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A Study of Efficacy and Safety of Betadine Pleurodesis

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Conflicts of Interest: Nil.

Abstract

Background: Pleurodesis is a procedure to achieve symphysis between the two layers of pleura aimed at preventing accumulation of either air or fluid in the pleural space. The most common indication is malignant pleural effusion. A plethora of chemical agents have been used for pleurodesis and iodopovidone (Betadine) is one such agents. This study was undertaken to evaluate the efficacy and safety of Betadine (lodopovidone) as an agent for chemical pleurodesis.

Methods: It is a prospective clinical study conducted at Government Hospital for Chest and Communicable Diseases (GHCCD), Visakhapatnam. A total of 44 patients were included. All the patients had either malignant pleural effusion or spontaneous pneumothorax. After the Inter Costal Tube drainage (ICTD) each patient underwent pleurodesis with 10% Betadine at varying times. The patients were then followed up as an outpatient for 3 months. During the follow up, all the patients were assessed by chest X-ray (CXR) at 1 week, 1 month and 3 months. The radiological resolution and the subjective response of the patients were assessed. Results: 44 patients were analyzed (14 females, 30 males). 64% of the cases were malignant pleural effusion and 36% were cases of spontaneous pneumothorax. Post Betadine pleurodesis, 29 (66%) patients complained of mild pain followed by dyspnea 8 (18%) and low grade fever 6 (14%). Recurrence was observed in 3(11.6%) patients at 3rd month visit and in 1(3.8%) patient at 1st month visit in Malignant Pleural Effusion (MPE) group. Recurrence was observed in 1(6. 25%) patient in pneumothorax (PNTX) group at 3rd month visit. 22(84. 6%) patients of MPE group and 15(93.75%) patients of pneumothorax group achieved successful pleurodesis. Failure of the pleurodesis procedure was observed in 4(15.4%) patients of MPE group and 1 (6.25%) patient of pneumothorax group. **Conclusion:** From this study, it can be concluded that in resource constrained setups, Betadine is a reasonable choice for chemical pleurodesis.

Keywords: Betadine, Pleurodesis.

Introduction

Pleurodesis is a procedure to achieve symphysis between the two layers of pleura aimed at preventing accumulation of either air or fluid in the pleural space[1]. The most common indication is malignant pleural effusion. The technique is used for recurrent pneumothoraces and in

selected patients with non malignant pleural effusions. Pleurodesis can be achieved by either a chemical agent or by physical abrasion of the pleural surfaces during thoracotomy or thoracoscopy.

An ideal chemical agent for pleurodesis should be highly efficacious with a high molecular weight and chemical polarity, low regional clearance, rapid systemic clearance with a steep dose-response curve, and should be inexpensive, easily accessible, easily administered and well tolerated with minimal or no side-effects[2]. No such agent exists and the search for an ideal agent continues.

The management of malignant pleural effusion and spontaneous pneumothorax has always been a cause for serious concern among chest physicians as the symptoms, such as dyspnea and chest pain, can be very distressing for patients, who may turn up frequently to undergo repeated interventions in order to get relief from their symptoms. The high cost and emotional trauma caused by these cases may sometimes result in a loss of faith in physicians. However, over the past several years, chemical pleurodesis has evolved as the most widely accepted treatment method for these problems, especially when the underlying cause cannot be rectified[3].

A plethora of chemical agents have been used for pleurodesis in the literature[4], and include talc[5], tetracyclines[6], quinacrine[7], antineoplastic drugs (bleomycin, mitomycin, nitrogen mustard)[8], immunomodulating agents (interferon [IFN]-alpha and IFN-gamma)[9,10],silver nitrate[11], biological agents (suspension of killed Corynebacterium parvum or Streptococcus pyogenes [OK 432])[12-14], and finally iodopovidone[15]. However, each agent has its own set of advantages and disadvantages, and the agent that is to be used must be selected judiciously.

This study was conducted to establish the efficacy and safety of Betadine (iodopovidone) as an agent of chemical pleurodesis in patients with malignant pleural effusion and pneumothorax of primary and secondary spontaneous types.

The aim of the study is to evaluate the efficacy and safety of Betadine (lodopovidone) as an agent for chemical pleurodesis.

