IBOM MEDICAL JOURNAL
Vol.17 No.3 | September - December, 2024 | Pages 534 - 539
www.ibommedicaljournal.org

Does intraprocedure patient positioning affect outcome of chemical pleurodesis for malignant pleural effusion?

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Abstract

Background: Chemical pleurodesis using tetracycline is an acceptable and commonly employed palliation for malignant pleural effusion. Rotation of patient during pleurodesis using the powder from tetracycline capsule is still practised in some centres and is undoubtedly associated with additional stress on the patients. The practice of rotation can only be eliminated after a properly designed study on the outcome of pleurodesis with rotation and non-rotation would fail to show benefit of rotation.
Objective: To determine the association between patients positioning and the outcome of tetracycline pleurodesis in patients with malignant pleural effusion.
Patients and methods: It is a prospective randomized study involving adults patients with cytologically proven malignant pleural effusion. Patients were randomized into 2 groups (rotation and supine) using alternate sampling technique. Tube thoracostomy was done and tetracycline pleurodesis using 2g of powder from tetracycline capsule via slurry instillation method was carried out. The outcome of the pleurodesis was assessed with a chest radiograph on the 30th day after removal of chest tube.
Results: There were 51 patients studied with malignant pleural effusion. These consisted of 12 males (23.5%) and 39 females (76.5%). Twenty-five patients (49.0%) were rotated in the study while 26 patients (51.0%) were on supine position. A total of 30 patients (58.8%) achieved complete response, 16 patients (31.4%) achieved partial response while 5 patients (9.8%) had failed response. The study also showed that in the rotated group, 23 patients (92%) had successful response and 23 patients (88.5%) in the supine group also achieved successful response (P = 0.175); there was no significant difference between the two groups.
Conclusion: This study showed that, though the powder from tetracycline capsule is only slightly soluble in water, it gives a good and similar successful outcome in both arms of the study. This implies that positioning of patient during pleurodesis plays no significant role in the outcome of tetracycline pleurodesis using the powder from tetracycline capsule.

Keywords: Chemical pleurodesis, tetracycline pleurodesis, malignant pleural effusion, patient positioning, rotation

Introduction

Commonly used chemical pleurodesants include Talc, tetracycline and its derivatives, mitoxantrone, bleomycin, silver nitrate, iodoprovidone.[1] However, tetracycline, talc and bleomycin are considered as primary sclerosing agents.[2] They have been widely employed in many studies with variable success rates. Talc, either by slurry or insufflation, has the highest success rate of about 91%.[3] Parenteral tetracycline had been studied extensively and a

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DOI: 10.61386/imj.v17i3.515

range of success rate of 50%-92% had been documented.[4,5] Chest tube insertion and tetracycline pleurodesis using the powder from tetracycline capsules, in one study, was found to be effective with a success rate of 77%.[6] This outcome is comparable to studies done with parenteral tetracycline which is no longer available in the market.

Tetracycline capsules and talc are cheap and readily available. Despite the efficacy of talc pleurodesis, there are concerns about its short-term safety as there have been a number of reports of respiratory failure after both talc poudrage and slurry and some of the patients did not survive the episode of respiratory failure.[7-9] This adverse effect of respiratory failure, though with a low incidence of about 1%,[10] has been a major drawback on the use of talc, thus tetracycline becoming a popular pleurosant in our subregion.

Chemical pleurodesis using tetracycline is an acceptable and commonly employed treatment for malignant pleural effusion.[11] The antibiotic tetracycline has been recognized (and been in use) as a pleural sclerosant for over 2 decades.[12]

Rotation of the patients during chemical pleurodesis, including tetracycline pleurodesis, has been a common practice even at the moment. Patients are made to rotate through several positions viz: supine, prone, right and left lateral decubitus, and sitting position so that the chemical substance could come in contact with all pleural surfaces.[1] This undoubtedly imposes more stress on the patient and also costs additional personnel time. To ameliorate these, Lorch and his colleagues, demonstrated with the use of radiolabelled tetracycline that after intrapleural instillation, tetracycline is distributed completely throughout the pleural space within seconds, and the distribution is not enhanced by patient's rotation.[13] In a follow-up to this, another study also proved this assertion with an inference that there was no difference in success rate with tetracycline and minocycline in patients rotated and those kept only on supine position.[14] These studies were carried out using parenteral tetracycline. Following the withdrawal of parenteral tetracycline from the market in 1991, tetracycline derivatives (doxycycline and minocycline) were used as alternatives to tetracycline.[15]

