

# Efficacy and Safety of Povidone-iodine Pleurodesis in Malignant Pleural Effusions

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## Abstract

**Introduction:** Malignant pleural effusion (MPE) is determined by the detection of malignant cells in pleural fluid or pleural tissue. Neoplasm of lung, breast, ovary and lymphoma are the causes of more than 75% of MPE. Pleurodesis is a usual technique in the management of MPE to achieve a symphysis between two layers of the pleura, and various chemical agents have been used in an attempt to produce pleurodesis. With regard to complications and limitations of these sclerosing agents, efficacy and safety of povidone-iodine have been investigated in this study. **Materials and Methods:** Between June 2014 and June 2016, 63 consecutive patients were admitted to the Department of Thoracic Surgery because of symptomatic MPE. After insertion of a chest tube, pleurodesis with instillation of povidone-iodine was performed. Thyroid and renal function tests were checked, and success rate as well as recurrence of MPE was monitored in the next follow-up visits. **Results:** The complete response to this procedure was about 53.57%, and failure of treatment was 10.71% with efficacy of 82.2%. The most common complication was pain during instillation (26.9%). Changes in thyroid and renal function tests were not significant. **Conclusion:** Povidone-iodine is a safe and effective agent with minor side effects in pleurodesis of patients with MPEs and can be used as an accessible and low-cost alternative than other sclerosing agents.

**Keywords:** Malignant pleural effusion, pleurodesis, povidone-iodine

## INTRODUCTION

Malignant pleural effusion (MPE) is a condition that malignant cells are presented in the pleural fluid. The most common cause of MPE is lung cancer (30%). Breast carcinoma is the second most common, followed by ovarian and gastric cancer that are next in frequency.<sup>[1-3]</sup> MPE is usually associated with poor prognostic cancers. Exertional dyspnea and respiratory distress are the most common symptoms of MPE.<sup>[1,4]</sup> Chemotherapy could control the pleural effusion and relieve symptoms of MPE in some malignancies such as small lung carcinoma and lymphoma.<sup>[5]</sup> In the setting of chemotherapy failure and re-accumulation of fluid in the pleural space, MPE can be managed by recurrent thoracentesis, pleurodesis, pleurectomy, pleuroperitoneal shunting, and chronic indwelling pleural catheter.<sup>[6-8]</sup>

Pleurodesis is a usual technique in the management of MPE to achieve a symphysis between two layers of the pleura to prevent accumulation of fluid in the pleural space using

different sclerosing agents such as tetracycline, nitrogen mustard, bleomycin, talc, and povidone-iodine.<sup>[4,9-12]</sup>

Efficacy assessment of specific sclerosing agents has been difficult and problematic because reported trials have assessed limited numbers of patients, used conflicting success criteria, and employed different pleurodesis techniques.<sup>[13,14]</sup>

Povidone-iodine is a broad-spectrum and low-cost antiseptic agent widely available in different forms such as topical solution, topical ointment, shampoo, and surgical scrub.<sup>[2,3]</sup>

The aim of this study was to investigate safety and efficacy of topical solution of povidone-iodine in pleurodesis

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**How to cite this article:** Kahrom H, Aghajanzadeh M, Asgari MR, Kahrom M. Efficacy and safety of povidone-iodine pleurodesis in malignant pleural effusions. *Indian J Palliat Care* 2017;23:53-6.

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10.4103/0973-1075.197958

procedure of MPEs and its effects on thyroid and kidney function tests.

## MATERIALS AND METHODS

Between June 2014 and June 2016, 63 consecutive patients were admitted to the Department of Thoracic Surgery of Razi and Arya Hospitals in Guilan (Rasht, Iran) because of symptomatic MPE. Inclusion criteria were all patients with documented MPE established by the positive result of pleural effusion cytology or pleural biopsy and history of malignancy. Excluded from this series were patients with use of corticosteroids in recent week, chemotherapy in recent 4 weeks, short life expectancy, abnormal thyroid and kidney function tests, and incomplete lung re-expansion after chest tube insertion. The study protocol was approved by the Medico-Ethical Review Committee of Respiratory Inflammatory Diseases Research Center of Guilan University of Medical Sciences. Written informed consent was signed by each patient before enrollment. Because systemic absorption of iodine in povidone-iodine can alter the thyroid gland and kidney function, thyroid (thyroid-stimulating hormone [TSH], total and free T4, total and free T3) and kidney (serum urea, creatinine and glomerular filtration rate) functions were routinely measured before pleurodesis and at 1 week after the performance of the procedure.

