Recurrence of Malignant Pleural Effusion Following Pleurodesis: Is There a Difference Between Use of Povidone-Iodine or Cyclophosphamide?

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Abstract

Background: Malignant pleural effusion is associated with poor quality of life. The success of pleurodesis varies with different agents, with talc being the most effective. It is however not available in Nigeria. This study aimed to determine the efficacy of povidone iodine and cyclophosphamide, the two commonly available agents for pleurodesis **Methods**: A prospective simple randomized enrollment of consecutive patients with malignant pleural effusion over a five year period (2008-2012). **Results**: Thirty four patients were analyzed with a M:F ratio of 1:2.4. Breast cancer was responsible for almost half (47.1%) of the effusions. Although the povidone iodine group was slightly younger both groups were similar. There was no difference in the effusion recurrence for both groups. Age, duration of symptoms and cancer type were not predictors of recurrence of effusion following pleurodesis. **Conclusions**: Both agents are readily available and perform well with minimal side effects. However, povidone iodine being cheaper may be a more affordable alternative.

Key Words: Malignant effusion, Pleurodesis, Povidone-iodine, Cyclophosphamide

Introduction

Malignant pleural effusions are a cause of significant morbidity and mortality in patients at an advanced stage of disseminated neoplastic disease. These patients have a poor quality of life with dyspnea, cough and chest pain. Although this suggests end stage disease with very short life expectancy, prompt, well judged and skilled management of the effusion can alleviate breathlessness and improve quality of life (1). Malignant effusions arise from primary or secondary tumors in the pleura, with majority arising from metastatic sources. Lung and breast tumors account for about 75% of metastatic sources while lymphomas, gastric and ovarian cancers amongst others are responsible for the remaining 25% (2,3). Pleurodesis results in obliteration of the pleural space as a result of formation of fibrous adhesions between the parietal and visceral pleura. These adhesions can be created either by mechanical abrasion or chemical means with varying rates of success (4). An ideal agent for pleurodesis must be highly effective, easy to administer, safe, inexpensive and readily available (5). Talc, the most widely used agent for pleurodesis is not readily available in Nigeria and is therefore, expensive to procure (5,6). Povidone iodine, a commonly available topical antiseptic, has been shown to be safe and effective when used for pleurodesis (7,8). Anti neoplastic drugs eg bleomycin have been utilized successfully for pleurodesis and it is on this basis that cyclophosphamide, another commonly employed anti neoplastic agent used as systemic chemotherapy especially in breast cancer has been employed for pleurodesis in our centre albeit anecdotally (5,9). Its use as an agent for pleurodesis has been previously documented in Nigeria, although it has not been compared with povidone iodine, another readily available agent (10). This study aimed at comparing the time to recurrence of effusion with these two affordable, available and relatively safe agents as a measure of success of pleurodesis.

Methods

During a 5-year period (2008-2012), all consenting patients presenting with symptomatic pleural effusion with associated malignant conditions were approached to enroll into the study. A convenience sample of sixty was chosen. Of the 60 patients approached and 53 accepted to join the study. Of these 19 were not included in the final analysis of patients for the following reasons; 10 patients died before the first follow up, 5 relocated and could not be reached by the study team and 4 withdrew their consent. The follow-up period was one year. Consecutive patients were enrolled by simple randomization (coin tossing) into either cyclophosphamide or povidone iodine groups by two of the authors (AS & OA). The groups were blinded only to the final assessor (AB).

Exclusion criteria were WHO performance score >3, patients with known allergies to iodine, thyroid disease, or loculated effusions.

A size 28FR chest tube (size 20 FR for the only paediatric patient), (Argyle, Tyco Healthcare) was inserted in the mid-axillary line through the fifth intercostal space and connected to an under- water seal drainage. When complete lung expansion with radiologic verification was achieved with daily drainage of less than 100mls of effusion, pleurodesis was performed at the bedside.

All patients received 20 mls of isotonic saline solution containing 2mg/kg lignocaine and 15 minutes later, an 80 mls pleurodesis solution containing either 20mls of 10% Povidone iodine (Jawa Int Ltd. Isolo, Nigeria. NAFDAC Reg No: A4-0939) diluted with 60mls of isotonic saline or 20mls of 1g/m2 Cyclophosphamide (Cyclocel, Celon Labs, India. NAFDAC Reg No: A4-4987) diluted with 60mls of isotonic saline after which the chest tube was clamped for 4 hours. The thoracostomy tube was removed as soon as the drainage decreased to less than 100ml/day and the chest xray confirmed lung re-expansion and no residual pleural effusion. Pleurodesis was repeated after 7 days if the drainage remained more than 200mls/day.

Pain was assessed at 5 minute intervals after pleurodesis and recorded using a Visual Analogue Scale (12).

