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BETADINE[®] IN CHEMICAL PLEURODESIS

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Abstract

Malignant pleural effusions (MPEs) represent a common complication which can occur in any neoplastic disease. Between October 2012 and December 2013 we performed a prospective study aimed to establish the adequate treatment for malignant pleural effusions. 85 patients were included in this study, diagnosed and treated in the Thoracic Surgery Department of the Central Military Emergency University Hospital. 46 patients underwent chemical pleurodesis with betadine[®] (through thoracoscopic surgery – 30 patients – or through a chest drainage tube – 16 patients), while for 39 patients talcum powder was chosen as the agent for pleurodesis (through thoracoscopic surgery – 28 patients – or through a chest drainage tube – 11 patients with major surgical risk). The most frequent cancers with secondary MPEs were lung cancers (50 patients). The efficiency of the two methods was the same. The most used chemical pleurodesis procedure was the thoracoscopic surgery (58 patients). The most used agent for pleurodesis was Betadine[®] (30 patients).

Chemical pleurodesis with Betadine[®] is a safe procedure, which can be used intraoperative (thoracoscopic surgery) or through a chest drainage tube (for patients with major surgical risk). Chemical pleurodesis with Betadine[®] plays an important role in addressing MPEs because of its high therapeutic efficiency and lower complications rate when compared to other agents (talcum powder).

Rezumat

Pleureziile maligne reprezintă o complicație comună care poate surveni în cursul oricărei boli neoplazice. În perioada octombrie 2012 – decembrie 2013 am efectuat un studiu retrospectiv cu scopul de a stabili tratamentul adecvat pentru pleureziile maligne. În această perioadă au fost luați în studiu 85 de bolnavi diagnosticați și tratați pentru pleurezii maligne în secția de chirurgie toracică din SUUMC. La 46 de pacienți s-a efectuat pleurodeză chimică cu betadină (aplicată intraoperator prin chirurgie toracoscopică la 30 de bolnavi sau pe tubul de dren pleural la 16 pacienți cu contraindicații chirurgicale) iar la 39 de pacienți a fost ales talcul ca substanță de pleurodeză chimică (aplicat fie intraoperator prin insuflare toracoscopică la 28 de bolnavi fie prin instilare pe tubul de dren pleural sub formă de suspensie la 11 pacienți cu riscuri chirurgicale majore). Cele mai frecvente

cancere primitive care au stat la originea pleureziilor maligne abordate în studiul nostru au fost cancerele pulmonare (50 de cazuri). Eficiența ambelor metode de pleurodeză a fost similară, la 98% dintre pacienți. Procedul cel mai folosit a fost pleurodeza chimică prin chirurgie torascopică (58 de cazuri). Metoda cea mai folosită pentru împiedicarea recidivei revărsatului malign pleural a fost pleurodeza intraoperatorie cu betadină (30 de cazuri).

Pleurodeza chimică cu betadină utilizată fie intraoperator (prin chirurgie torascopică) fie pe tubul de dren pleural (la bolnavii cu contraindicații chirurgicale) joacă un rol important în abordarea cazurilor de pleurezii neoplazice datorită eficienței terapeutice ridicate și datorită reacțiilor adverse mai reduse decât în cazul altor agenți de pleurodeză (talc).

Keywords: Betadine[®], talc, malignant pleural effusion, thorascopic, chemical pleurodesis.

Introduction

Malignant pleural effusions (MPE) arise in advanced stages of malignancies and frequently herald a poor prognosis. MPEs mostly develop in patients with lung cancer, breast cancer and lymphoma, but any neoplastic disease can determine, at a certain time, a pleural effusion. Most patients with MPEs are symptomatic. The most common symptom is exertional dyspnoea. Most patients undergo chemotherapy or local treatments to palliate symptoms such as dyspnoea, cough and chest pain, in order to improve the quality of life [2, 3, 4].

Pleurodesis must be preceded by a thorough paraclinical evaluation of the patient. The presence of mediastinal displacement on the same side as the pleural effusion imposes a bronchoscopic exam in order to evaluate a possible bronchial obstruction – this situation is a contraindication for pleurodesis. The introduction of pleurodesis was necessary because most of malignant pleural effusions are not responding to chemotherapy or radiotherapy [11].

Intraoperative pleurodesis (thorascopic or through a thoracotomy) is performed by insufflating powders with sclerosant effect (e.g. talcum). Postoperative pleurodesis consists of intrapleural instillation of fibrotic solutions through the chest drainage tube (surgically inserted through a minimal pleurotomy or through thorascopic surgery).

The management of refractory MPEs includes local therapeutic methods such as thoracentesis, pleurodesis, pleurectomy, or pleuroperitoneal shunting. Instilling of sclerosant agents into the pleural cavity (pleurodesis) is a common method for the management of MPEs [5].

