RESEARCH ARTICLE

THE EFFICACY AND SAFETY OF MEDICAL THORACOSCOPY IN DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSIONS.

Erhan Ugurlu[1], Goksel Altinisik[2], Ali İhsan Yildiz[3] and Gokhan Yuncu[4].
1. MD, Pamukkale University Medicine Faculty Chest Disease Department, Denizli, Turkey.
2. MD, Prof. Dr. Pamukkale University Medicine Faculty Chest Disease Department, Denizli, Turkey.
3. MD, Servergazi Hospital Chest Disease Deparment, Denizli, Turkey.
4. MD, Prof. Dr. Liv Hospital Thoracic Surgery Clinic, İstanbul, Turkey.

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Abstract
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Objectives: Medical thoracoscopy is an investigational and sometimes a therapeutic procedure for pleural diseases indicated to diagnose the pleural effusions remains non-diagnostic after using less invasive techniques. The aim of the study was to evaluate the efficacy and safety of medical thoracoscopy in differential diagnosis of pleural effusions.
Methods: This is a retrospective observational study. Fifty consecutive patients had thoracoscopy between June 2007 and June 2009.
Results: Mean age was 64±10 years and 64% of the patients was male. Malignancy was diagnosed in 24 (48%) of all thoracoscopies. Adenocarcinoma was diagnosed in 15 (31%), other malignancies in 5 (10%) and malignant mesothelioma in 4 (8%) patients. Pleural biopsies revealed chronic nonspecific pleuritis in 19 (38%) patients, granulomatous inflammation in 1 (2%) patients. The procedure was considered non-diagnostic in 4 (8%) patients. There was no major complication, but minor complications in 5 patients (10%); 3 minimal expansion defects, 1 remarkable but transient subcutaneous emphysema and 1 empyema.
Conclusion: In conclusion, selecting patients in whom less invasive methods were unsuccessful or patients who have strong possibility for malignancy might increase the diagnostic and therapeutic yield of the thoracoscopy in respiratory medicine practice. It is an efficient and safe procedure.

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Introduction:-

Both terms "pleuroscopy" and "medical thoracoscopy" refer to a minimally invasive procedure which allows the examination of the pleural space in a spontaneously breathing patient. [1, 2] It is an investigational and sometimes a therapeutic procedure for pleural diseases indicated to diagnose the pleural effusions remains non-diagnostic after examination with clinical presentation, radiology, thoracentesis and less invasive biopsy techniques. The cause of pleural effusions remains undiagnosed in about 25% of cases after initial work-up including thoracentesis with fluid analysis. [3, 4] Medical thoracoscopy has a high diagnostic yield (90-100%) for pleural effusions of unclear origin

Corresponding Author:- Erhan Ugurlu.
Address:- MD, Pamukkale University Medicine Faculty Chest Disease Department, Denizli, Turkey.

making it an extremely valuable tool in these conditions. [3, 5, 6] Apart from its use for diagnostic purposes, medical thoracoscopy is frequently performed to achieve pleurodesis in patients with recurrent malign pleural effusions. [3, 7-9]

Thoracoscopy performed in the bronchoscopy suite under local anesthesia, usually is limited to exploration of the pleural cavity, parietal pleura biopsy, pleurodesis, and chest tube insertion under direct visual guidance. [2] However, it provides avoidance from general anesthesia, double-lumen endotracheal tube intubation, and use of operating room (all are obligatory for video-assisted thoracoscopic surgery) for those indications of daily practice in pulmonary medicine.

It is a procedure which could be performed by a chest physician. The aim of the study was to evaluate the efficacy and safety of medical thoracoscopy in differential diagnosis of pleural effusions.