Methodology

It is prospective analytical study conducted among 44 patients in the Department of Pulmonary Medicine, Government Hospital for Chest and Communicable diseases affiliated to Andhra medical college. The study was approved by the ethical committee of the institution.

Inclusion criteria are

- Malignant pleural effusion
- Spontaneous pneumothorax - primary or secondary

Exclusion criteria

- Patients with history of previous pleurodesis
- Incomplete lung expansion after chest tube insertion
- Patients with thyroid disease
- Critically ill patients
- Malignant effusion with endobronchial obstruction
- Malignant effusion with central mediastinum
- Patients with history of allergies
- Loculated effusions/pneumothorax
- Presence of Broncho pleural fistula

Study procedure:In each of the patients selected for this study, an appropriate size intercostal tube was inserted into the fourth/fifth intercostal space along the mid axillary line using the operative tube thoracostomy technique. The fluid was allowed to drain out slowly through the water seal drainage system over the course of 48 hours to prevent the development of reexpansion pulmonary edema. After complete drainage of the pleural fluid and confirmation of expansion of the lung, both clinically and radiologically, pleurodesis was performed

with 10% Betadine (Idopovidone). In cases of spontaneous pneumothorax, pleurodesis was performed only after ensuring that there was no broncho-pleurai fistula and that the lung had expanded completely. Each patient received pre-medication in the form of 2% xylocaine at a dose of 2mg/kg in 50 ml of normal saline solution through an intercostal chest tube. In some patients who were very apprehensive, 5 mg of intravenous midazolam was administered for sedation. The pleurodesis solution, containing a mixture of 20 ml of 10% Betadine (lodopovidone) and 80 ml normal saline, was injected into the pleural cavity through the chest tube. The solution was allowed to remain in the pleural cavity for about two hours by clamping the chest tube. In these two hours, the position of the patients was alternatively changed to various decubitus positions by the medical staff for even distribution of the pleurodesis agent. After declamping, the thoracostomy tube was removed as soon as the drainage, if any, decreased to <100 ml per day for three consecutive days and chest x-ray showed expanded lung. Negative pressure was not applied to any of the patients.

The patient was then followed up as an outpatient for 3 months. During the follow up, all patients were assessed with CXR at 1 week, 1 month and 3 months. The radiological resolution and the subjective response of the patients were assessed. "SUCCESS" is defined as symptomatic improvement of dyspnoea with complete radiographic resolution and any recurrence i.e. reaccumulation of either air or fluid in the pleural cavity is defined as "FAILURE".

Observations and Results

Among 44 patients included in the study, patients between 10-19 years of age were 3 (7%), between 20 to 29 years were 2 (5%), between 30-39 were 5 (11%), between 40 to 49 years of age were 4 (9%), between 50 to 59years of age were 21 (48%), and 60 and above were 9 (20%). In the study group the youngest patient was 15 years old and oldest was 70 years old.. Male to female ratio was 2.1 : 1 with 30 (68%) males and 14 (32%) females.

Out of the 44 cases, 28 (64%) were cases of malignant PLEF and 16 (36%) were cases of spontaneous Pneumothorax. Most of the lesions were present on right side i.e. 32 (73%) and left accounting for only 12 (27%). Of the 28 patients of malignant PLEF 20 (71%) patients had carcinoma of lung, 6 (22%) had breast carcinoma, 1(3.5%) had mesothelioma and 1(3.5%) had lymphoma. Of the 16 patients with pneumothorax, 2 (12%) had primary spontaneous pneumothorax, 14 (88%) had secondary spontaneous pneumothorax, of which 10 (63%) were secondary to COPD and 4 (25%) were secondary to Pulmonary Tuberculosis.

Following the procedure, i.e Betadine(Iodopovidine) pleurodesis 29(66%) patients complained of mild pain, 8(18%) complained dyspnoea and 6(14%) complained of low grade fever as seen in Table I.

TABLE I: *Post Procedure Complications*

Post procedure complications	Number of patients (n=44)
PAIN	29(66%)
DYSPNEA	8(18%)
FEVER	6(14%)

In the present study all the patients were followed-up for 3 months except two patients who were followed-up for 2 months only. These two patients with malignant pleural effusion died during the follow-up. However, the post-procedure 30 day mortality rate was 0%. The mean duration of follow up was 2.9 ± 0.2.

