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Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial☆

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Abstract

Objective: To compare the efficacy, safety, and outcome of thoracoscopic talc poudrage (TTP) versus povidone—iodine pleurodesis (PIP) through a thoracostomy tube as a palliative treatment of pleural effusion due to metastatic breast carcinoma (MBC). **Methods:** A total of 42 MBC patients were prospectively enrolled in a randomized controlled trial. Twenty-two patients received TTP (group A), whereas 20 patients (group B) underwent pleurodesis by instilling povidone—iodine through a thoracostomy tube, as a bedside procedure. **Results:** The mean age was 48.2 ± 9.9 (range: 29—64) years and 50.2 ± 7 (range: 32—62) years for groups A and B, respectively (p = ns). At presentation, all patients had moderate to severe dyspnea, New York Heart Association (NYHA) > II and Medical Research Council (MRC) dyspnea scale 3—5. Morbidity in both groups was low. Post-procedure analgesic requirements due to severe pleuritic chest pain were higher in group A (18% vs 0%, p = 0.2). Four patients in group A (18%) and one in group B (5%) were febrile (>38 °C) within 48 h of the procedure. Both groups achieved good symptom control, with improvement in MRC dyspnea scale (1—3). There were no in-hospital deaths. Post-procedure hospital stay was lower in group B (p = 0.009). The mean progression-free interval was 6.6 (range 3—15) months. At follow-up (mean: 22.6 (range: 8—48) months), recurrence of significant pleural effusion requiring intervention was noted in two and three patients in group A and group B, respectively (p = ns). **Conclusion:** Povidone—iodine can be considered as a good alternative to TTP to ensure effective pleurodesis for patients with malignant pleural effusion due to MBC. The drug is available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary.

Keywords: Pleurodesis; Malignant pleural effusion; Talc; Iodine

1. Introduction

Recurrent malignant pleural effusion causing debilitating dyspnea is common in patients with neoplastic disease. Metastatic breast cancer accounts for 25% of all malignant pleural effusions as the second most prevalent cause of pleural effusion after bronchogenic carcinoma [1], and 7—11% of breast cancer patients will require treatment during the course of the disease [2]. The quality of life is adversely affected with reports of progressive dyspnea, dry cough, chest pain and reduced physical activity [3]. The appearance of malignant pleural effusion denotes the presence of pleural metastases. However, patients with breast cancer and pleural metastases are not considered to be in the terminal stage of the disease, and with systemic chemotherapy and/or hormonal management, the median survival may extend from several months to years [4,5]. In this setting, the surgical option for pleurodesis is recommended and drainage of the pleural cavity, re-expansion of the lung and obliteration of the pleural space is the palliative treatment of choice, which also limits recurrence [6,7].

Over the past few years, chemical pleurodesis has evolved with a wide variety of available agents. In practice, talc pleurodesis is the surgical pleurodesis of choice for recurrent malignant effusion, with a reported success rate of 90% [8,9]. In the past, in Egypt, the health pharmaceutical surveillance

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office (a Food and Drug Administration (FDA)-like organization) disapproved the use of talc due to its complications. Although currently there is no clear directive, talc remains an unavailable drug in the Egyptian market. Despite its cost effectiveness, talc is still not imported into the country; instead, bleomycin, which is expensive and less effective, is being used. Povidone—iodine (in a 10% solution), which is primarily used as an antiseptic, has been shown to be an inexpensive, available, and mostly effective alternative sclerosing agent in some series [10].

This study was conducted to compare the efficacy and safety of 10% povidone—iodine and thoracoscopic talc insufflation, for the pleurodesis of recurrent malignant pleural effusions. Local iodine pleurodesis was offered to patients as a bedside procedure, whereas the most commonly used video-assisted thoracoscopic (VATS) talc poudrage was done under general anesthesia.

2. Patients and methods

The study was conducted at the Department of Chest Medicine and Cardiothoracic Surgery in Cairo University Hospitals from January 2002 to December 2005. A total of 44 patients with malignant pleural effusion, as a complication of breast carcinoma, were enrolled in a prospective randomized control trial, after informed consent was obtained from each patient. All patients either had metastasis as their first presentation, or had relapsed after chemotherapy during their follow-up. Randomization was performed using the sealed envelope technique. The study was approved by the Local Hospital Ethics Committee.

