TETRACYCLINE PLEURODESIS FOR MALIGNANT PLEURAL EFFUSION-A REVIEW OF 38 CASES

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SUMMARY

Malignancy is a common cause of pleural effusion accounting for about 40% of symptomatic pleural effusion with congestive cardiac failure and infection being the other leading causes[1]. The aim of this retrospective study was to establish the effectiveness of tetracycline pleurodesis in malignant pleural effusion using the powder from tetracycline capsules and compare the results with other studies done elsewhere.

Thirty eight cases of malignant pleural effusion were sampled from the admissions over a four year period at the National Cardiothoracic Centre, Korle Bu. Factors that were considered before pleurodesis was carried out include relief of dyspnoea after therapeutic thoracocentesis, general health of the patient and the presence of trapped lung .

Of the 38 cases, 32 were diagnosed as breast cancer (84%), 4 were ovarian cancer (10%), one endometrial carcinoma (3%), and one fallopian tube cancer (3%). Sixty one percent of patients achieved complete symphysis of the pleura with no recurrence. There was recurrence with loculation in 16% of the cases. These patients were left alone since they did not develop significant dyspnoea on exertion. In 23% of patients, the procedure was unsuccessful and significant reaccumulation of pleural fluid occurred.

It is concluded that tetracycline pleurodesis using the powder obtained from the capsules is a simple and satisfactory palliation for malignant pleural effusion.

Keywords: Malignant pleural effusion, Tetracycline powder, Pleurodesis.

INTRODUCTION

Pleural effusion is an abnormal accumulation of fluid in the pleural space. Neoplastic disease causes 13% to 40% of all the pleural effusions and account for 70% of all massive effusions[2]. Pleural effusion develops in nearly one half of all patients with metastatic cancer. Bronchogenic and breast cancer account for 75% of malignant pleural effusions with the remaining 25% represented by a cross section of other neoplastic diseases[3]. Malignant effusions are usually moderate to large (500-2000mls). Ten percent are less than 500mls and 10% occur with massive effusion where the hemithorax is completely opacified[2].

Pleural effusion restricts ventilation and causes progressive shortness of breath, orthopnoea and tachycardia. Pleural deposits of tumour cause pleuritic pain. These symptoms can occur gradually or suddenly [4]. Untreated, death usually ensues within a few months due to primary disease or to complications related to the effusion.

Pleurodesis in these patients is carried out to prevent reaccumulation of the effusion, relief of symptoms and avoid the need for repeated hospitalization for thoracocentesis. Numerous clinical studies have been performed to determine the optimal pleurodesis strategy. The aim of our study was to assess the efficacy of tetracycline powder pleurodesis as a palliative treatment of malignant pleural effusion.

METHOD

In this retrospective study, case notes of all patients admitted to the National Cardiothoracic Centre over the 4 year period (2001-2004) with malignant pleural effusion for drainage and pleurodesis were retrieved for study. The patients included in the study satisfied the following inclusion criteria:

- Diagnosed with a primary malignancy
- Recurrent symptomatic malignant pleural effusion cytopathologically documented
- Evidence of expansion of the lung after drainage and absence of bronchial obstruction and/or fibrosis preventing lung expansion.

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Patients were excluded if a history of cardiac disease was found. Pretreatment assessment was performed during admission and it included history and physical examination, full blood count and a pre-drainage base line posteroanterior and lateral chest radiographs.

A chest tube (24f-32f) was inserted into the midaxillary line through the 5^{th} or 6^{th} intercostal space under local anaesthesia. In some cases , additional intravenous narcotics were administered. The pleural effusion was drained by gravity using under water sealed drainage. Massive pleural effusions were drained gradually. An initial 1000mls was drained followed by about 500mls/hr. Pleural drainage was temporarily suspended when the patient complained of discomfort in the chest or cough. Daily tube outputs were recorded and when drainage fell below 100mls in 24hours, posterior-anterior chest radiographs were obtained to ensure that the fluid had been sufficiently evacuated, there were no loculated collections and the lung had fully re-expanded. Then the patients were eligible for pleurodesis.