Table II: *Recurrence At Follow Up*		
Recurrence At Follow Up	Malignant Pleural Effusion (N=26)	Pneumothoraxn (N=16)
First Week	0	0
First Month	1(3.8%)	0
Third Month	3(11.6%)	1(6.25%)

From Table II we observe that out of the 28 patients of malignant pleural effusion, 2 patients died in 3rd month and hence could not be assessed for response. Recurrence was observed in 3(11.6%) patients at 3rd month visit and in 1(3.8%) patient at 1st month visit in malignant pleural effusion group. Recurrence was observed in 1(6.25%) patient at the end of 3rd month in pneumothorax group.

"SUCCESS "is defined as symptomatic improvement of dyspnoea with complete radiographic resolution and any recurrence i.e. reaccumulation of either air or fluid in the pleural cavity is defined as "FAILURE.

TABLE III :Treatment Outcome		
Indication for Pleurodesis	Success	Failure
Malignant pleural effusion	22(84.6%)	4(15.4%)
Pneumothorax	15(93.75%)	1(6.25%)

Out of the total 44 patients, 22(84. 6%) patients of MPE group and 15(93. 75%) patients of PNTX group achieved successful pleurodesis as shown in Table III. In the MPE group treatment outcome is calculated for 26 patients only as out of the total 28 patients of MPE, 2 patients died in 3rd month. Failure of the pleurodesis procedure was observed in 4(15.4%) patients of MPE group and 1(6. 25%) patient of PNTX group i.e. they required a repeat ICT insertion and second pleurodesis to achieve complete obliteration of the pleural cavity.

Discussion

Chemical pleurodesis is the procedure of choice in the management of malignant pleural effusion of any cause, and a recognized treatment option in the management of patients with primary or secondary spontaneous pneumothorax in order to prevent recurrence. The basic mechanism involves chemical or physical irritation of pleural surface to promote an inflammatory response and subsequent adhesion formation. The response of the pleura to an injury is a complex and incompletely understood multifactorial process that can result in the development of fibrosis with the obliteration of the pleural space, or it can result in restoration of the pleura to its normal state. The mechanism of pleurodesis seems to differ from agent to agent. The balance between the procoagulant system and the fibrinolytic system determines the outcome of intrapleural injection of a substance for pleurodesis[16]. Successful pleurodesis occurs if the procoagulant system dominates, but if the fibrinolytic system dominates pleurodesis does not occur, because pleurodesis occurs only if the intrapleural fibrinolytic activity decreases.

The choice of the sclerosing agent is determined by the efficacy of the agent, its cost, accessibility, safety, ease of administration and the number of administrations needed to achieve a complete response. A number of pleural irritants have been used such as silver nitrate, bleomycin, autologous blood, tetracycline derivatives and talc. There is no global consensus on the currently available best chemical agent for pleurodesis. The most commonly used agent is talc followed by tetracycline derivatives and bleomycin[17].

Talc is considered the most effective chemical agent for malignant pleural effusions[18], and talc insufflation through thoracoscopy is currently considered to be the best method for chemical pleurodesis especially for spontaneous pneumothoraces. There were serious concerns about the safety of talc with reports of acute respiratory distress syndrome (ARDS) following its administration[19], which have been negated subsequently[20]. In a meta-analysis[18], talc was found to be the most effective agent for pleurodesis, and thoracoscopic talc

insufflation is the preferred technique for pleurodesis based on efficacy. The drawbacks of talc slurry/insufflation are prolonged drainage and incomplete symphysis. Though there was no evidence of an increase in mortality following talc pleurodesis, there are serious concerns about the safety of talc. Talc is known to cause systemic embolization and is a potential cause of ARDS and respiratory failure[21,22]. The small size of the talc particle (<15 microns) and dose of >5gm may be associated with higher incidence of ARDS. However, its limited availability and cost remains a constraint for poor patients in countries with limited resources.