Chest radiography was performed in all patients to determine the severity of pleural effusion (moderate, extension of effusion to hill of the lung and severe, extension of effusion above hill of the lung). A chest tube (28 F) was inserted into the mid-axillary line through the sixth intercostal space and placed in suitable position directed toward diaphragm. The chest tube was connected to a water-sealed drainage system with low-pressure suction ( $-20$  cm H<sub>2</sub>O). Control chest radiography was performed for evaluation of complete lung expansion. Intermittent low doses of intravenous pethidine were administered for pain relief. A mixture of 20 ml of 10% topical solution of povidone-iodine and 40 ml of normal saline was instilled through the chest tube in 30 min and the chest tube was clamped for 4 h. Chest tube was removed when its drainage was  $<100$  ml/day. All patients were evaluated for dyspnea, chest pain, fever, vertigo, fatigue, and sweating during 24 h period. After pleurodesis and discharge, all patients were scheduled to be visited after 2 and 4 weeks and after 6 months.

During follow-up visit, patients with dyspnea were studied with chest radiography for better evaluation of pleural effusion recurrence. The patients' responses to this procedure are defined as excellent or complete response (symptomatic improvement of dyspnea with complete radiographic resolution of the pleural effusion), effective or good response (symptomatic improvement with recurrent mild pleural effusion that did not require additional thoracentesis or chest tube insertion), fair or treatment failure (as recurrent pleural effusion that required chest tube insertions or thoracentesis). All data were collected prospectively on standard forms and entered into a

computerized database. IBM, SPSS Statistics Version 21.0 (Armonk, NY) was used for statistical analysis. All data were expressed as mean  $\pm$  standard deviation. Clinical data were compared by the Mann–Whitney *U*-test, Chi-square test, and independent *t*-test when appropriate. A  $P < 0.05$  was considered statistically significant.

## RESULTS

Between June 2014 and June 2016, 63 consecutive patients with MPE were enrolled in this study. Mean age of patients was  $62.1 \pm 11.4$  years (range 20–81 years) and 77.8% of patients were male (49 patients). The most common underlying disease was lung cancer ( $n = 24$ , 38.1%) [Table 1]. Follow-up ranged between 6 and 30 months (mean:  $14 \pm 3.5$  months).

Complete or good response was achieved in 46 patients (82.2%) and treatment failure occurred in 10 patients (17.8%) after 6 months of follow-up. The success rates in different types of underlying cancer are showed in Table 1.

The most common complication after pleurodesis procedure of the patients was pain (26.9% had mild to moderate pain). Six patients showed air leakage (Grade 1) after pleurodesis that resolved after 2 days and no patient showed pleuritic chest pain, dyspnea, hypotension, visual loss, or fever. Seven patients died during the follow-up period due to their underlying malignancies.

Statistically, there was no significant relationship between success rate of pleurodesis and type of malignancy ( $P = 0.071$ ), age ( $P = 0.074$ ), and sex ( $P = 0.346$ ).

Assessment of serum level of thyroid hormones and renal function tests showed no statistically significant changes before and after use of povidone-iodine [Table 2]. Furthermore, we did not observe any signs or symptoms of hyper- or hypo-thyroidism in any patient.

## DISCUSSION

MPE is determined by the presence of malignant cells in the pleural fluid. MPE is a common complication in advanced stages of many malignancies.<sup>[13,15]</sup> Common strategy to address this problem includes frequent thoracentesis through thoracostomy

**Table 1: Success rates of pleurodesis in different types of underlying cancer**

Type of cancer	<i>n</i> (%)	Complete (6 months), %
Lung	24 (38.1)	35
Lymph	10 (15.9)	70
Colon	9 (14.3)	44.4
Breast	8 (12.7)	71.4
Gastric	5 (7.9)	100
Ovary	3 (4.8)	66.7
Kidney	3 (4.8)	66.7
Pancreas	1 (1.6)	0.0

**Table 2: Assessment of serum level of thyroid hormones and renal function tests before and after use of povidone-iodine**

Serum test	Mean (before)	Mean (after)	P
TSH	3.44 (μIU/L)	2.95 (μIU/L)	0.910
T3	1.42 (Pmol/L)	1.42 (Pmol/L)	0.925
T4	8.20 (Pmol/L)	8.22 (Pmol/L)	0.960
BUN	14.2 (mg/dl)	14.2 (mg/dl)	0.969
Cr	0.97 (mg/dl)	1.09 (mg/dl)	0.071

TSH: Thyroid-stimulating hormone, BUN: Blood urea nitrogen, Cr: Creatinine

tubes or pleural catheters with or without pleurodesis that can effectively relieve the respiratory symptoms. Repeated simple thoracentesis, especially in high-protein exudates effusions, can lead to hypoproteinemia that will lead to more rapid reaccumulation of pleural fluid; hence, in most patients with MPE, palliative treatment necessitates pleurodesis with sclerosing agents.