The exclusion criteria in this study were patients with performance status >3, those with known allergies to iodine, trapped lung, those in whom there was no change in Medical Research council (MRC) dyspnea scale after thoracentesis, pleural fluid pH < 7.2, or glucose < 60 mg dl^{-1}, and those with extrathoracic metastasis.

Clinical demographic variables of the study patients included: age, stage of disease (radiological imaging), estrogen and progesterone receptor status, human epidermal growth factor receptor 2 (HER2) gene expression, symptoms including MRC dyspnea scale, disease-free interval, adjuvant chemotherapy, and first-line metastatic chemotherapy. Both groups received the same protocol for adjuvant chemotherapy, which included FAC (5-flurouracil, adriamycin, and cyclophosphamide) or docetaxel. Patients who had metastasis as their first presentation were treated with the FAC protocol, whereas those with disease relapse and who had previously received adjuvant chemotherapy were administered docetaxel as a single agent. The progression-free interval was defined as the period that the patient showed no relapse of breast cancer both local and metastatic.

Therapeutic thoracentesis was performed in all patients, and the pleural fluid amounts were recorded and sent for biochemical (pH, protein, lactate dehydrogenase (LDH), and glucose), bacteriological and cytological evaluation. Patients were then randomized into two groups by uploading their ID numbers into randomization software (Adaptive Randomization, outcome-adaptive randomization program). One study arm was group A with 22 patients who received video-assisted thoracoscopic (VATS) drainage, adhesiolysis, and talc poudrage (Steritalc® F2, manufactured by Novatech, France), and the other one was group B with 20 patients, who underwent VATS drainage and adhesiolysis and received bedside pleurodesis with 10% povidone—iodine (Betadine®, manufactured by Nile Co. for Pharmaceuticals and Chemical Industries, Cairo, A.R.E; licensed by Mundi Pharma AG, Basel, Switzerland).

2.1. Surgical technique

Under general anesthesia with a double-lumen endotracheal tube, VATS evaluation of the affected hemithorax was performed using two 5-mm port sites. The pleural fluid was drained fully, and adhesiolysis performed using blunt and sharp dissection. Re-inflation of the lung by the anesthesiologist (to a maximum airway pressure of 30 mmHg) excluded trapped lung; further, there were no reported air leaks. Multiple pleural biopsies were taken for histological confirmation. Group A patients received insufflation with 4 g of talc under thoracoscopic guidance while sedated, whereas group B patients recovered and received at the bedside the iodine—povidone pleurodesis solution. Twenty milliliters of 10% povidone—iodine and 30 ml of normal saline were injected into the pleural cavity through the intercostal chest drain, which was then clamped for 4 h before re-opening. This was done on the same day after thoracoscopy, after insuring the absence of air leaks and in fully conscious patients, capable of coughing. Prior to povidone—iodine infusion, each patient received pre-medication in the form of 20 ml lidocaine (Xylocaine 2%, Astra Zeneca) in 30 ml of normal saline solution through the chest tube. Drains were removed if the chest radiograph confirmed satisfactory lung expansion, and the 24-h drainage was less than 100 ml, with no air leak. All patients were discharged on the same day when their chest tube was removed.

2.2. Follow-up

All patients had the same follow-up schedule with appointments every 3 months. At all visits, chest X-ray and symptoms were evaluated. The efficacy of pleurodesis was defined in three levels of response: complete (absence of pleural fluid reaccumulation), partial (residual pleural fluid or reaccumulation, which did not require further thoracocentesis or remained asymptomatic), and failed (additional pleural procedures were necessary). A normal chest X-ray or radiological reaccumulation of pleural fluid without recurrence of dyspnea or the need for thoracentesis was reported as a success. In both groups, repeated ultrasound-guided thoracentesis was carried out for patients with failed pleurodesis and repeated reaccumulation of effusion at weekly intervals, and when required, they were offered PleurX catheter (Denver Biomedical Inc., Denver, CO, USA) for home management of their effusions.

2.3. Statistical analysis

The data were statistically analyzed using Microsoft Excel 2003. The continuous variables were expressed as mean

Table 1. Patients' preoperative characteristics.

