

# Iodopovidone Pleurodesis for Recurrent Pleural Effusions\*

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**Study objective:** Chemical pleurodesis may be the best available treatment for recurrent and troublesome pleural effusions when the underlying cause cannot be corrected. A wide variety of pleural irritants have been used, but the search for the ideal agent for pleurodesis continues. The purpose of our study is to evaluate the efficacy and safety of iodopovidone as an agent for pleurodesis in patients with recurrent pleural effusion.

**Design and setting:** Multicenter prospective study.

**Intervention:** The pleurodesis solution consisted of a mixture of 20 mL 10% iodopovidone and 80 mL normal saline solution. It was infused and left in the pleural cavity for 2 h. In 12 patients, pleurodesis was performed through a tube thoracostomy, and in the remaining 40 patients it was carried out at the end of diagnostic thoracoscopy.

**Results:** Fifty-two patients were included, with a mean ( $\pm$  SEM) age of  $56.6 \pm 1.84$  years. Eighty-five percent of the cases were related to a malignant neoplasm. A complete response, with no reaccumulation of fluid during follow-up, was obtained in 50 patients (96.1%). A second procedure was successful in the two remaining patients. Three patients (5.8%) experienced intense pleuritic pain and systemic hypotension after the instillation of the sclerosing agent. They recovered without incident. The mean length of follow-up was  $13 \pm 1.46$  months, with a median of 8.5 months. There were no 30-day postoperative deaths.

**Conclusions:** Iodopovidone is an effective, safe, readily available, and inexpensive alternative to achieve chemical pleurodesis in cases of recurrent, incapacitating effusions, regardless of etiology. (CHEST 2002; 122:581-583)

**Key words:** iodopovidone; malignant pleural effusion; pleurodesis

Chemical pleurodesis may be the best available treatment for recurrent and troublesome pleural effusions when the underlying cause cannot be corrected. A wide spectrum of pleural irritants has been used, but the search for the ideal agent for pleurodesis continues. The ideal agent for pleurodesis must be effective, safe, inexpensive, and readily available. The substance most commonly used is talc, which is highly effective and widely available. However, there are serious concerns about its safety. Systemic embolization of talc has been shown in

animal studies<sup>1</sup> as well as in humans.<sup>2</sup> More importantly, ARDS occurs in as many as 9% of patients receiving talc intrapleurally.<sup>3</sup> Silver nitrate has been proposed as a possible alternative, but its use is associated with chest pain,<sup>4</sup> which might be related to the concentration of the silver nitrate in the sclerosing solution.

Iodopovidone is a topical antiseptic that has been reported as a promising agent pleurodesis in two small series of patients.<sup>5,6</sup> The purpose of our study was to evaluate the efficacy and safety of this agent when used for pleurodesis in patients with recurrent pleural effusions.

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## MATERIALS AND METHODS

The study included patients from 14 hospitals (4 were public hospitals) in Tijuana and Ensenada, Mexico. During the period between September 1996 and June 2001, 52 consecutive patients with symptomatic malignant or recurrent exudative pleural effusion received iodopovidone for chemical pleurodesis. None of the

patients had undergone prior attempts at pleurodesis with other agents. Informed consent to perform the procedure was obtained from every patient.

Patients with known hypersensitivity to iodine, patients with thyroid disease, patients who had experienced unsuccessful re-expansion of the lung after tube thoracostomy, and patients with very limited life expectancy (*ie*, < 30 days) were excluded.

The effusion was classified as exudative according to the criteria of Light et al.<sup>7</sup> When the diagnosis was not obtained through pleural fluid examination or other noninvasive techniques, video-assisted thoracoscopy was performed to obtain pleural tissue for microbiological and histopathologic analyses.

#### Pleurodesis Technique

A chest tube (28F) was inserted into the midaxillary line through the fifth intercostal space and was connected to a water-sealed drainage system to achieve complete drainage of the effusion and lung reexpansion. Reexpansion was verified radiographically. The drainage of fluid was done over the course of 48 h to avoid the development of reexpansion pulmonary edema. As soon as the effusion was completely drained and the lung fully expanded, pleurodesis was performed at the bedside.

Fifty milliliters of normal saline solution containing 2 mg/kg (ideal body weight) lidocaine were infused through the chest tube. Simultaneously, doses of IV midazolam (5 mg) and nalbuphine (5 mg) were administered for sedation and systemic analgesia, respectively. After 15 min, a pleurodesis solution containing a mixture of 20 mL 10% iodopovidone (Isodine; Boehringer Ingelheim-Promeco; Mexico City, Mexico) and 80 mL normal saline solution was infused into the pleural cavity, after which the tube was clamped for 2 h. After 2 h, the chest tube was unclamped, and, thereafter, negative pressure (−15 cm H<sub>2</sub>O) was applied to the chest tube. The thoracostomy tube was removed as soon as the chest radiograph showed total lung reexpansion and no residual pleural effusion.

Thoracoscopy for pleural biopsy was performed in a standard fashion, either under general anesthesia or local anesthesia without intubation. It was performed with a video-assisted system and a 12-mm rigid telescope with an instrumentation channel, needing only a one-port approach. If the frozen sections were reported to be positive for malignancy, at the end of the procedure, after breakdown of all pleural adhesions and complete drainage of the pleural fluid, iodopovidone was instilled in the pleural cavity (without premedication in patients under general anesthesia). A chest tube was inserted and clamped on completion of the procedure. After 2 h, the chest tube was unclamped and negative pressure (−15 cm H<sub>2</sub>O) was applied to the chest tube.

Chest radiography was performed daily until the chest tube was removed. Radiographic control was used to verify complete fluid drainage and pulmonary expansion. As soon as this was achieved, the chest tube was removed, and the subject was observed as an outpatient.

