One group underwent a combined treatment approach involving both TTP and IPC insertion, whereas the other group received TTP as a standalone intervention.

6. Ultrasound examination was performed on all patients to assess the amount and location of pleural effusion and adhesions in the pleural cavity. The optimal site for thoracoscopy was determined.
7. Each patient underwent a thoracoscopic talc poudrage procedure according to the standards set by the 10th floor Pulmonary Disease Unit in the Bhumisiri Mangkhalanusorn Building. The equipment used during the procedure was consistent for all patients, except for the chest tube, which was selected based on the patient's study group. The procedural steps were as follows:
    1) Upon arrival of the patient to the operating room, vital signs including blood pressure, heart rate, and oxygen saturation level were measured and monitored throughout the procedure.
    2) The patient was positioned in a lateral decubitus position with the side to be operated on facing upwards.
    3) Oxygen was administered to the patient through a nasal cannula or other previously used device before the procedure. The oxygen saturation level in the blood was maintained above 90% during the procedure.
    4) An ultrasound examination was performed to assess the amount of fluid and confirm the location for the thoracoscopy.
    5) After positioning the patient and identifying the location for the procedure using ultrasound, the operating physician cleaned and disinfected the skin with chlorhexidine and covered the area with a sterile drape, leaving only the site for the procedure exposed.
    6) The patient was given a sedative intravenously, specifically Midazolam and Fentanyl, at the discretion of the operating physician, with the dosage depending on the individual patient.
    7) The surgeon injected 1% lidocaine into the area where the procedure would be performed, starting from the skin layer, subcutaneous layer, and going down to the parietal pleura layer.
    8) After the sedative intravenously and local anesthesia took effect, the surgeon used a scalpel to make an incision parallel to the skin crease, approximately 1.5-2 centimeters in length, to insert the equipment used for thoracoscope (port and thocar).
    9) After inserting the thocar, the pleural effusion was completely drained using a suction machine.
    10) The surgeon conducted a comprehensive examination of the pleural cavity, took a pleural biopsy for pathological examination, and used a thoracoscope to evenly distribute 4-8 grams of talc powder between the parietal and visceral pleura layers. This procedure was performed under direct vision to ensure that the talc powder was evenly distributed throughout the entire pleural cavity.
    11) After talc poudrage, the surgeon inserted a chest drainage tube according to the study group. In the control group, a standard size 20F intercostal drain (ICD) was inserted, while in the experimental group, a size 16F indwelling pleural catheter (IPC) was inserted. The thocar was removed, and the incision was sutured. The drainage tube was

connected to a bottle for fluid drainage and low-pressure suction (-20 cmH2O).

12) After the procedure, all patients underwent chest X-rays to check the position of the drainage tube and lung expansion.
13) After the procedure, the patients were monitored for symptoms in the ward, with daily recording of the amount of fluid drained and repeat chest X-ray assessments.
    i. The experimental group with IPC could be discharged from the hospital once their lungs had expanded, there were no complications, and the drainage bottle was replaced with a drainage bag for fluid drainage. The patient and their caregiver were taught how to take care of the tube and the process of releasing fluid from the bag.
    ii. The control group with a normally inserted chest tube could have the tube removed when the amount of fluid drained was less than 2-4 milliliters per kilogram per day for two consecutive days, and there were no other complications. They could be discharged from the hospital after the tube was removed.
14) After discharge from the hospital, both groups had follow-up appointments for monitoring:
    i. 1-2 weeks after the procedure, the wound, sutures, and any complications were checked. The experimental group with IPC had their tube removal considered at the follow-up appointment.
    ii. Follow-up appointments and repeat chest X-rays were scheduled at 1-2 weeks, 6 weeks, and 12 weeks subsequent to the intervention in order to assess the patient's status and ascertain the effectiveness of the pleurodesis. The quantification of pleural effusion on the chest radiographs was performed by an independent physician who was not affiliated with this study.

8. The assessment of a patient's pain level using the visual analog scale was conducted within 2-4 hours after the completion of the surgical procedure or when the patient was fully awake, to eliminate the effects of the sedative given during the procedure. Another assessment was performed before discharge and during the follow-up visit to evaluate the patient's condition after returning home.
9. The success of the pleurodesis was based on the dyspnea symptom of the patients. In some cases, it may have been necessary to perform a repeated drainage of pleural effusion due to an increase in the amount of fluid present. Additionally, a chest X-ray was taken 12 weeks after the procedure to evaluate the outcome of the treatment.

Data collection

Data was collected from the pleural procedural room, located on the 10th floor of the Pulmonary Disease Unit in the Bhumisiri Mangkhalanusorn Building, King Chulalongkorn Memorial Hospital. The responsibility of data collection was assigned to the researcher, while the research assistant was tasked with recording the data.

All participants were provided with an explanation of the procedural details and methods, as well as the advantages and disadvantages associated with both procedures. They were also informed about the potential side effects and complications that could arise before, during, and after the procedure. Additionally, the participants were required to give their informed consent by signing a consent form prior to their involvement in the research.

Data collection was conducted in three phases, as outlined below:

Phase 1: Prior to the Thoracoscopy Procedure

1. General patient information was collected, including:
    a. Age, gender, type of cancer, comorbidities, current medications, level of dyspnea, patient condition, and overall quality of life.
    b. Results of chest X-ray.
    c. Results of pleural elastance and pleural fluid examination.
2. Laboratory test results were obtained, including:
    a. Complete blood count (CBC), blood urea nitrogen (BUN), creatinine, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), serum protein, and serum lactate dehydrogenase (LDH).
    b. Analysis of pleural fluid, including pleural fluid cell count, cell differentiation, pH level, LDH, sugar, protein, and albumin.
    c. Bedside ultrasonography was performed to evaluate the quantity of fluid and fibrosis in the pleural cavity.