The present study aimed to investigate the efficacy and safety of pleurodesis with povidone-iodine (Betadine[®]), as an inexpensive alternative

agent for the local management of pleural effusion in patients with MPEs admitted in Thoracic Surgery Department of Central Military Emergency University Hospital between 2012 and 2013.

Materials and Methods

From October 2012 to December 2013, 85 patients were admitted to the Department of Thoracic Surgery within “Carol Davila” Central Military Emergency University Hospital, Bucharest, Romania, with symptomatic malignant pleural effusion. All patients were documented with malignant pleural effusion, diagnostic established by the positive result of pleural effusion cytology, or by intraoperative pleural biopsy. Also, all patients included in this study had normal renal function. A total of 85 patients were included in the study, after each one of them gave their informed consent. The study was approved by the Ethics Committee of our institution. Because of the possibility of systemic absorption of the iodine from the povidone-iodine solution, and the severity of a possible thyroid disease, thyroid function testing was performed before this procedure. Therefore, the patients with thyroid disease were excluded from the study.

Minimally invasive thoracic surgery was performed under general anaesthesia, using the standard thoracoscopic line provided by Storz[®]. The setup included a 30° or 45° telescope, video camera, cold light source, aspiration and cauterization systems, as well as specific thoracoscopic instruments, high-definition LCD display and a video documenting system.

Pleural drainage through a minimally pleurotomy was performed under local anaesthesia, using open surgery instruments.

In the current study, it was used Betadine[®] (povidone-iodine) in the form of 2% topical solution, 50 mL (introduced inside the pleural cavity at the end of the thoracoscopic surgical intervention, or through the chest drainage tube – when minimal pleurotomy was performed) or talcum powder (magnesium silicate) applied intraoperatively through poudrage (5 grams of talcum powder) or as a suspension (5 grams of talcum powder in 100 mL of serum) on the chest tube. The used talcum powder was prepared in the hospital pharmacy and sterilized (talcum powder used for medical purposes must not contain asbestos and particle dimensions must be under 50 µm) [N.B.]. It must be sterilized by dry heat, gamma rays or ethyleneoxide. Sterilized this way, the talcum powder remains sterile for at least one year, if properly stored.

The response to this procedure, treatment failure and the patients' complains were evaluated. The authors define “complete response” as symptomatic improvement of dyspnoea with complete radiographic

resolution of the pleural effusion, “partial response” as symptomatic improvement with recurrent pleural effusion that did not require additional thoracentesis and “treatment failure” as recurrent pleural effusion that required thoracentesis. All data were analysed using SPSS (version 16.5). Values $p < 0.05$ with CI = 95% were considered statistically significant.

Results and Discussion

Eighty-five patients with refractory MPEs were eligible to enter the current study. The average age of patients was 64.7 ± 8.4 (49-80) years-old. Forty-five patients (52.95%) were women and forty (47.05%) were men (Figure 1).

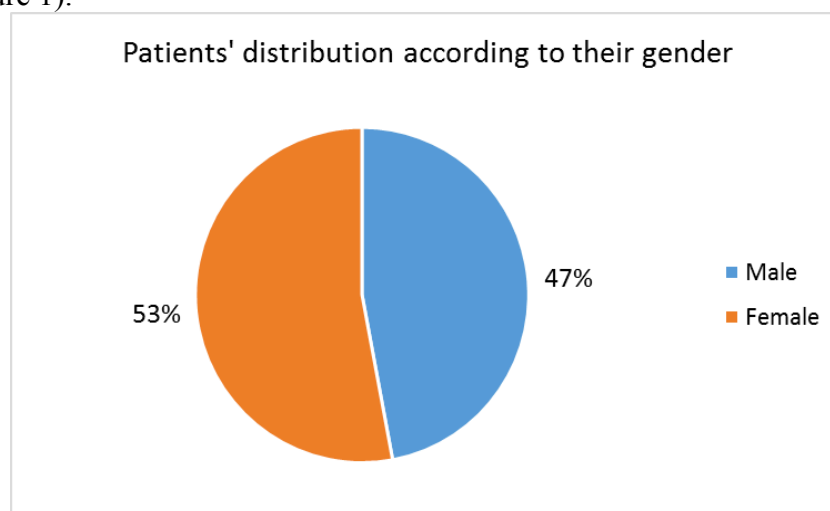


Figure 1.
Clinical demographics of the patients

The analysis of the surgical techniques we performed (thoracoscopic surgery or minimal pleurotomy) for the treatment of MPEs showed a predominance for minimally invasive thoracoscopic procedures (58 patients, 68.23%) over the classic surgery procedures (27 chest drainage tubes, 31.76%).

The analysis of chemical pleurodesis methods showed the preference for Betadine[®] usage (46 patients) over talcum powder (39 patients).