Material and Method:-
Patient selection:-
The study was designed to investigate retrospectively the data of patients who had medical thoracoscopy during a-two-year period in the department of pulmonary medicine. Patients were selected among the patients who applied or sent for consultation to our clinic because of pleural effusion and in whom medical thoracoscopy had been indicated after initial investigation, including thoracentesis and/or needle biopsy. The contraindications were same unstable cardiac and hemodynamic status, bleeding diathesis, respiratory failure, and occluded pleural cavity. The indications were as listed below: Pleural effusions with unknown etiology, high suspicion of malign pleural effusion, suspicion of tuberculosis pleurisy with non-diagnostic previous needle biopsy, complicated parapneumonic pleural effusion, and repetitive uncontrolled and symptomatic benign pleurisy.

All consecutive thoracoscopies performed between June 2007 and June 2009 was reviewed. A retrospective analysis was performed via a chart review with respect to sex, age, underlying/accompanying medical condition, thoracentesis results (macroscopic, biochemical, microbiological and cytological), per-operative findings, postoperative histological diagnosis, duration of closed tube thoracoscopy remained in place, duration of hospitalization and any complications associated with the procedure.

The transudative and exudative discrimination of the pleural fluid was made by using Light criteria. [10]
Complications related with the medical thoracoscopy were classified as minor or major, respectively, according to spontaneous improvement or need for additional intervention such as thoracotomy, mechanical ventilation for respiratory failure, and death. Procedure related mortality was defined as death during the procedure or within 2 weeks after the procedure. Since underlying and/or accompanying disorders could interfere with the situation, the accepted time period was short. However, if the problem related with prolong complication caused by medical thoracoscopy was occurred, it has been also noted.

For the talc pleurodesis, the success was evaluated by posteroanterior chest roentgenogram or additionally by thorax computerized tomography when needed. No recurrence was determined as successful pleurodesis and either recurrence in pleural effusion or expansion defect was determined as failure in pleurodesis.

Statistical analyses were done via *Statistical Package for the Social Sciences* (SPSS) for Windows (17.0 version). Data were presented as percentage, mean±standard deviation and median as appropriate. The comparisons were done by using Mann-Whitney U test and χ-square test or ANOVA test as appropriate. $p < 0.05$ was considered as statistically significant.

Training:-
Although medical thoracoscopy is being more and more popular among chest physicians, it is not a routine procedure yet to be taught in most of the training departments. There are hands-on courses and another opportunity is to have training period in special centers that their number is increasing in many European countries. [1, 11] In our pulmonary medicine department, medical thoracoscopy procedure has been implemented with adaptation from its original technique. [1-3, 12, 13]

Procedure:-
The medical thoracoscopies were performed in a fully equipped room also used as bronchoscopy suite. Premedication was done by intramuscular application of non-steroidal anti-inflammatory drug and intravenous 2mg midazolam.

Patients were placed in the lateral decubitus position with the pleural effusion side up. Thoracoscopy had been performed under local anesthesia and with conscious sedation. For local anesthesia, Prilocaine 2% (20mg/ml) had been given 15ml totally into all layers of the entry site placed in the intercostals space. The entry point was determined according to the indication; generally, at the posterior axillary line and 5th or 6th intercostals space. A needle aspiration was performed to confirm the presence of fluid, and a small incision was made and blunt dissection with scissor was used to make the entrance of trocar easier. All the pleural fluid was aspirated before the visualization of the pleural space without the risk of re-expansion lung edema since the pneumothorax could be done intentionally.

Only one-port insertion was used to insert rigid thoracoscope (0-degree telescope, Karl Storz, Germany) via a 7mm-trocar (with obturator and canulla). A cold light source and video camera were implemented to the telescope. It's been able to view the entire pleural surface of the thorax as well as a majority of the thoracic contents after gentle retraction of the lung which was already collapsed because of artificial pneumothorax. Visually directed biopsies were obtained from the parietal pleura lesions via 5mm forceps.