Phase 2: During the Procedure

1. Vital signs of the patient were monitored.
2. The amount of talc used during the procedure was recorded.
3. The duration of the procedure, from incision to wound closure, was documented.
4. The type of chest tube employed for drainage was noted.
5. Any complications that arose during the procedure and hospital stay were documented.
6. Results of post-operative chest radiograph examination were recorded.

Phase 3: Patient Follow-up

1. Pain and dyspnea experienced by the patient after the procedure were assessed using a visual analog scale.

2. Post-operative complications such as cellulitis around the incision site, infection at the chest tube insertion site, or infection in the pleural space were monitored.
3. The overall quality of life was evaluated using the EQ-5D-5L questionnaire.
4. The patient's performance status was assessed using the ECOG score.
5. Follow-up chest radiograph examinations were conducted and results were recorded.
6. Any hospital admissions during the follow-up period were documented.
7. Any additional pleural interventions received by the patient were recorded.

Data Analysis

The data collected for this study was analyzed using the intention-to-treat approach and the SPSS software. The results were subsequently presented in the following formats:

1. Quantitative variables, such as age, weight, and number of days hospitalized, which followed a normal distribution, were presented as mean ± standard deviation (SD). Non-normally distributed data were presented as median and interquartile range (IQR).
2. Qualitative variables, including gender, comorbidities, and disease diagnosis, were presented as frequencies and percentages relative to the total number of patients.
3. To compare data between two groups of patients, the Student t-test was employed to compare mean values for continuous variables that followed a normal distribution. The Mann-Whitney U test was used for continuous variables that did not follow a normal distribution.
4. The Pearson Chi-square or Fisher's exact test was used to compare data between two groups for categorical variables, depending on the appropriateness of the test.
5. The primary objective of this research was to investigate the non-inferiority of the pleurodesis success rate. Confidence interval analysis was utilized to evaluate the primary objective, while p-values were used to assess secondary objectives.

Chapter 4
Results

This is a preliminary report of 26 patients who were selected to participate in the study based on the inclusion criteria for enrollment. These patients were randomly assigned to two groups: one group received pleurodesis through thoracoscopic talc poudrage combined with indwelling pleural catheter insertion (TTP+IPC), while the other group received pleurodesis through thoracoscopic talc pleudrage alone (TTP alone).

Patient baseline characteristics

Upon analysis of the general population data, it was discovered that the patients in the study were predominantly female, with 19 females and 7 males. Both study groups had an similar number of male and female patients. The mean age of the patients was 61 years (61.58±12.34), with an average age of 61.07 years for the TTP alone group and 62.17 years for the TTP + IPC group. However, there was no significant difference between the ages of the two groups. The BMI was found to be similar in both groups. Additionally, there was no significant statistical difference observed between the number of patients with underlying diseases, including diabetes, hypertension, venous thromboembolism, coronary artery disease, cerebrovascular disease, HIV infection, and other diseases, in both study groups.

Histological examination confirmed the presence of pleural malignancy in all patients, indicating that they had metastatic pleural neoplasms rather than primary neoplasms of the pleura. The analysis of pleural fluid profile revealed no significant differences in the levels of protein, albumin, LDH, sugar, and pH between the two study groups. The majority of the primary cancer types identified were lung and breast cancer, with a total of 23 out of 26 patients affected. In the TTP alone group, 71.43% of patients had lung cancer, while in the TTP+IPC group, 66.67% had the same condition. Breast cancer was present in 21.43% of patients in the TTP alone group and 16.67% of patients in the TTP+IPC group. No significant difference was observed between the two groups. It is noteworthy that most patients in this study had multiple metastatic sites.

Regarding cancer treatment, all patients underwent treatment throughout the follow-up period, either through chemotherapy, targeted therapy/immune checkpoint inhibitor, or a combination of both. Both study groups had comparable proportions of patients receiving chemotherapy, targeted therapy, immunotherapy (specifically immune checkpoint inhibitors), and thoracic radiation. No significant disparities were noted between the groups concerning the utilization of other medications, such as antiplatelet or anticoagulant therapy, as well as corticosteroids.

In this study, both study groups had similar performance status, as evaluated by the Eastern Cooperative Oncology Group (ECOG). Most of the patients had an ECOG score of 2. The baseline visual analogue scale (VAS) scores for chest tightness and thoracic pain were similar between the two groups. However, the TTP+IPC group had a significantly higher baseline VAS score for dyspnea compared to the TTP alone group. The TTP alone group had an average VAS dyspnea score of 6.36, whereas the TTP+IPC group had a score of 7.50 ($p=0.026$). Additionally, the TTP+IPC group had a significantly lower baseline utility index of EQ 5D-5L score compared to the TTP

alone group, but there was no statistically significant difference in the baseline VAS quality of life score between the two groups.

The pleuroscopy procedure did not reveal any significant differences in pleural elastance between the two groups. The mean pleural elastance was 9.59 in the TTP alone group and 9.26 in the TTP+IPC group. Ultrasound findings were similar in both groups, with most patients having minimal fibrin in the pleural cavity. The depth of pleural fluid was slightly higher in the TTP alone group compared to the TTP+IPC group, with values of 99.21 mm and 88.5 mm, respectively. The amount of pleural effusion assessed by chest X-ray, calculated by dividing the pleural fluid level by the hemithorax, was also higher in the TTP alone group with 49.75% compared to TTP+IPC group with 40.27%. However, there was no statistically significant difference in the depth of pleural fluid. Pleuroscopy was performed in a similar manner for both right and left sides. There were no significant differences between the two groups in terms of the number of pleural tissue biopsy pieces obtained, the amount of talc used for talc poudrage, the procedural time, or the occurrence of complications during the procedure. Summay of patients' baseline characteristics and procedural detail as shown in *Table 4 and Table 5, respectively.*

Table 4 Summary of patients baseline characteristics.