Publications using the powder from tetracycline capsules for chemical pleurodesis are scanty and it's even more difficult to find a comparative study using the powder from tetracycline capsules to assess the efficacy of pleurodesis in relation to patients positioning. A retrospective study in our West African subregion has elucidated that using the powder from tetracycline capsule for pleurodesis gives similar success rate as the parenteral form of tetracycline.[6]

The presence of malignant pleural effusion denotes an advanced malignant disease with the risk of re-accumulation after drainage, thus palliation with tube thoracostomy and pleurodesis to prevent or delay re-accumulation becomes widely used option.[1,16-18] Chemical pleurodesis with tetracycline has been commonly employed for treatment of malignant pleural effusion.[11] Rotation of patients during tetracycline pleurodesis has been a common practice even at the moment. However, it had been proven that intrapleural instillation of parental tetracycline, a water soluble substance, to achieve chemical pleurodesis does not require rotation of patients as the tetracycline is distributed completely throughout the pleural space within seconds, and the distribution is not enhanced by patient's rotation.[13] With the use of the powder from tetracycline capsule which is less water soluble than the parenteral form, rotation of patients during pleurodesis is still commonly practised.

This study was designed to demonstrate the relationship of patients positioning and the outcome of tetracycline pleurodesis using the powder from tetracycline capsule.

Material and method

Study design

This was a prospective randomized study that was undertaken in the cardiothoracic surgery unit of University of Uyo Teaching Hospital, Uyo, Nigeria.

Study protocol

On presentation, the each patient was clinically evaluated, a chest radiograph (posteroanterior and lateral views) obtained and a diagnostic thoracentesis done to ascertain the presence of pleural effusion, as well as sending about 50ml of the pleural aspirate for cytology. Histopathologists were involved in the cytological diagnosis. The chest radiographs were also reported by consultant radiologists. With confirmation of symptomatic

pleural effusion, closed thoracostomy tube drainage was performed using standard technique. In patients with high index of suspicion for malignant pleural effusion e.g. aged patients, those with massive pleural effusion seen on chest radiograph, or patients with proven malignancy, a pleural biopsy was pertinent using Abram's needle during the tube thoracostomy procedure. After the chest tube insertion, a chest radiograph was obtained again to ascertain the position of the chest tube.

Chest tube drainage and care was done using standard protocol. Volume of the drainage and nature of the fluid (serous, serosanguinous, haemorrhagic) were recorded daily on the in-patient chart. When the daily chest drainage fell below 100ml per day for at least 2 consecutive days and pleural fluid was serous, a chest radiograph was obtained to assess re-expansion of the lung. Consultant radiologists assessed the chest radiograph for lung re-expansion. The same radiologists reported on all chest radiographs of all the patients involved in this study. If there was full lung re-expansion, the patient was re-evaluated for pleurodesis. Patients who gave consent and met the inclusion criteria were randomized into R - and S - groups for pleurodesis. R-group contained patients that were rotated through several positions while S-group had patients placed on supine position only. Patients with odd numbers belonged to R- group while those with even numbers belonged to S - group. Chemical pleurodesis using tetracycline was done via slurry. The powder from 2g of tetracycline capsule (tetramac) was dissolved in 50ml of sterile water and 10ml of 2% plain lignocaine added and mixed thoroughly. One gram of paracetamol tablet was also given to the patient about 30mins before commencement of this procedure. The prepared solution of tetracycline and lignocaine (60ml volume) was instilled through the chest tube (slurry method) with the patient on supine position and the chest tube clamped. Patients in S-group maintained the supine position for 2 hours while those in R-group rotated every 20mins through various positions viz: supine, left lateral, prone, right lateral, and sitting. At the end of this dwell time (2 hours) the chest tube was unclamped for both groups. If the pleural fluid drainage was less than 100ml within the next 24 hours, the chest tube was removed the following day and a chest radiograph obtained. However, if the drainage was > 100ml per day for more than 2 consecutive days, the pleurodesis would be repeated.