The MPEs were also analysed regarding the origin of the primary tumour. For this purpose, data from the patients' charts (anamnesis, imaging exams, fiber bronchoscopy), as well as histopathology results from pleural or pericardium biopsies were used. In 12 cases, despite the analysis of the mentioned data, the primary cancer could not be identified. The

histopathologist recommended supplemental immunohistochemical tests for these patients.

The most frequent primary tumours with secondary MPEs were lung cancers (52 patients) – Table I.

Table I

The most common primary malignancies

Primary tumour	No. of patients	%
Lung	52	61.17
Breast	10	11.76
Mesothelioma	8	9.41
Mediastinal tumours	3	3.52
Unknown	12	14.11

For patients who underwent thoracoscopic surgery with general anaesthesia (58 patients), parietal pleural biopsies were also performed. For 30 patients we used Betadine[®] for pleurodesis and for 28 patients talcum powder. For 27 patients a simple chest tube drainage with local anaesthesia was preferred, due to the weak biologic status of the patients. All the patients showed a complete pulmonary expansion after the pleural liquid's evacuation.

No intraoperative accidents or incidents were recorded during this study. Postoperatively we encountered several complications, such as fever, thoracic pain, emphasis of respiratory dyspnoea, pleural empyema. These findings are detailed in Table II, for Betadine[®] and talcum powder use.

Table II

Complications related to chemical pleurodesis

Postoperative complications	Talcum powder		Betadine [®]	
	No. of patients	%	No. of patients	%
Fever	25	64.10	2	4.34
Thoracic pain	4	10.25	12	26.08
Dyspnoea	2	5.12	2	4.34
Pulmonary thromboembolism	1	2.56	0	0.00
Empyema	1	2.56	0	0.00

We observed the following early postoperative complications for the patients treated with talcum powder (39 patients): fever (25 patients), thoracic pain (4 patients – all of them from the chest tube drainage group of 11 patients), emphasis of dyspnoea (2 patients) and one patient with pulmonary thromboembolism. As a late complication, we had 1 patient with pleural empyema.

As for the patients with Betadine[®] pleurodesis (46 patients), we encountered the following early complications: thoracic pain (12 patients

out of the 16 with chest tube drainage), fever (2 patients) and emphasis of dyspnoea (2 patients). No vital or late complications were observed.

We obtained a complete response to talcum powder pleurodesis for 30 patients (76.93%), while 7 patients had only a partial response (17.94%). Treatment failure was recorded for 2 patients (5.13%). The overall success rate was 94.87% (n=39) (Table III).

Table III
Results (clinical and imagistic) for talcum powder pleurodesis

	No. of patients	%
Complete response to talcum powder pleurodesis	30	76.93
Partial response to talcum powder pleurodesis	7	17.94
Treatment failure	2	5.13

Regarding Betadine[®] pleurodesis, we had the following results: 35 patients (76.08%) with complete response, 9 patients with a partial response (19.56%) and treatment failure were recorded for 2 patients (4.34%). The overall success rate was 95.64% (n=46) (Table IV).

Table IV
Results (clinical and imagistic) for Betadine[®] pleurodesis

	No. of patients	%
Complete response to Betadine [®] pleurodesis	35	76.08
Partial response to Betadine [®] pleurodesis	9	19.56
Treatment failure	2	4.34

Malignant pleural effusions (MPEs) represent common and debilitating complications of a wide array of malignancies that may be primary to the pleura or to other intra- or extra-thoracic sites.

Moghissi stated that there are two types of pleural effusions associated with neoplastic disease: Type I (real malignant pleural effusions – MPE) and Type II (paramalignant or paraneoplastic effusions) [1]. The term MPEs defines pleural effusions that result from direct infiltration of the pleura by cancer cells. Pleural effusions caused by indirect effects of cancers over the pleural cavity, such as obstruction of mediastinal lymph nodes, bronchial obstruction, pulmonary embolism, superior vena cava syndrome or decreased oncotic pressure, are defined as paramalignant or paraneoplastic effusions [2]. Type II pleural effusions are histologically characterized by the absence of neoplastic cells in the pleural fluid, as well as “clean” pleural biopsy (no malignant cells) [3].

More than 75% of MPEs are caused by carcinomas of the lung, breast or ovary, or by lymphomas, with metastatic adenocarcinoma being the most common histological type [4]. Other causes include malignancies

of the genitourinary or gastrointestinal tract, with up to 10% of the patients having unknown primary cancer sites. Understanding the pathophysiology behind malignant pleural effusion is helpful in evaluating and developing effective therapies.