Characteristics	TTP (n=14)	TTP+IPC (n=12)	p-value
Age, years (mean ± SD)	61.07 ± 9.22	62.17 ± 15.64	0.834
Sex			
Female (n,%)	11 (78.60)	8 (66.67)	0.665
BMI (kg/m^2) (mean ± SD)	22.22 ± 4.46	23.84 ± 4.66	0.376
Underlying disease (n,%)			
Diabetes mellitus	5 (35.70)	2 (16.67)	0.699
Hypertension	6 (42.89)	7 (42.89)	0.429
Venous thromboembolism	0	0	
Coronary artery disease	0	0	
Cerebrovascular disease	0	1 (8.33)	0.48
HIV infection	1 (7.14)	0	0.999
Other disease	3 (21.43)	2 (16.67)	0.999
Type of primary cancer (n,%)			
Lung	10 (71.43)	8 (66.67)	0.999
Breast	3 (21.43)	2 (16.67)	0.999
Colorectal cancer	0	0	
Hematologic malignancy	0	0	
Gynecologic/prostate	1 (7.14)	0	0.999
Hepatobiliary cancer	0	1 (8.33)	0.462
Other cancer	0	1 (8.33)	0.462

Characteristics	TTP (n=14)	TTP+IPC (n=12)	p-value
Metastatic site (n,%)			
pleura	14 (100.00)	12 (100.00)	0.999
pericardium	1 (7.14)	1 (8.33)	0.999
lung	5 (35.71)	3 (25.00)	0.683
Lymph node	5 (35.71)	3 (25.00)	0.683
Bone	4 (28.57)	3 (25.00)	0.999
Brain	2 (14.29)	0	0.483
Liver	0	2 (20.00)	0.163
Adrenal gland	1 (7.14)	1 (8.33)	0.999
Current treatment (n,%)			
Chemotherapy	7 (50.0)	10 (83.3)	0.110
Targeted/immunotherapy	8 (57.14)	4 (33.33)	0.267
Chest wall radiation	1 (7.14)	2 (16.67)	0.58
%pleural effusion from chest radiograph (median, IQR)	49.75 (32.92 - 63.86)	40.27 (28.70 - 49.78)	0.123
Pleural fluid profile			
Protein (mean ± SD)	4.88 ± 0.52	4.68 ± 0.82	0.469
Albumin (mean ± SD)	2.51 ± 0.52	2.65 ± 0.54	0.523
LDH (median, IQR)	383.0 (221 - 393)	314.5 (174.5 - 434.5)	0.873
Sugar (median, IQR)	105 (97 - 113)	99.5 (94.5 - 120)	0.938
pH (median, IQR)	7.46 (7.42 - 7.48)	7.47 (7.45 - 7.5)	0.207
White blood cell (median, IQR)	1103 (647 - 1923)	787 (399.5 - 1043.5)	0.198
%Lymphocyte (mean ± SD)	84.56 ± 9.2	83.53 ± 9.00	0.750
Red blood cell (median, IQR)	9500 (1000 - 29000)	8000 (2000 - 12800)	0.518
ECOG score (n,%)			
ECOG 1	3 (21.43)	3 (25.00)	
ECOG 2	11 (78.57)	9 (75.00)	
Pleural elastance (mean ± SD)	9.59 ± 2.26	9.26 ± 2.98	0.747
VAS dyspnea score[a] (mean ± SD)	6.36 ± 1.01	7.50 ± 1.45	0.026
VAS chest tightness score[a] (mean ± SD)	4.64 ± 1.39	6.17 ± 2.29	0.051
VAS pain score[a] (mean ± SD)	2.5 ± 0.65	2.5 ± 0.9	0.999
VAS QoL (mean ± SD)[b]	50.00 ± 6.50	45.83 ± 3.59	0.078
EQ-5D-5L score (mean ± SD)[b]	0.68 ± 0.09	0.59 ± 0.020	0.020

Characteristics	TTP (n=14)	TTP+IPC (n=12)	p-value
Medication (n,%)			
Antiplatelet/anticoagulant	1 (7.14)	2 (16.67)	0.58
Corticosteroid	0	0	0.999

Note IQR; inter-quartile range, SD; standard deviation, n; number of patients, BMI; body mass index, TTP; thoracoscopic talc poudrage, IPC; indwelling pleural catheter, LDH; lactate dehydrogenase, ECOG; Eastern Cooperative Oncology Group, VAS; visual analog scale, QoL; quality of life, EQ-5D-5L; EuroQoL 5-Dimension 5-Level questionnaire

[a]self-reported thoracic pain, chest tightness, and dyspnea were measure using VAS ranging from 0-10, with score 0 indicating the complete absent of symptoms and 10 the maximum possible level of symptoms.

[b]EuroQol 5-dimension 5-level questionnaire responses were converted into a utility score raging from -0.42 to 1.00 and score on the VAS ranging from 0-100 mm. with higher score indicating better quality of life.