If there was a previously diagnosed malignancy (lung, breast etc.) and/or typical appearance of nodularity in parietal pleura, pleurodesis was performed via talc insufflations (5gr) during the thoracoscopy. In some patients, pleurodesis was performed as talc slurry (5gr) applied via tube thoracostomy when the malign histopathology had been proven post-operatively.

The patient was transferred to in-patient clinic after thoracoscopy with tube thoracostomy and closed drainage system, and followed clinically and radiologically since the fluid drainage had been less that 150ml a day. Then the chest tube had been removed as appropriate.

Results:-

Fifty consecutive patients had thoracoscopy between June 2007 and June 2009. Mean age was 64 ± 10 years (43-86) and there was no statistically significant difference in mean age between males and females. Thirty-two patients (64%) were male.

There was no accompanied disease in 7 (14%) of the patients prior to thoracoscopy. Malignancy was the most common accompanied disease with the ratio of 46% (23 patients) and followed by chronic systemic disease in 18 patients (36%). Pneumonia was present in 2 (4%) patients.

Thoracentesis and blind closed parietal pleura biopsy via Abrams needle were performed previously in 46 (92%) and 10 (20%) patients, respectively. The appearance of thoracentesis fluids was serous in half of the patients who had the procedure and serosanguinous, hemorrhagic and purulent appearances were occurred in 17 (34%), 5 (10%) and 3 (6%) of the patients, respectively. Transudative/exudative ratio of pleurisies was 2/44. Two transudative pleurisies were symptomatic, progressive and repetitive, the cytology results were benign and the biopsies were revealed nonspecific pleuritis. Abrams needle biopsies were non-diagnostic in 8 patients (80%); among the diagnostic results of biopsies, 1 patient had mesothelioma, 1 patient had adenocarcinoma.

Bronchoscopy had been performed in 24 (48%) patients. Nine of them were reported as normal bronchial tree (38%) and endobronchial tumor had been observed in 8 of all bronchoscopies (33%). The rest was revealed indirect finding of external compression (29%).

All amount of pleural fluid aspirated during thoracoscopy was sent to cytological exanimations in 49 patients. Cytological examination of 33 pleural fluids was revealed as benign (67%) and the rest were malign pleural effusions. The discrimination of cytology results according to the final histopathology results was given in Table 1.

Biopsy result	Benign cytology n(%)	Malign cytology n(%)	P value
Nonspecific pleuritis	19 (57.6)	-	
Adenocarcinoma	4 (12.1)	11 (68.8)	0.0001
Other malign	3 (9.1)	2 (12.5)	NS
Mesothelioma	3 (9.1)	1 (6.3)	NS
Granulomatous inflammation	1 (3)	-	
Acute inflammation (empyema)	1 (3)	-	
Non-diagnostic	2 (6.1)	2 (12.5)*	NS
Total (49)	33	16	

Table 1. The relationship between the biopsy results and the cytology results of pleural fluid obtained during the thoracoscopy.

NS: nonsignificant

* 1 patient had previously diagnosed and treated squamous cell lung carcinoma, 1 patient had previously diagnosed and treated breast carcinoma; both died within 3 months after thoracoscopy.

Among patients with benign cytology results, the malignancy was diagnosed via thoracoscopic biopsy in 10 patients (30%). Benign cytology could not be confirmed in 2 of 19 non-specific pleuritis patients (10%) because of the short follow-up period less than 6 months. In two patients, only the cytology results of the pleural fluid obtained via thoracoscopy were malign but not proven by biopsy; both died within 3 months after the procedure.

By the exploration, the appearance of parietal pleura was defined as nodules in 23 patients (46%), fibrous adhesions in 11 patients (22%), normal in 8 patients (16%), pleural plaque-like lesions in 7 patients (14%), and mass in 1 patient (2%). The nodules and plaque-like lesions were more predominant in posterior and inferior part of the related thorax.

Thoracoscopic parietal pleura biopsy had been performed in 49 patients (98%). One patient was reported diffuse fibrous adhesions and biopsy had not been taken in that patient. The results of histopathological examinations were given in Table 2. Malign pleurisy was diagnosed in 24 (48%) of the patients.