The fluid for pleurodesis consisted of 12.5mls of 2% lidocaine made up to 50mls with normal saline. Tetracycline powder obtained from tetracycline capsules (35mg/kg body weight) was added to this fluid. The mixture was drawn into a 50ml syringe and then instilled into the pleural cavity through the chest tube. The tube was clamped for 2hours and then released. If the post-sclerotherapy drainage was <100mls per day, the tube was removed and if drainage was >300mls per day pleurodesis was repeated.

Complications related to the procedure were recorded. Postero-anterior and lateral chest X- rays were carried out after removal of the chest tube in order to compare with films that will be obtained after one month.

Clinical response was evaluated according to Paladine`s criteria[5]:

- Complete response (CR): Fluids do not accumulate during the first 30 days.
- Partial response (PR): Recurrence of small amount of effusion which does not need to be drained.
- No response (PD): Recurrence of effusion which needs to be evacuated.

RESULTS

Thirty eight women were included in this study. The mean age of the group was 51.1yrs. Of the 38 women, 32 (84%) were diagnosed as breast cancer, 4 (10%) as ovarian cancer, one (3%) endometrial cancer and one (3%) cancer of fallopian tube.

Dyspnoea was the most common presenting complaint and common to all the 38 (100%) patients studied. The other symptoms are shown in Table 1.

Table 1 Presenting symptoms of patients with malignant pleural effusion.

Symptom	No. of Patients	Percentage
Dyspnoea	38	100%
Chest Pain	36	94%
Cough	32	84%
General malaise	9	23%
Weight loss	10	26%

Complete response was achieved in 23(61%) of the women; 5 (16%) of the women achieved partial response and in 10 (23%) no response was noticed and pleurodesis had to be repeated with 40% success.

Complications observed after the tetracycline pleurodesis were chest pain in 7 (18%) immediately after the introduction of the mixture into the pleural cavity and fever in 8 (21%) which lasted between 24 to 48 hours.

DISCUSSION

Malignant pleural effusion is a common complication of end stage malignancy significantly impairing quality of life[6]. The deteriorating effect on quality of life includes repeated hospitalization, altered pulmonary function, fatigue, and the requirement for numerous interventional procedures. Most effusions do not respond to systemic chemotherapy and the treatment is generally palliative[6].

Dyspnoea was the most common presenting symptom in patients with malignant pleural effusion in our study. This is also true in studies done elsewhere[1,3,6,7]. The extent of the dyspnoea depends on the volume of the effusion and the underlying condition of the lung[8]. About 23% to 26% of our patients experienced malaise and weight loss. In the report of a study carried out in the USA, 20% of patients experienced malaise and weight loss[1].

Chest tube insertion and tetracycline pleurodesis using tetracycline capsules was found to be effective and cheap. From our results, the use of tetra-

cycline powder obtained from the capsules is comparable to parenteral tetracycline which is no longer available on the market. In this study the success rate (CR +PR) of 77% is comparable to other studies in which parenteral tetracycline was used with success rates between 50% to 92%[7]. Thoracoscopic instillation of parenteral tetracycline has been studied in two randomized trials for malignant effusions in breast cancer. The complete response rate at one month for both trials was 76%[7]. The complete response rate in our study was 61%, comparable to a study done in Egypt using parenteral tetracycline with a success rate of 60%[9]

The mechanism of pleurodesis is based on pleural irritation to create an inflammatory reaction leading to fibrogenesis[8]. The cellular and molecular mechanisms involved in pleurodesis include the activation of the coagulation cascade of the pleura, fibrin deposition, fibroblast recruitment, activation, proliferation and collagen deposition[8]. Anthony and colleagues have demonstrated increased growth factor-like activity in mesothelial cells exposed to tetracycline leading to fibroblast proliferation. This activity gradually decays once the tetracycline is removed[7]. Furthermore, research suggests that systemic activation of coagulation takes place during pleurodesis. Thus, prevention of systemic activation of coagulation with prophylactic heparin should be taken into account in patients who are undergoing pleurodesis for palliative treatment of malignant effusions[8]. Our patients received prophylactic doses of heparin i.e. 100iu/kg daily subcutaneously until the chest tube was removed. There are other common agents used for pleurodesis.