Table 5 Pleuroscope procedural detail

Detail	TTP (n=14)	TTP+IPC (n=12)	p-value
Ultrasound pleural finding			
Ultrasound pleural fluid	99.21 ± 14.92	88.5 ± 23.46	0.171
depth, mm (mean ± SD)	13 (92.86)	11 (91.67)	0.999
Fibrin (n,%)	1 (7.14)	2 (16.67)	0.58
Location (n,%)			
Site of procedure			
Right (n,%)	8 (57.14)	7 (58.33)	0.999
Thoracoscopy details			
Tissue biopsies, pieces (median, IQR)	6 (6 - 6)	5 (4.5 - 6)	0.789
Talc, g (median, IQR)	8 (8 - 8)	8 (8 - 8)	0.999
Procedure time (minutes) (mean ± SD)	54.43 ± 9.72	51.42 ± 11.29	0.572
Complication during procedure (n,%)	3 (21.43)	1 (8.33)	0.472

Primary outcome

The research conducted a comparative analysis of the efficacy of two methods for achieving pleurodesis: thoracoscopic talc poudrage (TTP) as a standalone procedure, and thoracoscopic talc poudrage combined with the insertion of an indwelling pleural catheter (TTP+IPC). After a period of twelve weeks following the procedures, the success rate of pleurodesis was determined. In the TTP group, consisting of 14 patients, a success rate of 64.29% was observed, with 9 patients achieving success (6 complete successes and 3 partial successes). On the other hand, in the TTP+IPC group, which comprised 9 patients, the success rate was 88.89%, with 8 patients achieving success (7 complete successes and 1 partial success). The difference between the two groups was calculated to be 24.60%, with a 95% confidence interval ranging from -7.83% to 57.03%.

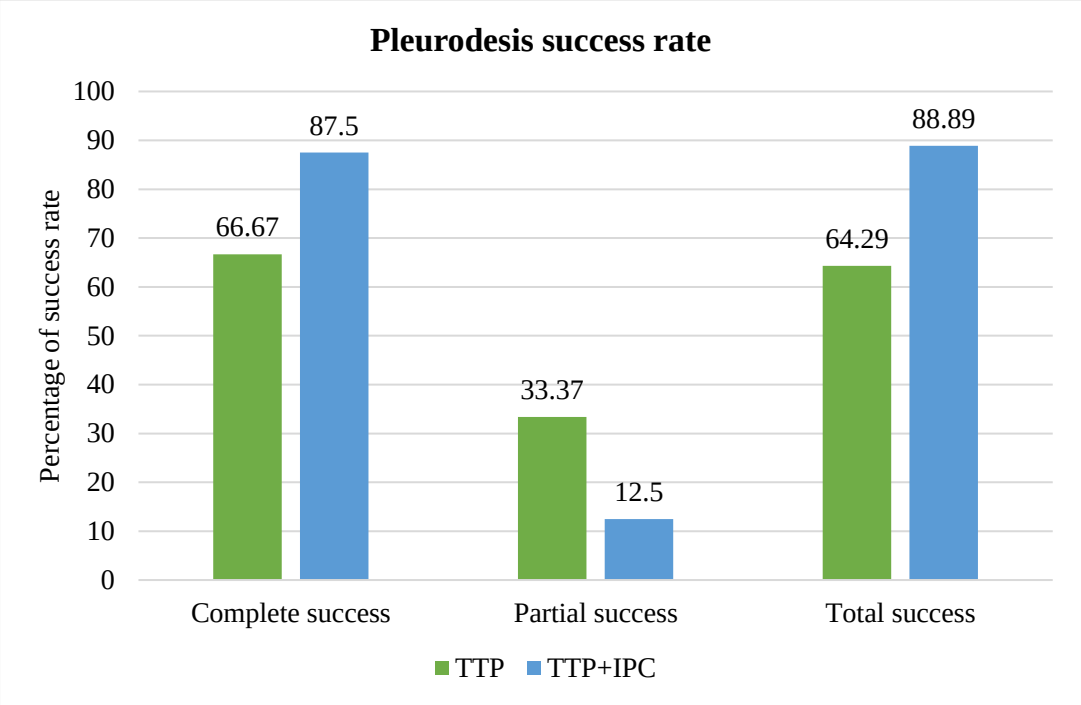


Figure 5 Pleurodesis success rate at 12 weeks

Secondary outcomes

At 6 weeks after the procedure, the pleurodesis success rate was 10 of 14 patients (71.43%) in the TTP group and 10 of 10 patients (100%) in the TTP+IPC group, with a difference of 28.57% [95%CI, 4.91 to 52.23].

Two patients from the TTP+IPC group passed away; one due to the progression of a disease and infection and the other suspected of having experienced cardiac arrest as a consequence of a severe infection. However, no significant difference was observed between the groups in terms of all-cause mortality during the 12-week period following the procedure.

The research findings indicate that the median duration of hospital length of stay (LOS) after the procedure was significantly different between the TTP group and the TTP+IPC group. Specifically, the TTP group had a median duration of 3 days (IQR, 3 to 4) while the TTP+IPC group had a median duration of 1.5 days (IQR, 1 to 2), with a $p < 0.001$. Moreover, the median number of nights that patients spent in the hospital within 12 weeks after the procedure, which includes the initial stay for trial treatment, was also significantly different between the two groups. The TTP group had a median of 3.5 nights (IQR, 3 to 6.75), while the TTP+IPC group had a median of 2 nights (IQR, 1 to 8), with a $p = 0.010$. It is noteworthy that neither group had hospitalization due to pleural-related conditions.