By assessing the parietal pleura appearance according to the biopsy results, nodules were occurred predominantly as a sign for malignancy. The discrimination was given in Table 2.

Biopsy result	Nodules	Fibrous adhesions	Plaque-like lesion	Normal	Mass
Nonspecific pleuritis	4*	7	3	5	-
Adenocarcinoma	12	-	3	-	-
Other malign	4	-		1	-
Mesothelioma	2	-	1	-	1
Granulomatous inflammation	1		-	-	-
Acute inflammation		1	-	-	-
Non-diagnostic	-	2	-	2	-
Total (49)	23	10	7	8	1

Table 2. The relationship between the biopsy results and the appearances of parietal pleura during the thoracoscopy
* 1 was diagnosed M. tuberculosis (Lowenstein-Jensen culture positive), 3 patients had one or a few gelatinous nodules observed.

The diagnoses were in a wide spectrum. The most common diagnosis was nonspecific pleuritis and that result was investigated in details to clarify the clinical evaluation. Among the specific diagnoses, adenocarcinoma was the most frequent diagnosis. The data were given in Table 3.

Diagnosis	N (%)	Details
Nonspecific pleuritis	19 (39)	10 no accompanying disease 5 co-existing lung cancer (1 excitus) 1 renal cell carcinoma (no recurrence) 1 lymphoma (no recurrence) 1 tuberculosis (microbiologically proven) 1 congestive heart failure (excitus)
Adenocarcinoma	15 (31)	6 lung carcinoma (1 co-existing small cell lung carcinoma) 8 breast carcinoma 1 pancreas adenocarcinoma
Other malign	5 (10)	2 squamous cell lung carcinoma 2 lymphoma 1 synovial sarcoma
Mesothelioma	4 (8)	
Granulomatous inflammation	1 (2)	1 rheumatoid pleurisy
Acute inflammation (empyema)	1 (2)	Microbiologically proven
Non-diagnostic	4 (8)	1 large cell lung carcinoma (via consequent thoracotomy) 1 CABG (no recurrence) 1 squamous cell lung carcinoma (excitus) 1 breast carcinoma (excitus)

Table 3. The histopathology results of the 49 patients in whom pleural biopsy was performed and the discrimination of the details in related diagnosis
CABG: coronary artery by-pass surgery

Talc pleurodesis had been performed in 28 patients (56%) as thoracoscopic talc poudrage in 17 patients (61%) and instillation through a thoracostomy tube (talc slurry) in 11 patients (39%). Only in 2 patients, the result was noted as failure (4%); 1 because of persistent minimal apical expansion defect and 1 because of recurrence of the pleurisy (2 had thoracoscopic talc poudrage). In 2 lung cancer patients, one in each group, the outcome of the pleurodesis could not be evaluated since the patients died within 1 year after pleurodesis. The median duration of hospitalization and duration of tube thoracostomy were shorter in thoracoscopic pleurodesis (talc poudrage) group when compared with the pleurodesis via tube thoracostomy (talc slurry) group and no pleurodesis group (Table 4).

	Hospitalization (day)	Tube thoracostomy (day)
No pleurodesis	15.7 ± 7.0	8.8 ± 5.7
Talc poudrage	7.0 ± 3.7*	4.4 ± 2.2**
Talc slurry	15.7 ± 4.8	9.0 ± 4.5

Table 4. The comparison of the mean duration for hospitalization and tube thoracostomy according to the pleurodesis group (* $p=0.0001$, ** $p=0.001$). The values are presented as mean ± standard deviation.
Mean duration of hospitalization was $13.4 ± 6.4$ days (3-34) and mean duration of tube thoracostomy was $6.5 ± 3.8$ days (2-18).