Talc has been proven to be one of the most effective sclerosing agents for treating malignant pleural effusion[10]. Success rate varies between 88%-100%[3,11,12]. Talc poudrage or slurry is usually well tolerated and pleuritic chest pain and mild fever are the most common side effects observed. A serious complication associated with the use of talc is acute respiratory distress syndrome or acute pneumonitis[7,11]. The mechanism of acute talc pneumonitis is unclear. The dose of talc and the physical characteristics (size and type) appear to be the most important determinants for the development of this complication[7]. It has also been suggested that minimal pulmonary reserve and severe debilitated state of end stage malignancy in these patients markedly increase the risk[11].

Doxycycline has been proposed as an alternative to tetracycline with a similar success rate ranging from 25% to 100%[10]. This is because the intravenous form of tetracycline is no longer widely available. The major disadvantage to the use of doxycycline is the need for repeated instillations to obtain a satisfactory response[7]. The associated prolonged intercostal tube indwelling time potentially increases patient discomfort, the risk of infection and overall treatment cost.

Bleomycin is the most widely used antineoplastic agent for the management of malignant pleural effusion. Its mechanism of action is predominantly as a chemical sclerosant similar to talc and tetracycline. Forty five percent of the administered bleomycin is absorbed systemically with minimal or no myelosupression. Success rate after single administration varies from 58% to 85%[7]. The drawback to the use of bleomycin is the cost (about $50 per treatment dose compared to less than 50cents for tetracycline) and the necessity for personnel familiar with the administration of cytotoxic drugs[7.]

Other agents used rarely include minocycline, mitoxantrone, corynebacterium parvum extract, interferons, interleukins and several chemotherapeutic agents.

The size of intercostal tubes has been looked at in many studies. Conventional large bore tubes (24F-32F) have been employed in most studies including ours involving sclerosing agents. This is because of the fear that pleural fluid may clot the smaller tubes and defeat the purpose of the intercostal tube insertion. The use of smaller tubes have been studied and Clementson *et al* in a randomized study using tetracycline as a sclerosing agent compared a small bore tube 10F with a large bore tube 24F[7]. Although no significant difference in success rate was observed between the two groups, the small bore catheter was associated with less discomfort[7,11]. In another nonrandomized study small bore tubes (10F) were considered more successful than large bore tubes[7,11]. Rotation of patients has been described in most pleurodesis studies following intrapleural injection of sclerosing agents. As in other studies, patients in this study were not rotated after instillation of the sclerosing agent[7,11]. It is time consuming and may cause further discomfort to these patients. A study using radiolabled tetracycline has shown that tetracycline is dispersed throughout the pleural space within seconds and rotation of the patient did not influence the distribution of the agent[7].

In our study, after introduction of the tetracycline the chest tube was clamped for two hours and then

released. Mesothelial cells initiate the inflammatory cascade that leads to a fibrotic response and mesothelial cell injury occurs within minutes after contact with the chemical agent. The 1-2 hour dwell time is adequate because the two pleural surfaces should be juxtaposed as soon as possible[10]. The dwell time should not be increased unnecessarily.

There was no serious complication associated with the procedure using tetracycline capsules. The adverse effects recorded in our study were chest pain which occurred in 7 (18%) and fever in 8 (21%). Intrapleural administration of sclerosing agents is associated with chest pain and fever .The incidence varies from 7% to 43% for chest pain and fever from 10% to 59%[7,11,13]. Lignocaine is the best studied local anaesthetic for intrapleural administration. The onset of action of lignocaine is almost immediate and this was used in our study in preparing the pleurodesis agent.

CONCLUSION

Malignant pleural effusion is a common complication of end stage malignancy. Management is palliative and chemical pleurodesis using tetracycline capsule via bedside tube thoracostomy has been shown to be effective in our study. Tetracycline capsule is cheap (less than 50 cents per treatment dose), readily available and associated with minimal side effects.

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