For definition purposes, the success of iodopovidone pleurodesis was defined as the absence of pleural fluid during follow-up. Any reaccumulation was considered to be a failure or recurrence.

#### Statistical Analysis

The data are expressed as the mean ± SEM and the median. Information was processed using a statistical software program (SPSS, version 10.0; SPSS; Chicago, IL).

## RESULTS

A cohort of 52 consecutive patients was included. Twenty-one patients (40.4%) were men. The mean age for the entire group was 56.6 ± 1.84 years. Eighty-five percent of the cases were related to a malignant neoplasm, either primary or metastatic. The complete list of causative diseases is shown in Table 1.

All the patients had a large (*ie*, a volume of at least 1,000 mL) recurrent pleural effusion (which was defined as the reaccumulation of fluid after complete drainage) that was associated with dyspnea. The effusion was allowed to drain (not > 1,000 mL per day to prevent the occurrence of reexpansion pulmonary edema) through a chest tube connected to a water-sealed drainage system.

In 12 patients (23.1%), pleurodesis was performed through a chest tube. In the 40 remaining patients (76.9%), a thoracoscopy was performed to obtain pleural tissue for diagnostic purposes, and the sclerosing agent was instilled at the end of the procedure. In 35 patients, thoracoscopy was carried out under general anesthesia.

A complete response, with no reaccumulation of fluid during follow-up, was obtained in 50 patients (96.1%). In the two patients in whom pleurodesis failed (both from the thoracoscopy group), a second procedure through a chest tube was successful. The serum iodine levels were not measured after the procedure, but none of the patients presented signs or symptoms of hyperthyroidism.

Due to the irritating effect of the sclerosing solution on the pleural surface, we expected the subjects to experience pleuritic pain or a vasovagal reflex during or after the procedure, but only three patients (5.8%), the three patients with mesothelioma, experienced intense pleuritic pain and systemic hypotension after the instillation of the sclerosing

**Table 1—Diseases Causing Pleural Effusion**

Disease	Patients	
	No.	%
Adenocarcinoma	23	44.2
Breast cancer	11	21.1
Mesothelioma	5	9.7
Unspecific chronic pleuritis	3	5.8
Lymphoma	2	3.9
Systemic Lupus Erythematosus	2	3.9
Adenosquamous carcinoma	2	3.9
Sarcoidosis	1	1.9
Chylothorax	1	1.9
Rheumatoid Arthritis	1	1.9
Metastatic cancer (unknown primary)	1	1.9
Total	52	100.1

agent. These patients had undergone diagnostic thoracoscopy under general anesthesia. They were already receiving high doses of narcotic analgesics to control the pain associated with their tumors. The hypotension was treated with IV fluids, and the pain was controlled with a 10-mg dose of IV nalbupine. The episode lasted between 45 min and 2 h. The three patients recovered without incident.

The mean length of follow-up was  $13 \pm 1.46$  months, with a median of 8.5 months. Twenty-two patients died during follow-up (42.3%), with a mean length of survival after pleurodesis of  $12 \pm 2.01$  months.

The 30-day mortality rate was 0%. There was one case of tumoral seeding at the site of the thoracoscopy port, but it was surgically removed under local anesthesia, without recurrence.

## DISCUSSION

Chemical pleurodesis is the procedure of choice in the management of recurrent pleural effusions. The ideal agent for pleurodesis should produce pleurodesis effectively, safely, and in the shortest possible time. Although talc is effective, there is increasing concern about its safety.<sup>1-3</sup> Recently, Lee et al<sup>8</sup> reported excellent results using transforming growth factor- $\beta_2$  as an agent for pleurodesis in rabbits, however, this agent is not widely available.

The effectiveness of iodopovidone as a sclerosing agent for pleurodesis has been described previously in two case series.<sup>5,6</sup> Iodopovidone<sup>9</sup> is an iodine-based topical antiseptic. It is extensively absorbed from mucosal surfaces that may lead to  $10^4$ -fold increases in serum iodine concentrations, compared to normal values. It may be absorbed by the thyroid gland and may appear in saliva, sweat, and milk. Iodopovidone undergoes minimal metabolism and is excreted practically unchanged in the urine. The mechanism by which iodopovidone exerts its pleurodesis activity is unknown. It may be related to the low pH of the sclerosing solution (pH, 2.97).

Morales-Gómez et al<sup>5</sup> performed pleurodesis with iodopovidone in 39 patients with malignant pleural effusions, achieving control of the effusion in 33 patients (91.6%). Kelly-Garcia et al<sup>6</sup> reported the use of iodopovidone in 14 patients with a 64.2% success rate. In both series, pleurodesis was performed through tube thoracostomy. Neither study reported significant adverse effects. Our higher success rate might be related to the fact that, in the majority of

cases, pleurodesis was performed at the end of diagnostic thoracoscopy, during which fluid loculations and pleural adhesions can be eliminated.

In this group of patients, the large majority of whom had neoplastic pleural disease, iodopovidone proved to be an extremely effective and safe agent for pleurodesis. The efficacy of iodopovidone is comparable to that of talc, but without the risk of severe complications such as ARDS. Pleurodesis with iodopovidone can be performed under local anesthesia with excellent tolerance. The three patients who experienced intense pain during the procedure were already receiving high doses of narcotic analgesics. Some degree of tolerance to the analgesic effect of opioids is commonly established within a few weeks of commencing therapy.<sup>10</sup> This may explain the intensity of the pain in these three patients.

In conclusion, iodopovidone is an effective, safe, readily available, and inexpensive alternative with which to achieve chemical pleurodesis in cases of recurrent, incapacitating effusions, regardless of their etiology.

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