The most important principle in obtaining an efficient pleurodesis is the achievement of a completely evacuated pleural cavity and a pulmonary expansion as complete as possible before utilizing sclerotic agents. This aspect permits the creation of adherences between the two pleural sheets. According to their effects, substances utilized for pleurodesis can be grouped in two main categories: cytostatic agents (controlling the pleural effusion by reducing the tumour volume) and sclerotic agents (pro-inflammatory, fibrotic effect).

Talcum powder pleurodesis was first utilized by Bethune in 1935. Because talcum is insoluble, it is mostly utilized as powder, introduced during thoracoscopy, or, rarely, through thoracotomy. For patient incapable of sustaining a surgical intervention, we prefer the administration of a suspension of talcum through the chest drainage tube, after minimal pleurotomy or after thoracoscopy with local anaesthesia.

There are studies showing a similar efficiency (about 90%) in MPEs' treatment regardless of the method in which talcum is instilled: intraoperative poudrage (talcum powder insufflation) or instillation through the drainage tube [13]. Analysing the patients included in this study, we observed better results for intraoperative poudrage, probably because of a more uniform distribution of the talcum particles over the pleural surface. Respecting the pleurodesis principles, talcum poudrage requires a complete pulmonary expansion and fluid evacuation, avoiding the risk of infection on residual cavities.

Povidone-iodine (Betadine[®]) is an iodine-based topical antiseptic agent, extensively absorbed from mucosal surfaces, leading to an increase in serum iodine concentration. It can be absorbed by the thyroid gland and may appear in saliva, sweat and milk, and is excreted unchanged in the urine. Although the exact mechanism by which povidone-iodine exerts its pleurodesis activity is unclear, it is thought to be related to the low pH of the sclerotic solution (pH =2.97) [21]. It is also a very efficient pleurodesis agent. The recommended dose is 100 mL of 2% Betadine[®] [21] or 50 mL of 2% Betadine[®] [21], administered at the end of the thoracoscopic surgical intervention or over the chest drainage tube. In these studies, the efficiency of Betadine[®] in prevention of re-accumulation pleural fluid was similar to talcum, while its adverse effects were reduced and less important. As adverse effects for Betadine[®] pleurodesis, intense pleural pain and systemic

hypotension may appear in some patients [21]. No deaths were recorded for Betadine[®] pleurodesis. Other authors reported cases with loss of sight after pleurodesis with 200-500 mL of 10% Betadine[®] solution [22]. Recent studies [5] state that Betadine[®] is an efficient alternative for tetracycline and talcum, obtaining a good pleurodesis in patients with MPEs. Povidone-iodine is the most inexpensive among these agents. Although povidone-iodine is highly absorbed from mucosal surfaces and causes excess in serum levels of iodine and thereby may be associated with thyroid dysfunction, Yeginsu et al. [23] reported no changes in the serum levels of thyroid hormone at 24 and 72 hours after pleurodesis and in 8.7 month-follow-up period.

Conclusions

Malignant pleural effusions represent an important clinical condition among patients with underlying neoplastic disease. Although therapy is directed towards palliation of symptoms, the correct management of therapeutically options can increase patients' survival and quality of life. Through careful assessment of the effusion and the pleural space, combined with an evaluation of the patient's prognosis and functional capacity, an appropriate intervention exists in order to provide effective palliation in almost every clinical circumstance.

The statistical analysis showed that MPEs are more likely in patients aged 50 to 69 years. Considering the low rates of complications, lower hospitalization and lower expenses for the medical unit, the most adequate procedure in this case is thoracoscopic pleurodesis.

Talcum pleurodesis has a high efficiency rate (about 95%) in the treatment of MPEs, regardless of the method used: intraoperative poudrage or suspension instillation over the chest drainage tube. On the studied patients we remarked the superiority of intraoperative poudrage, perhaps due to a more uniform distribution of the particles inside the pleural cavity. Because of the risk of death represented by the usage of intraoperative talcum poudrage is not significantly greater than for other substances, we consider useful the research for other pleurodesis methods in patients with MPEs [14, 15, 16].

Betadine[®] pleurodesis can be useful because of a high quality pleurodesis in 96% of the cases and because of its lower risk of complications (there were no deadly complications described worldwide). Thoracic pain is more frequent when instilling Betadine[®] over the chest drainage tube when compared with talcum powder. This syndrome can be prevented by administrating lidocaine over the chest drainage tube and by

utilizing usual analgesics. The utilization of Betadine[®] is prohibited for patients with known allergies to iodine or with several thyroid conditions (for evaluating the effect of povidone-iodine on thyroid gland, we recommend performing thyroid function tests before and one week after the pleurodesis) [9]. Another advantage of Betadine[®] over talcum is its antiseptic effect (antibiotic and antifungal), preventing the infection of a possible postoperative cavity [21].

Povidone-iodine is an effective, inexpensive, safe and feasible agent for chemical pleurodesis in the management of MPEs.

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