Tetracycline derivatives such as doxycycline, minocycline though cheap, easily available and safe, produce intense pain inspite of intra pleural xylocaine. Tetracycline derivatives such as doxycycline and minocycline are effective in producing pleurodesis in patients with malignant pleural effusion. When five reports with a total of 110 patients are combined, there was control of the effusion at 30 days in 91 patients (83%). The usual dose of doxycycline is 500 mg. There has also been one report in which the administration of minocycline 300 to 500 mg produced a complete response at 30 days in 62.5% of patients and a partial response (no need for further thoracentesis) in an additional 25%. The primary side effect when pleurodesis is performed with a tetracycline derivative is severe chest pain and the chest pain tends to be worse in patients who receive the tetracycline derivative for a pneumothorax. It is recommended that patients who receive a tetracycline derivative for pleurodesis be given lorazepam or midazolam in addition to local instillation of xylocaine.

Iodopovidone is an inexpensive and widely available topical antiseptic[23] and it has been shown to be safe and effective in several studies. Iodopovidone is a reasonable alternative to other commonly used pleurodesing agents such as the tetracycline derivatives or talc slurry. Povidone-iodine is an iodine-based topical antiseptic agent, extensively absorbed from mucosal surfaces, leading to increase in serum iodine concentrations[3]. It may be absorbed by the thyroid gland and may appear in saliva, sweat and milk and is excreted unchanged in the urine[3]. 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 solution (pH=2.97)[3]. Additionally, iodine has strong oxidative and cytotoxic properties that may induce a potent inflammatory response to initiate the pleural symphysis[24]. Theoretically the mechanism could also be similar to that described recently for talc, i.e. production of fibroblast growth factor. It is also probable that iodopovidone may act as a cytotoxic agent on different tumour cell lines in malignant pleural effusions. Although the first report of chemical pleurodesis with iodopovidone was published in 1991[25], it is only recently that interest has been rekindled in this agent because of its safety and ease of availability.

In summary, success rate of betadine (iodopovidone) pleurodesis in the present study was 88.09%, which is almost equal to the efficacy of talc pleurodesis (93%) and other inexpensive agents used for chemical pleurodesis which include silver nitrate (75-90%), quinacrine (64-100%)[26], tetracycline (67%) and doxycycline (72%). The efficacy of betadine (iodopovidone) was regardless of the etiology (pleural effusion vs. pneumothorax). Talc causes lung injury with more than 35 cases of ARDS related to talc pleurodesis reported in the literature. On the other hand betadine (iodopovidone) is associated with minimal side effects. The only significant side effect of betadine (iodopovidone) was the occurrence of chest pain. Two studies[15,27] have systematically assessed the occurrence of chest pain by the VAS scale. Hypotension was reported in two studies[3,28] and was found associated with chest pain

and is likely to be vasovagal in origin. But, in the present study no case of hypotension was reported.However, iodine can cause severe allergic reactions, especially in patients with allergic diathesis, and thus one should be prepared to deal with this emergency. Iodine may also precipitate thyrotoxicosis in patients with subclinical hyperthyroidism (Jod-Basedow effect)[29]. In the present study, the serum iodine levels were not measured, but none of the patients presented with signs and symptoms of hypo-or hyperthyroidism. In the literature, there were no deaths or ARDS associated with this agent. There is a single report of visual loss associated with iodopovidone pleurodesis using 200-500 ml of 10 per cent iodopovidone[30]. The recommended dose is 20 ml of 10 percent iodopovidone with 80 ml of normal saline administered intrapleurally through tube thoracostomy or thoracoscopy[31]. With the above dose visual loss was not reported in any of the patients.The efficacy of betadine (iodopovidone) is in par with that of talc, with the advantage of no serious complications, such as acute respiratory distress syndrome. Moreover, pleurodesis with betadine (iodopovidone) can be performed under local anaesthesia with excellent tolerance and acceptability. The results of the present study re-affirm that betadine (iodopovidone) pleurodesis is associated with high success rates, with efficacy rate of 84.6% and 93.75% in pleural effusion and pneumothoraces respectively. From this study, it can be concluded that in resource constrained countries like India, betadine (iodopovidone) may be a reasonable choice for chemical pleurodesis in cases of recurrent pleural effusion and pneumothorax, as it is cheap, easily available, safe and highly effective.

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