Chemical pleurodesis is one of the best options for the treatment of patients with refractory MPE and recurrent pleural effusions, either with tube thoracostomy or thoracoscopy.<sup>[5,16,17]</sup> The main question is the choice of the sclerosing agent, which is not only determined by the efficacy of the chemical agent but also by its safety, availability, cost, ease of use, and number of administrations to achieve a complete response, since there is no general consensus on the currently accessible best sclerosing agent for pleurodesis.

During the past 75 years, many chemical agents such as talc, quinacrine, erythromycin, antineoplastic agents (nitrogen mustard, bleomycin, mitoxantrone), povidone-iodine, tetracycline derivatives, and silver nitrate have been instilled into the pleural cavity in an attempt to create pleurodesis as the simplest and the most cost-effective way to control MPE.<sup>[11,18,19]</sup> Talc is considered the most effective and successful chemical agent for MPEs and is widely used with a success rate of 90%.<sup>[2,4]</sup> However, its use could be associated with serious complications, including acute respiratory distress syndrome, acute pneumonitis, systemic embolization, and mortality. As talc powder is not available in Iran, bleomycin is used routinely with less efficacy and higher cost. Povidone-iodine is readily accessible and inexpensive alternative agent to achieve chemical pleurodesis in patients with recurrent, incapacitating pleural effusions, regardless of etiology. The only notable side effect of povidone-iodine is the occurrence of chest pain, which has been described to a different degree in various studies.<sup>[1-5]</sup> The purpose of this study was to assess the efficacy and safety of this chemical agent in pleurodesis of patients with recurrent MPEs.

Betadine is a topical antiseptic agent that consists of iodine as an active ingredient, which is widely absorbed from mucosal surfaces and increases serum iodine concentration. Iodine can be absorbed by the thyroid gland and is excreted in the body fluids such as saliva, sweat, milk, and urine. Although the exact mechanism of pleurodesis with betadine is unclear, it seems to be associated with low pH material (pH = 2.97).<sup>[1,4]</sup>

Olivares-Torres *et al.* reported the use of betadine for pleurodesis of 52 patients in whom 96.1% of MPE was controlled.<sup>[4]</sup> Agarwal *et al.* obtained complete response of 86.5% in a similar study.<sup>[1]</sup> In the review of six studies including 265 patients who had undergone chemical pleurodesis with povidone-iodine, average rate of success was 90.6% with efficacy rate of 82.2%. In our study, complete or good response was achieved in 46 patients (82.2%).

The main side effect of betadine injection in pleural cavity is mild pain in patients that Neto *et al.* reported in 16% of their patients.<sup>[16]</sup> In a similar study, Caglayan *et al.* in Turkey found chest pain in 16.2% of cases, fever in 6.9%, and subcutaneous emphysema in 2 cases.<sup>[2]</sup> In our study, pain was evaluated and classified with visual analog scale, and according to these criteria, 6.3% of patients had mild pain and 20.6% showed moderate pain. After povidone-iodine instillation, 6 patients had air leak that was resolved after 1 day.

Usage of topical povidone-iodine and other iodine-base contrast agents can cause thyroid dysfunction. Increase in serum level of exogenous iodine not only can inhibit thyroid hormone synthesis but also can cause thyrotoxicosis in some patients. Yeginsu *et al.* studied the changes in thyroid function tests including TSH, T3, and T4 before and after pleurodesis with povidone-iodine and they reported no significant changes.<sup>[20]</sup> Similarly, in this study, we did not find any remarkable change in thyroid function tests before and after pleurodesis with betadine in 63 patients. In normal adults without any underlying thyroid problems, systemic absorption of iodine can be tolerable and this explains the lack of changes in thyroid function tests. Similarly, serum urea and creatinine levels of patient in this study showed no significant changes after pleurodesis with povidone-iodine.

The results of this study suggest that povidone-iodine is a safe and effective agent with minor side effects in pleurodesis and treatment of MPE and proposed povidone-iodine as a proper, accessible, and low-cost alternative sclerosing agent.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

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