	Group A (n = 22 pts)	Group B (n = 20 pts)	p-value
Age (years)			
Range	29–64	32–62	
Mean ± SD	48.2 ± 9.9	50.2 ± 7	0.5
Performance status scale (ECOG)	0–1	0–1	
Disease stage (no. pts (%))			
II[a]	8 (36%)	6 (30%)	1.0
III[a]	2 (9%)	3 (15%)	0.9
IV	12 (55%)	11 (55%)	0.9
Receptor status (no. pts (%))			
ER (+ve)	12 (55%)	12 (60%)	0.9
PR (+ve)	15 (68%)	15 (75%)	0.9
HER2 (−ve)	6 (27%)	4 (20%)	0.9
Duration of progression of disease (months mean ± SD)	11.5 ± 4.3	11.7 ± 3.8	0.8
Pleural effusion as the first presenting symptom (no. pts (%))	12 (54%)	10 (50%)	0.9

Pts: patients, SD: standard deviation, ER: estrogen receptors, PR: progesterone receptors, HER: HER 2 neu gene over-expression, ns: not significant.
[a] A relapse from a previous stage II or III.

values ± standard deviation (SD) and compared using the unpaired t-test. The discrete variables were compared using the χ^2 test and Fisher's exact test. p Values of less than 0.05 were considered significant.

3. Results

A total of 42 patients with malignant pleural effusion due to breast carcinoma were enrolled during the study period and randomized into two groups. As many as 22 patients in group A underwent VATS adhesiolysis and talc poudrage, while 20 patients in group B were treated with VATS adhesiolysis and bedside 10% povidone–iodine instillation through the intercostal chest drain for pleurodesis. There was no difference in the preoperative demographic and clinical details between the two groups (Tables 1 and 2). Malignant pleural effusion with pulmonary atelectasis was confirmed thoracoscopically in all patients. The mean operative time was 31 min (range: 21–54 min), with no significant differences between the two groups, and all patients were extubated in the theater.

In all patients, dyspnea and cough symptoms were greatly improved after drainage and pleurodesis. Most specifically, all patients post-procedurally were in the I and II MRC scale of dyspnea in both study arms, as seen in Table 3. The mean total pleural fluid drained was 2977 ± 790 ml and 3087 ± 778 ml for groups A and B, respectively (p = 0.6). All patients had good outcomes with no bleeding complications and were discharged on both radiological and clinical evidence of complete resolution of their pleural effusion.

Table 2. Pre-procedure MRC dyspnea scale of patients.

MRC dyspnea scale pre-procedure	Group A (n = 22 pts)	Group B (n = 20 pts)	p-value
III (no. pts (%))	10 (45%)	7 (35%)	0.87
IV (no. pts (%))	9 (41%)	7 (35%)	0.97
V (no. pts (%))	3 (14%)	6 (30%)	0.50

Pts: patients.

Table 3. Post-procedure MRC dyspnea scale of patients.

MRC dyspnea scale post-procedure	Group A (n = 22 pts)	Group B (n = 20 pts)	p-value
I (no. pts (%))	14 (64%)	15 (75%)	0.92
II (no. pts (%))	8 (36%)	5 (25%)	0.79

Pts: patients.

The post-procedural hospital stay was significantly lesser for group B with a mean of 5.7 ± 2 and 4.5 ± 1.1 days for groups A and B, respectively (p = 0.009) (Table 4).

No mortality related to the procedure or perioperative mortality was observed. There were similar survival rates between the two groups and totally at follow-up, 32 patients (76%) were alive at 8 months, 22 (52%) patients at 2 years, and 10 patients (23%) were alive at 4 years (p = ns, Table 4).

During early follow-up, in group A, there was complete response with no fluid reaccumulation in 19 (87%) patients, and failure in two (9%) patients. Only one patient had partial response with radiological reaccumulation at 2 months post-procedure, but never developed any clinical dyspnea during the 14-months' follow-up. The other two patients developed clinical recurrence, with dyspnea appearing 39 and 51 days post-procedure, and were considered as failures. In group B, at the early post-procedure follow-up, three (15%) patients developed reaccumulation of fluid with the recurrence of dyspnea at 33, 41, and 49 days, respectively. All patients in group B showed no loculations and, therefore, a small-bore chest tube was placed and iodine was used again. In the other study arm, in patients who had talc pleurodesis, loculations of effusions were observed and were repeatedly aspirated with an ultrasound guide. In general, patients who experienced repeated reaccumulations were offered a placement of an ultrasound-guided PleurX catheter.