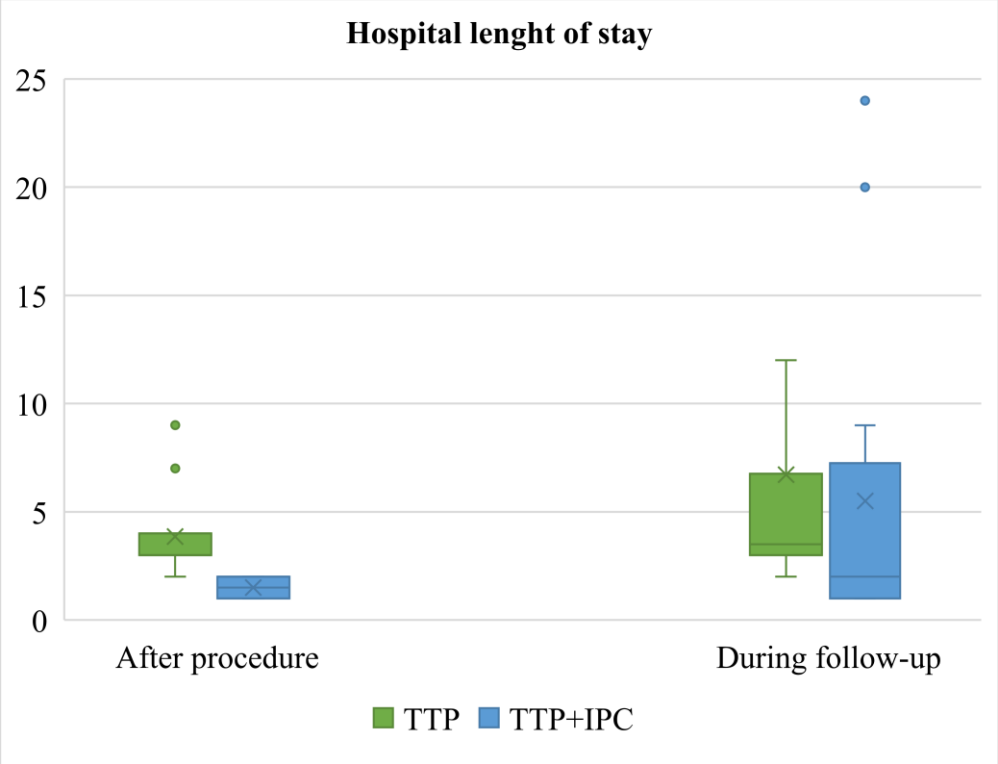


Figure 6 Hospital length of stay after procedure and during follow-up.

The results of the research indicate that the group treated with TTP+IPC achieved a significant reduction in the mean VAS scores for dyspnea and chest tightness at 1, 6, and 12 weeks. Specifically, the mean VAS dyspnea scores for the TTP+IPC group at 1, 6, and 12 weeks were 2.92, 2.67, and 1.56, respectively, with a total reduction from the baseline score of 6.33. In contrast to the TTP+IPC group, the mean VAS dyspnea scores for the TTP alone group at 1, 6, and 12 weeks were 3.14, 2.71, and 2.86, respectively, with a total reduction from the baseline score of 3.5.

The VAS thoracic pain score after 12 weeks did not exhibit a noteworthy difference between the groups. However, during the initial week following the procedure, the group receiving both TTP and IPC showed a significantly lower mean VAS pain score. The VAS pain score for the TTP+IPC group before discharge was 2.08, whereas for the TTP alone group it was 3.07. After a follow-up of one week, the

VAS pain score for the TTP+IPC group was 1.17, while for the TTP alone group it was 2.5. In addition, the group receiving both TTP and TPC had a lower usage of analgesic medications compared to the TTP alone group (4 tablets versus 11 tablets, p<0.001).

The EQ-5D-5L score, which was converted to a utility score, was higher in the group receiving both TTP and IPC compared to the TTP alone group at 12 weeks (0.94 ± 0.08 versus 0.79 ± 0.10, p=0.001). However, there was no significant difference in the VAS quality of life score between the two groups. Summary of secondary outcomes as shown in *Table 6.*

Table 6 Secondary outcomes of the study

Outcomes	TTP (n=14)	TTP+IPC (n=10)	p-value
Pleurodesis success at 6 weeks(n,%)	10 (71.43%)	10 (100.00%)	0.114
All-cause mortality at 12 weeks(n,%)	0	2 (18.18)	0.183
LOS after the procedure, day (median, IQR)	3.0(3 - 4)	1.5 (1 - 2)	<0.001
The hospitalized duration during follow-up (median, IQR)			
Hospitalization due to pleural condition	0 (0 - 0)	0 (0 - 0)	0.999
The total hospitalized duration during follow-up	3.5 (3 - 6.75)	2 (1 - 8)	0.010
Change in VAS dyspnea score from baseline (mean ± SD)			
Baseline	6.36 ± 1.01	7.50 ± 1.45	0.026
1 week	-3.31 ± 1.25	-4.83 ± 1.19	0.003
6 weeks	-3.64 ± 1.15	-5.82 ± 1.17	<0.001
12 weeks	-3.5 ± 1.91	-6.33 ± 2.12	0.003
Change in VAS chest tightness. score from baseline (mean ± SD)			
Baseline	4.64 ± 1.39	6.17 ± 2.29	0.048
1 week	-1.79 ± 1.63	-3.83 ± 1.53	0.003
6 weeks	-2.43 ± 1.95	-5.27 ± 1.79	0.001
12 weeks	-2.71 ± 2.33	-5.78 ± 2.64	0.008
VAS pain score before discharge (mean ± SD)	3.07 ±1.38	2.08 ±0.515	0.004
Change in thoracic pain score from baseline (mean ± SD)			
Baseline	2.5 ± 0.65	2.5 ± 0.9	0.999
1 week	0.00 ± 1.04	-1.33 ± 0.98	0.003
6 weeks	-1.64 ± 1.08	-2.27 ± 1.19	0.18
12 weeks	-1.71 ± 0.83	-2.33 ± 1.32	0.179