There were no procedure-related deaths or intra-operative accidents. Open-chest surgery intervention was never required. There was no major complication, but minor complications in 5 patients (10%); 3 minimal expansion defects, 1 remarkable but transient subcutaneous emphysema and 1 empyema. Although not during the procedure, 6 patients died in the follow-up period. Early mortality (1 month after the thoracoscopy) was in 3 patients; 1 breast cancer with lymphangitis carcinomatosa, 1 severe heart failure and emphysema, 1 Stage IV lung cancer. Other 3 patients who died were diagnosed as lung cancer and the time periods between the thoracoscopy and time of deaths was 6, 9, and 15 months.

The medical thoracoscopies were classified as effective and ineffective according to the evaluation of the pleura biopsy and microbiology results, and the follow-up notes (for non-specific pleuritis and non-diagnostic biopsy results) together. The procedure was considered as effective in 45 patients (90%). Of 4 patients with normal pleura in biopsy results (6%), 1 was diagnosed as non-specific pleuritis via open biopsy, but large cell lung cancer was confirmed by lobectomy, 1 lymphoma, 1 squamous cell lung carcinoma and all three patients died within 3 months of follow-up period. Other patient with normal pleura findings in biopsy had had coronary by-pass surgery and no recurrence had been occurred 1 year after thoracoscopy and that was considered as effective. Since the outcome in two of the patients with non-specific pleuritis couldn't be evaluated because of the short follow-up period, those were accepted as ineffective.

Discussion:-

Pleural effusions indicate the presence of disease which may be pulmonary, pleural, or extrapulmonary. As the differential diagnosis is wide, a systematic approach to investigation is necessary. The aim is to establish a diagnosis swiftly while minimizing unnecessary invasive investigation. [6] A diagnostic algorithm for the investigation of a pleural effusion would be very useful during the work-up. In our department, we do perform blind closed biopsy via Abrams needle as an initial diagnostic procedure following thoracentesis when the suspicion of tuberculosis pleurisy is high (i.e. young patient, exudative pleural effusion with high adenosine deaminase level, lymphocyte predominance). If the diagnosis could not be proven by histopathological and microbiological examinations, medical thoracoscopy was performed. In a patient with the high malignancy suspicion (i.e. smoker or with asbestoses exposure history or previously diagnosed malignancy of lung or any other organ, atypical cells in pleural fluid cytology), the medical thoracoscopy is usually the first choice of biopsy techniques since June 2007. Unfortunately, it is not always easy to define the patients "highly suspicious for malignancy". Ferrer *et al*. have suggested that using four criteria (no fever, symptomatic for more than 1 month, blood-tinged fluid, CT findings suggestive for malignancy) was found adequately valuable in 95% of the patients. [14]

The reasons of having more male patients and in old ages, underlying malignancy in 46% of patients might be related with that diagnostic algorithm. Similar age range and male predominance have been also reported in several studies. [12, 15-17] Emad *et al*. have been reported that the pleuroscopy was superior to closed biopsy in older age group. [18]

Thoracoscopy have the advantage of visualization of the parietal pleura and taking biopsy from the lesions. In an early study, rigid thoracoscopy has been found diagnostically superior and safe. [19] In the study of Harris *et al*, the diagnostic sensitivity of thoracoscopy for malignancy was reported 95% in 182 consecutive patients. [20] Menzies *et al*. have been reported a sensitivity of 91%, a specificity of 100% and a negative predictive value of 93% for the diagnosis of pleural malignancy. [21] Even when the cytology result is benign, histopathology could change the management. In our study, 23% of the patients with benign cytology report had been diagnosed malignancy by thoracoscopic biopsy. That finding is important for defining the role of medical thoracoscopy, especially in the patients with high suspicion for malignancy.