Response was recorded using Paladine's criteria (13) as:

Complete (CR) - when fluids did not accumulate during the first 30 days,

Partial (PR) – when there was recurrence of small amount of effusion which did not require drainage

None (PD) – recurrence of effusion needing evacuation

Ethical Clearance was given by the Hospitals' Ethical Committee and study was partly supported by a grant from the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife.

Results

Thirty four patients were enrolled into the study. There were 24 females and 10 males with equal numbers of males and females in the 2 groups i.e. 12 females and 5 males in each group. The mean age of the cyclophosphamide cohort was 51.9 ± 21.6 years while the povidone iodine group was slightly younger at 47.8 ± 15.3 years (p=0.52).

The most common presentation was dypsnoea on exertion (76.5%) with other symptoms of cough (11.8%) and weight loss (5.9%). Breast cancer was the etiology of the malignant effusion in almost half of the patients (47.1%) with bronchial, Hodgkins and ovarian cancer accounting for 8.9% each.

Only 1 patient required 2 attempts at pleurodesis. Seven (20.6%) patients eventually had recurrence of effusion. Almost all the patients had no pain (VAS – 0; 52.9%) or insignificant pain (VAS -1/2; 47.1%) during the procedure. There was no record of fever in any of the groups.

At 1 month post pleurodesis, twenty (58.9%) patients had complete response (CR) with ten (29.4%) patients having partial response (PR). Three (8.8%) patients had no response (PD) and 1 patient was lost to follow up.

Thirteen (75.6%) of those who used cyclophosphamide compared to seven (41.2%) of those who used povidone had a complete response (CR) by 1 month (p=0.12). No individual was lost to follow up among those using povidone while cyclophosphamide group had 1 (5.9%) loss to follow up. Eight (47.1%) had a partial recurrence among the povidone group compared to two (11.8%) in the cyclophosphamide group, (p=0.36) (Table 1).

Table 1. Response to pleurodesis in the two different cohorts at 1 month follow up

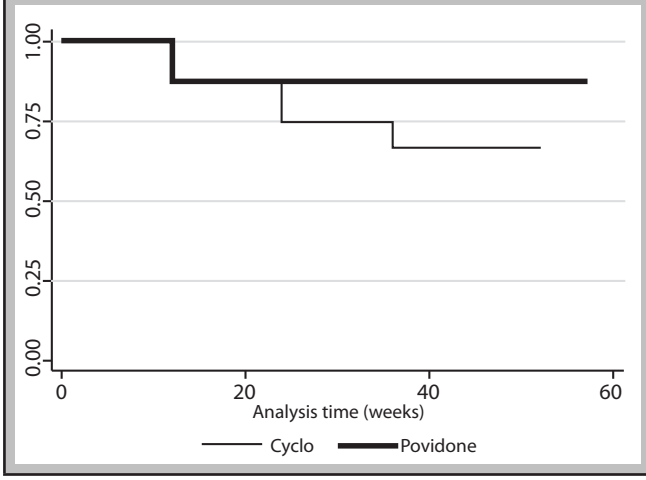
	AGENT		
RESPONSE	**CYCLOPHOSPHAMIDE (%)**	**POVIDONE(%)**	**TOTAL (%)**
COMPLETE	**13 (**76.47)	**7 (**41.16)	**20 (**58.82)
PARTIAL	**2 (**11.76)	**8 (**47.06)	**10 (**29.41)
NO RESPONSE	**1 (**5.88)	**2 (**11.76)	**3(**8.82)
LOST TO FOLLOW UP	**1 (**5.88)	**0 (0)**	**1 (**2.94)
TOTAL	**17 (**100)	**17 (**100)	**34 (**100)

At 3 months, only 1 of the 10 with partial recurrence of effusion (partial response) at 1 month had a complete resorption of the effusion. Seven of the 10 with partial recurrence at 1 month died before the 3rd month due to progression of disease. Further analysis of the initial 20 patients with complete response showed that at 3 months there was no record of recurrence or death. However, only nine (45%) were alive and without recurrence at 1 year post pleurodesis.

The incidence rate of effusion recurrence in the

cyclophosphamide group was 8.6 per 1000 person-week while that for povidone group was 4.9 per 1000 person-week. Figure 1 is a Kaplan-Meier graph comparing the time to recurrence of effusion experience of the povidone-iodine cohort to the cyclophosphamide cohort.

Figure 1. Kaplan-Meier graph showing the pleural effusion recurrence experience in both treatment cohorts



Using a multivariate Cox proportion hazards model to examine independent predictors of time to effusion recurrence, age, gender, duration of symptoms, cancer type and type of pleurodesis agent were not significant predictors (Table 2).