Outcomes	TTP (n=14)	TTP+IPC (n=10)	p-value
Analgesic medications, tab (median, IQR)			
Total analgesic medications	11 (8 - 14)	4 (4 - 6)	<0.001
Paracetamol	9 (8 - 10)	4 (3 - 5)	<0.001
Tramadol	0.5 (0 - 6)	0 (0 - 0)	0.038
%pleural effusion from chest radiograph (median, IQR)			
Baseline	49.75 (32.92 - 61.64)	39.12 (29.34 - 49.78)	0.123
1 week	12.62 (11.10 - 37.62)	7.61 (1.79 - 10.96)	0.014
6 weeks	12.41 (5.61 - 36.57)	4.38 (0.82 - 7.23)	0.007
12 weeks	11.14 (2.20 - 40.92)	4.22 (0.87 - 6.36)	0.186
EQ-5D-5L score (mean ± SD)			
Baseline	0.68 ± 0.09	0.59 ± 0.09	0.020
12 weeks	0.79 ± 0.10	0.94 ± 0.08	0.001
VAS QoL (mean ± SD)			
Baseline	50.00 ± 6.50	45.83 ± 3.59	0.06
12 weeks	65.00 ± 17.43	68.33 ± 18.2	0.664

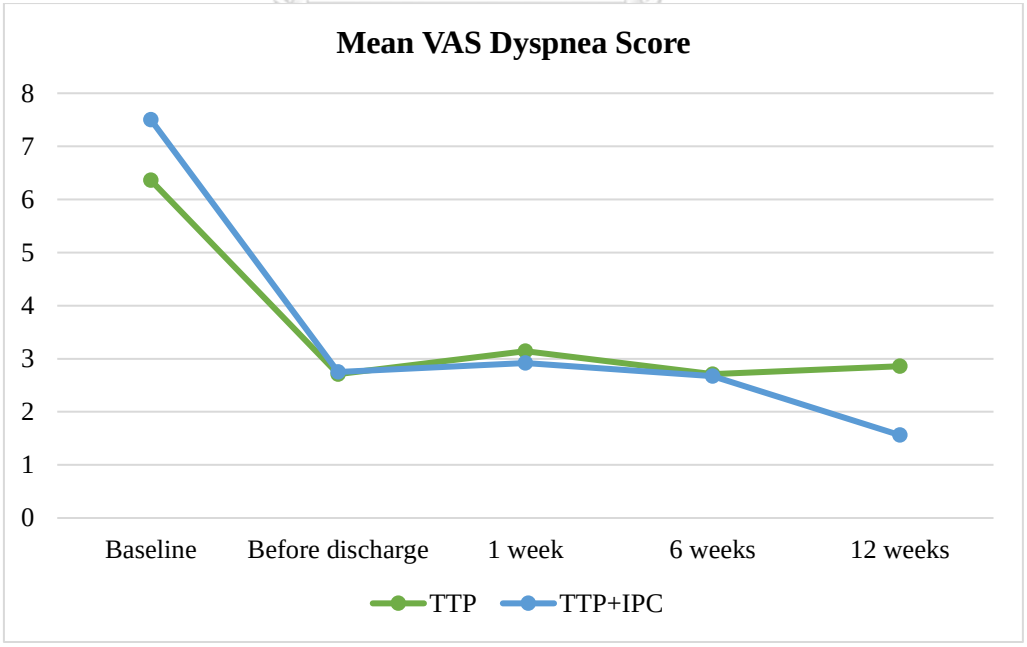


Figure 7 Mean VAS dyspnea score

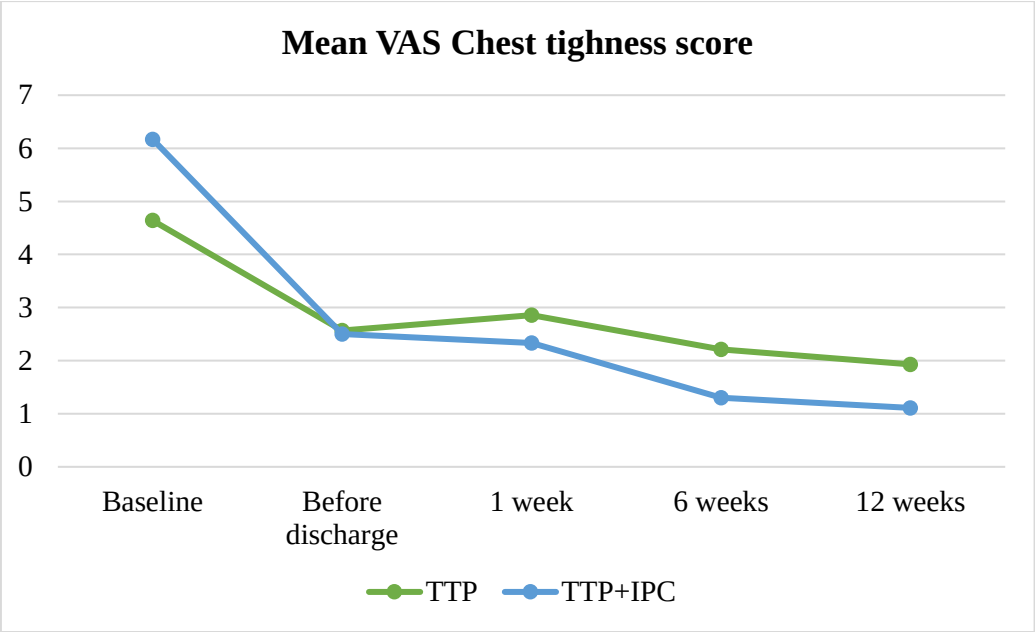


Figure 8 Mean VAS chest tightness score

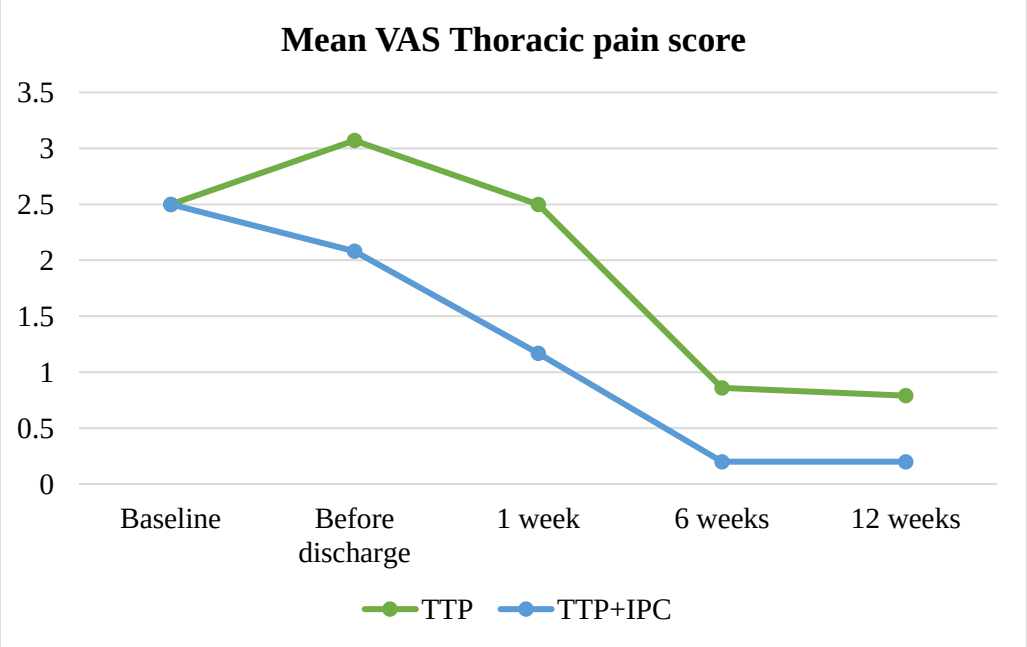


Figure 9 Mean VAS thoracic pain score

Chapter 5
Discussion

Discussion

In this study, we present the first randomized controlled trial (RCT) comparing the effectiveness of pleurodesis using a combination of thoracoscopic talc poudrage (TTP) and an indwelling pleural catheter (IPC) to using TTP alone for treating malignant pleural effusion. The primary objective was to determine if the combination of IPC and TTP had a success rate, within a margin of 20%, that was non-inferior to conventional TTP in treating malignant pleural effusion. Secondary objectives included evaluating hospital stay duration, dyspnea and breathlessness scores, quality of life, and complications between the two groups.

Based on our findings, the effectiveness of pleurodesis after 12 weeks was similar between the TTP+IPC group and the conventional TTP group. In the TTP group, 9 out of 14 patients (64.29%) achieved successful pleurodesis, while in the TTP+IPC group, 8 out of 9 patients (88.89%) achieved success. The observed difference in success rates was 24.60% [95% confidence