For the patients who diagnosed as "non-specific pleuritis", there is no consensus for the time period required to be confident with that diagnosis. Only 2 of 19 patients in our series could be followed less than 6 months and those patients were assessed among the ineffective thoracoscopy group. Others were accepted as diagnostic in final assessment. In other series, there has been same diagnosis obtained via thoracoscopic biopsies in 20-46% of the patients. [12, 15, 16, 19] By considering the information on low possibility of false negative results in patients who underwent thoracoscopy, non-specific pleuritis diagnosis seems to be reliable.

So far, the appearance of parietal pleura suggestive for malignancy was not mentioned in other thoracoscopy studies. [12, 15-17, 21] In our study, nodules were suggestive for malign diseases diagnosed in 18 of 23 patients (78%). Plaque-like lesions were also malignant in 57% of the patients with that appearance. When the appearance was normal, the possibility of having malignancy was found very low. Tuberculosis pleurisy represents with tiny white nodules more disseminated. [22] Further studies are needed to support the relation between the appearance of parietal pleura and the histopathology results.

The assessment of the outcome for medical thoracoscopy has been defined as diagnostic, effective or conclusive in different studies. [15-18] In our study, it was made with the classification as effective and ineffective thoracoscopy. By considering the results of histopathology and microbiology, and the follow-up notes (for non-specific pleuritis and

normal pleura in biopsy results) together, the procedure was found diagnostic in 45 patients (90%). That outcome is in the range of 90-100% which has been reported previously. [3, 6, 19, 23]

By performing medical thoracoscopy, the opportunity is also provided for talc pleurodesis. Thoracoscopy may therefore be therapeutic as well as diagnostic. [2, 6, 24] The decision for pleurodesis during thoracoscopy (talc poudrage) was made according to the presence of previously diagnosed lung or other organ malignancies. Since the histopathology result of the pleura biopsy has not been obtained yet at that time, pleural effusions in a patient with malignant disease was accepted as a candidate for talc pleurodesis. In the SEPAR guideline, it is being suggested to carry out pleurodesis when the clearly malignant lesions are observed. [25] Pleurodesis success rates with talc are typically high, ranging from 81% to 100%. [26] The success rate was slightly lower in talc poudrage group but the durations of both hospitalization and tube drainage were significantly less in that group when compared with talc slurry group. The overall success rate of pleurodesis was high in our study (92.8%). In the study of Kolschmann et al., the success rate of thoracoscopic pleurodesis has been reported as 82.6% and type of primary malignancy had no significant influence on success. [27]

Although the mean duration of hospitalization was not long in our study, the range was large. Accompanying diseases and underlying malignancy might be responsible from that finding. In the study of Blanc et al., the mean durations of hospitalization and tube drainage have been found similar to our results, but in contrary no pleurodesis group had shorter durations in their study. [15]

The complications of pleural procedures have been proclaimed as intrapleural hemorrhage, air leak, pleural infection, re-expansion edema, pulmonary embolism, and malignant seeding. [28] Medical thoracoscopy is an overall well-tolerated procedure and death is extremely rare complication. [2, 3] In our study, only a few minor complications and no death were occurred. Alrawi *et al*. have reported direct complication in 10% (requirement of endotracheal intubation in 2 patients). [12] Asymptomatic pneumothorax, arrhythmia, fever after talc pleurodesis and subcutaneous emphysema had been reported as minor complications in 8-19% of the thoracoscopies. [17, 18, 23] Only in the study of Blanc et al., 3 thoracoscopy-related deaths have been reported among 168 medical thoracoscopies. [15]

The experience medical thoracoscopy all over the world is growing and the numbers of chest physicians capable to perform that procedure is increasing by hands-on courses and training in specific centers.

In conclusion, selecting patients in whom less invasive methods were unsuccessful or the patients who have strong possibility for the malignancy might increase the diagnostic and therapeutic yield of the thoracoscopy in respiratory medicine practice and it has a short investigation time. Thoracoscopy is an efficient and safe procedure for many indications. It also gives the opportunity for talc pleurodesis or early intervention to the adhesions as therapeutic approaches.

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