During follow-up, no recurrence was detected at more than 6 months. There was no statistically significant

Table 4. Pleural effusion management and results.

	Group A (n = 22 pts)	Group B (n = 20 pts)	p-value
Success of agent used[a]	20 (91%)	17 (85%)	0.9
Response to treatment			
Complete (no. pts (%))	19 (87%)	17 (85%)	
Partial (no. pts (%))	1 (4%)	0 (0%)	
Failure (no. pts (%))	2 (9%)	3 (15%)	
Complications			
1. Pain[b] (no. pts (%))	4 (18%)	0 (0%)	0.2
2. Fever[c] (no. pts (%))	4 (18%)	1(5%)	0.5
Amount of pleural effusion drained (ml)	2977 ± 790	3087 ± 778	0.6
Post-procedure hospital stay (days)	5.7 ± 2	4.5 ± 1.1	0.02
Mean survival (months)	27.7	33.8	0.2
Survival at 8 months (no. pts (%))	15 (68%)	17 (85%)	0.9
Survival at 2 years (no. pts (%))	11 (50%)	11 (55%)	0.9
Survival at 4 years (no. pts (%))	6 (27%)	4 (20%)	0.8

Pts: patients.
[a] Efficacy of treatment was defined in three levels of response. Complete and partial response were considered as success.
[b] Pain was assessed and quantified by the number of patients who required (and at what frequency) intramuscular NSAID and narcotic based pain killers.
[c] The number and percentage of patients who experienced fever (up to 38 °C) within the 48 h post-procedure.

difference between the success rates in groups A and B (91% and 85%, respectively) (Table 4).

The most frequent complication was thoracic pain in 18% of patients who received talc pleurodesis post-procedurally, without reaching statistical significance compared with iodine patients. In these patients, pain was relieved by the administration of nonopioid, and when required, opioid analgesics. Visual loss was not reported in any of the patients and none of the patients presented with signs or symptoms of hyper- or hypothyroidism. The serum iodine levels were not measured post-procedure and thyroid abnormalities were assessed clinically without performing hormonal profiles.

4. Discussion

To our best knowledge, this is the first randomized controlled trial comparing povidone—iodine with talc pleurodesis. Our findings support povidone—iodine pleurodesis as a safe and also effective alternative means of preventing the recurrence of malignant pleural effusion at 30 days post-procedure. They also qualify intercostal drain administration that can be considered under local anesthesia. Moreover, the natural history of breast carcinoma, as in our study population, affords us long-term survival data, often not reported in other studies.

The reported success rate at long-term follow-up (4 years) was similar between the two study arms (91% and 85% in groups A and B, respectively, p = ns). The success rates of talc poudrage for pleurodesis in the published literature range from 68% to 97%. Variation in the definition of recurrence (radiological and clinical), and the choice of denominator may account for some discrepancies among studies [11]. There are limited data reporting the outcomes of povidone—iodine use in pleurodesis in the literature. Povidone—iodine is a topical antiseptic, and is less commonly used as a sclerosing agent. The reported success rates range from 64% to 96% [10,12], whereas in our study, the success rate was 85%.

The exclusion criteria used in the study, which included a poor performance status <3, pleural fluid pH < 7.2, or glucose < 60 mg dl^{-1}, and extrathoracic metastasis (brain computed tomography/magnetic resonance imaging (CT/MRI), staging reflect tumor burden), aimed at the survival time, in an effort to ensure long-term outcomes in both groups. Approximately one-third of malignant effusions have a pleural fluid pH of less than 7.3 at presentation. Biochemical parameters of pleural fluid, including pH and glucose, reflect tumor load. Malignant effusions with a low pH and glucose concentration have been shown to have a higher initial diagnostic yield on cytological examination, worse survival, and a poor response to pleurodesis compared to those with normal pH and glucose levels [13—16].