interval, -7.83 to 57.03]. These results suggest that pleurodesis using TTP+IPC for malignant pleural effusion may be as effective as TTP alone. However, it's important to note that the study design didn't allow us to definitively conclude the superiority of TTP+IPC over TTP, as the study was designed to assess non-inferiority.

The apparent higher efficacy of combined TTP+IPC compared to standard TTP could be explained by the continuous drainage provided by IPC in the combined group, even after patients returned home. This continuous drainage helps prevent further accumulation of pleural effusion and facilitates the formation of fibrosis, leading to the obliteration of the pleural space. In contrast, the control group requires the removal of the chest tube before discharge, which may allow for fluid accumulation and potentially impact pleurodesis outcomes.

We found a statistically significant reduction in hospital length of stay (LOS) for patients in the TTP+IPC group compared to those in the conventional TTP group (1.5[1-2] vs 3[3-4], $p<0.001$). This suggests that patients in the TTP+IPC group were discharged from the hospital one day after the procedure and managed residual pleural effusion drainage at home. These findings indicate that implementing the combined TTP+IPC approach has the potential to alleviate hospital resource demand and enhance bed availability, which is particularly important for hospitals facing bed availability challenges.

The higher baseline mean VAS dyspnea score observed in the TTP+IPC group may suggest that these patients initially experienced more severe symptoms. However, in an RCT study, baseline characteristics are typically comparable between treatment groups. It's important to note that this report is preliminary and lacks complete data. Further analysis is needed to thoroughly evaluate baseline characteristics and identify potential similarities in patient characteristics between the TTP+IPC and conventional TTP groups.