Table 2. Predictors of recurrence of effusion

	Univariate analysis HR (95% CI) p – value	Multivariate analysis HR (95% CI) p – value
Age (years)	0.98 (0.95 – 1.02) 0.30	0.99 (0.95 – 1.03) 0.53
Female sex	2.29 (0.51 – 10.33) 0.28	1.70 (0.29 – 11.69) 0.59
Duration of symptoms (months)	0.99 (0.98 – 1.01) 0.53	0.99 (0.97 – 1.01) 0.32
Cancer type		
Breast cancer	1	1
Other cancers	2.25 (0.43 – 11.66) 0.33	2.07 (0.26 – 16.39) 0.49
Agent		
Cyclophosphamide	1	1
Povidone	0.53 (0.10 – 2.79) 0.46	0.56 (0.098 – 3.19) 0.51

Discussion

Malignant pleural effusion is a cause of significant discomfort for patients under a tremendous burden of metastatic malignancy, many of whom are already terminally ill. In addition to the symptoms attributable to the primary malignancy, they are usually in severe respiratory distress and may benefit from tube thoracostomy to drain the effusion. Unfortunately, when the lung parenchyma has also been infiltrated, the respiratory compromise might be progressive.

Breast cancer and bronchogenic cancer, both occurring on or in the chest accounted for more than half of the patients (55%) in this series probably because of proximity and local spread to the pleura. This is similar to the findings of other workers (3). It is not surprising therefore, the preponderance of female patients as breast cancer is more common (14). Surprisingly, there was also a female preponderance of 2:1 among the patients with bronchogenic cancer, unlike epidemiological studies from the Western world (15).

We routinely administered 2mg/kg lignocaine, 15 minutes before instilling the pleurodesis agent and this may have accounted for the relatively painless procedure in these patients apart from the tolerable discomfort of the tube thoracostomy. None of our patients experienced the pain described with talc pleurodesis. Fever, another common side effect of pleurodesis, was not observed in any of our patients (16).

In the first follow up month, more patients (76.5%) had complete response with cyclophosphamide than those with povidone iodine (41.2%) and conversely, there were fewer patients (11.8%) in the cyclophosphamide group than the povidone iodine group (47.1%) with recurrence of effusion. Although this may suggest a better outcome with cyclophosphamide, there was no statistical difference in the performance of the 2 agents (p=0.12) and no difference in the initial recurrence rates (p=0.36) (Table 1).

Cyclophosphamide is a cytotoxic agent routinely used in the chemotherapeutic regimes of our breast cancer patients and other malignancies. It is not clear however, if intra-pleural in addition to parenteral administration will have an additive positive effect on the underlyng malignancy as the appropriate systemic dose is likely to have been given. A clear advantage over povidone iodine might have been expected if this was the case. One out of the seven breast cancer patients who were randomized to the cyclophosphamide group had a recurrence while while 4 out of 10 with non-breast cancer also randomized to the cyclophosphamide group developed recurrence.

This difference was not significant (p=0.25) and probably underscores the notion that prior use of systemic cyclophosphamide as in breast cancer patients, has no influence on effusion recurrence. Bleomycin, another cytotoxic agent was even less effective as a pleurodesis agent when compared with mepacrine, an anti malarial (16). From our data, our concern over possible cyclophosphamide toxicity was also unfounded as we did not detect any known side effects from using an intrapleural dose of 1mg/m^2. It is postulated that a malignant pleural effusion is pathologic with a poor absorption potential, hence the tendency for fluid recurrence, and possibly poor systemic absorption of drugs (17).

Since povidone iodine has had reports of its success

(88.7%) as a pleurodesis agent it remains to be documented the performance of an untested agent such as cyclophosphamide. Povidone-iodine however has a marginal cost benefit over cyclophosphamide (8). At six months follow up, 70% of those with initial complete response were still alive without recurrence and in relatively good health but by 1 year, only 45% were alive without recurrence. Even though the dismal survival of these terminally ill patients prevents a long follow up, the aim of managing these patients is palliative, and should be directed at improving the quality of life with minimal complications.

There was no difference in the effusion recurrence for both groups even though after the 6 month follow up, the incidence of recurrence became higher in the cyclophosphamide group at 8.6 per 1000 person-week compared with 4.9 per 1000 person-week in the povidone iodine group. There was also no difference with regards to gender. Age, duration of symptoms and cancer type were also not predictors of effusion recurrence.

The calculated power of the study is 47%. This limits the study as it may not be adequately powered to detect the differences between the two groups.

Conclusion

Both agents were readily available but neither showed a clear advantage over the other in initial complete response or recurrence of effusions. Both agents are a satisfactory alternative where talc is not readily available.

This study is limited by the small numbers of these patients that will survive for long follow up periods as they are already terminally ill.

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