Chest pain and fever are the most common adverse effects of all pleurodesis agents. The intensity of chest pain reported with talc has ranged from nonexistent to severe, but generally, it is minimal with an incidence of 7% [17]. Talc is also reported to cause fever (usually 38 °C) in 16—69% of cases, characteristically occurring 4—12 h after instillation and lasting no longer than 72 h [18]. Regarding the issue of these complications, our results were consistent with published morbidity reports. Four grams of talc was the standard amount administered at our center, to no adverse effects, with good results. On the other hand, the iodine—povidone population tended to have less analgesic requirements and recorded pyrexia incidents but these did not reach statistical significance.

Other complications related to talc pleurodesis, such as acute respiratory distress syndrome, were not observed in our study. It has been postulated that this follows the systemic absorption of talc, and is related to the dose and particle size [19]. In this study, we did not exceed a dose of 4 g of talc in any case, and we used Seritalc®, in which less than 50% of particles are less than 20 μm. This type of talc has been extensively used in Europe without any report of respiratory failure [20]. Concerns that povidone—iodine might be associated with visual loss were reported by Wagenfeld et al. in three cases during VATS. However, authors used an unusual amount of 200—500 ml of 10% povidone—iodine 'Jodobac'. They also noted that the safe amount to be used is 20 ml of 10% iodine, which is actually the amount that we have used in our study. As an additional safety practice, we administered this dose in a diluted form (in normal saline). Moreover, Wagenfeld et al. reported that they used Jodobac in patients who had normal pleura (patients who had pneumothorax), which might have increased absorption and toxicity [21]. However, in our study, we used iodine only in malignant effusions with pathological pleura that has a poor absorption potential (that could partly explain the pathophysiology of accumulated pleural effusion). We strongly believe that this practice has significantly increased povidone safety in our study, as none of our patients encountered any loss of vision.

There are no therapeutic guidelines in place to ensure optimal outcome. Malignant pleural effusions continue to be a common problem in patients with metastatic disease, leading to a significant reduction in quality of life secondary to symptoms such as dyspnea and cough. The treatment of malignant pleural effusions is palliative, and should be directed at improving the quality of life with minimal complications. The aim of pleurodesis in these patients is to prevent reaccumulation of the effusion and thereby of symptoms, and avoid the need for repeated hospitalization for thoracocentesis. Numerous clinical studies have been performed to try to determine the optimal pleurodesis strategy, and synthesis of the available evidence should facilitate this. The Cochrane Central Register of Controlled Trials was searched and the available evidence supported the need for chemical sclerosants for successful pleurodesis, the use of talc as the sclerosant of choice, and thoracoscopic pleurodesis as the preferred technique for pleurodesis based on efficacy [22]. Except for the shorter period of chest tube removal in the povidone—iodine group, this study shows no statistical difference in success or survival rates between the use of talc poudrage, which is considered to be the standard treatment, and the use of povidone—iodine as a sclerosing agent.

One of the limitations of this study is the small sample size. However, we have maximized the homogeneity of the study group by the choice of only breast cancer patient population, who have the advantage of better longevity and longer follow-up periods. The thoracoscopic procedure that all patients underwent was for diagnostic purposes, which ensured that both study arms are similar. Having established

the efficacy of the bedside iodine pleurodesis, we can safely recommend it to be performed without the need of thoracoscopic procedure. The most important parameters were not significantly different between the two groups. The negative results might be mainly a consequence of the insufficient number of patients. The statistical analysis was also limited with no computed confidence intervals to safely exclude clinically relevant difference. In addition, no survival analysis was performed.

Local iodine pleurodesis was shown to be an efficient pleurodesis agent and demonstrated a good safety profile in treating malignant pleural effusions. Based on the results of this study, povidone—iodine has a good success rate with few minor complications, can be infused through thoracostomy tube and repeated, if necessary, under local anesthesia with excellent tolerance. Therefore, we conclude that it can be considered as a cost effective alternative sclerosant for pleurodesis, in countries where talc is not available or contraindicated. As we continue our efforts to optimize the sclerotherapy protocol, we should recognize that this is a palliative procedure aimed at improving the quality of life of patients who suffer end-stage cancer. The efficacy of povidone—iodine should be further assessed in a larger sample and in pleural effusions that complicate other types of malignancy.

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