Additionally, the TTP+IPC group showed superior outcomes in various aspects compared to the conventional TTP group. Specifically, the TTP+IPC group had a greater reduction in dyspnea, as indicated by the mean VAS dyspnea score

change (-6.33±2.12 vs -3.5±1.91, p=0.003). Moreover, the mean VAS dyspnea score remained consistently lower throughout the follow-up period, both immediately after the procedure and during subsequent assessments. This positive outcome may be attributed to the higher pleurodesis rate observed in the combined TTP+IPC group.

Furthermore, the TTP+IPC group reported lower pain scores and reduced need for analgesic medications. This could be due to the use of a smaller catheter size in the IPC procedure, resulting in less discomfort and pain for the patients.

Overall, the combination of TTP and IPC demonstrated improved outcomes in terms of dyspnea reduction, pain management, and decreased analgesic requirements. These findings highlight the potential benefits of using the TTP+IPC approach in the treatment of malignant pleural effusion.

Moreover, the TTP+IPC group experienced an enhanced quality of life, as assessed by the EQ-5D-5L questionnaire, as they reported lower levels of dyspnea and improved ability to perform activities with less restriction. There were no significant differences in the incidence of complications between the two groups, and the procedure time was similar in both groups.

The results indicate that combining IPC with TTP could be a feasible option for managing malignant pleural effusion, potentially leading to improved outcomes such as reduced hospitalization and better symptom relief. This approach may also serve as a safe alternative to conventional TTP.

The success rate of pleurodesis in the TTP group was found to be lower than that reported in the recent TAPPS trial, where the success rate was 78%[39]. This discrepancy could be attributed to differences in patient characteristics such as underlying malignancy or disease extent. However, the TTP group still achieved a clinically meaningful success rate of 64.29%. The success rate achieved in the TTP+IPC group was comparable to that reported in previous studies. To date, only four studies have investigated combination strategies similar to ours. Reddy et al. described a rapid pleurodesis protocol in a pilot study of 30 patients, resulting in a mean hospital LOS of 3.19 days with a 92% pleurodesis success rate at six months, along with an improvement in dyspnea and quality of life scores[42]. A subsequent retrospective review of an additional 29 patients who underwent the same rapid pleurodesis protocol after the initial trial reported a median LOS of 2 days and a successful pleurodesis rate of 79%[43]. A small prospective study by Boujaoude et al., involving 29 patients compared with historical data, reported a 92% pleurodesis success rate for pleurodesis at one month, a median hospital stay of 3 days, and an improvement in dyspnea scores[44]. The most recent retrospective study by Foo et al., involving forty-five patients who underwent ambulatory combined thoracoscopic talc poudrage and IPC insertion, showed a pleurodesis success rate of 77.8% at six months, with most patients being discharged on the same day of the procedure[45].

Some of the protocol details are different; in the study by Reddy and Foo, both the IPC and a standard chest tube were inserted at the time of operation, and the chest tube was removed after confirm resolving of procedural-induced pneumothorax (an hour to day). While in our study, only the IPC was inserted, and it alone was used for all subsequent drainage. In previous studies, the reason for inserting both IPC and a standard chest tube was that the talc could clog the IPC and render it ineffective. However, the results of our study showed that chest tube drainage was unnecessary as the IPC was effective in all cases without instances of clogging. Furthermore, the

drainage bag was found to be effective for all TTP+IPC cases, which was used for all subsequent drainage.

However, the cost of treatment should be taken into consideration, even with the numerous benefits of the combined TTP+IPC approach. Although this study did not specifically examine the cost-effectiveness, the expense associated with IPC can be a concern. The approximate cost of an IPC unit is 11,000 baht, and it is currently not covered by universal healthcare coverage. Additionally, it is important to note that the use of IPC requires the ability of patients and caregivers to properly care for the IPC until it is removed. This requirement may be a significant limitation, as not all patients may be comfortable or capable of providing the necessary care.

Limitations

This study has several limitations that should be taken into consideration. First, in TTP+IPC group, patients and their caregiver need to be able to take care of the device before its removal. Second, the study was conducted on an open-label basis, which allowed for decisions regarding the need for further intervention during follow-up (the primary outcome). Third, the small sample size of this preliminary analysis limited the statistical power of the analysis, and the cost-effectiveness of the treatment method was not considered in this study, which is a crucial aspect to consider in healthcare research. Despite these limitations, the study provided valuable information about the feasibility, safety, and potential benefits of this intervention for a patient with malignant pleural effusion.

Conclusion

This study found that a combination of TTP (thoracoscopic talc poudrage) and IPC (indwelling pleural catheter) was effective in treating malignant pleural effusion and had a similar success rate as TTP alone in terms of pleurodesis. This combination approach had potential benefits such as a shorter LOS, lower post-operative pain, and better quality of life among patients with symptomatic malignant pleural effusion.

Recommendations

1. The combination of indwelling pleural catheter and thoracoscopic talc poudrage for pleurodesis can be considered as a viable treatment option for malignant pleural effusion. It offers a non-inferior success rate compared to conventional thoracoscopic talc poudrage alone, while also resulting in a shorter hospital length of stay, greater reduction in dyspnea, and lower pain score and analgesic usage.
2. Further studies with larger sample sizes and longer follow-up periods are needed to confirm the effectiveness of the combination of indwelling pleural catheter and thoracoscopic talc poudrage for pleurodesis.
3. More research is needed to explore the potential cost-effectiveness of this treatment option compared to other methods of pleurodesis.
4. Additional studies should be conducted to investigate the long-term effects of indwelling pleural catheter and thoracoscopic talc poudrage on quality of life and patient outcomes beyond 12 weeks.

5. Finally, it is recommended that clinicians should consider patient preferences, clinical characteristics, and individualized decision-making when deciding on the optimal treatment strategy for malignant pleural effusion.

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