Following successful pleurodesis, the patient was discharged for follow-up on out-patient basis. The first follow-up visit was a week following removal of chest tube. During this visit the thoracostomy wound was assessed and the suture removed. The 2nd follow-up visit was on the 30th day post-chest tube removal. The patient was evaluated with a recent chest radiograph reported by the same consultant radiologists who assessed the previous studies. This visit was used to assess the outcome of the pleurodesis. Subsequently, the follow-up periods were progressively longer. In addition, during each visit to the clinic, he/she was evaluated clinically and radiologically with a recent chest radiograph. Recurrence of clinical features such as dyspnoea, cough and chest pain, and abnormal chest examination findings may indicate re-accumulation of effusion and/or lung collapse or pulmonary metastasis. Progressive weight loss, bone pain and deterioration in performance status gave a clue to the progression of the malignancy. Patients would be followed-up for life-time and further management would be as need arises.

Assessment of response

The follow-up visit on the 30th day after removal of chest tube was used to assess the response (outcome) of the pleurodesis. Clinical and recent chest radiographic evaluations were done. The same consultant radiologist reported on all the chest radiographs and was blinded to R– and S– arms of the study. With chest radiographic findings, the response was categorized as follows:[6]

(I) Complete response when there was no evidence of pleural fluid re-accumulation.

(ii) Partial response when there was evidence of minimal pleural fluid accumulation and no intervention was required.

(iii) Failed response when the re-accumulated pleural fluid required pleural aspiration or tube thoracostomy.

Successful response to pleurodesis was defined as no pleural fluid re-accumulation or minimal pleural fluid re-accumulation not requiring further aspiration for one month (i.e complete and partial response).

Data analysis was done using SPSS version 20.

Results

Within the study period of one year, from June, 2018 to June 2019, 51 patients with cytologically proven malignant pleural effusion met the inclusion criteria and were enrolled. Data on socio-demographic characteristics, the protocols of tetracycline pleurodesis, and overall and group-based outcomes of pleurodesis were collated and analyzed.

The ages of the respondents ranged from 21 years to 83 years with a mean age of 47 years (Table 1). There were 39 females (76.5%) and 12 males (23.5%) in the study. The duration on admission ranged from 9-14 days (table 1) while the duration of chest tube drainage following pleurodesis ranged from 1 to 2 days.

Table 1: Socio-demographic characteristics of respondents by position

Variables	Position during Pleurodesis		Total n (%)	Statistical tests and values
	Rotated	Supine		
Age				
Less than 47	12 [48.0]	11 [42.3]	23 [45.1]	X^2=0.167
47 and above	13 [52.0]	15 [57.7]	28 [54.9]	P=0.683
Mean ± SD	44.84±12.60	49.27±18.36	47.09±15.80	T= 1.00; P=0.322
Sex				
Male	10 [40.0]	2 [7.7]	12 [23.5]	P=0.009+
Female	15 [60.0]	24 [92.3]	39 [76.5]	
Duration of Admission	12[10-13]	11 [9-14]	11 [9-14]	P=0.726

+ Fishers Exact. The 2 groups were similar in age and duration of admission [P=0.683 and 0.673 respectively] but were significantly different in sex as more males were rotated and more females not rotated [P=0.009]

Table 2a: Outcome of tetracycline pleurodesis in respondents

Variables	Responses to Tetracycline Pleurodesis			Total (%)	Statistical test and values
	Complete	Partial	None		
Position					
Rotated	18 [72.0]	5 [20.0]	2 [8.0]	25 [100]	P=0.175+
Supine	12 [46.0]	11 [42.3]	3 [11.5]	26 [100]	
Age group					
Less than 47 years	8 [34.8]	11 [47.8]	4 [17.4]	23 [100]	P=0.005+
47 years above	22 [78.6]	5 [17.9]	1 [3.6]	28 [100]	
Sex					
Males	6 [50.0]	4 [33.3]	2 [16.7]	12 [100]	P=0.627+
Females	24 [61.5]	12 [30.1]	3 [7.7]	39 [100]	
Complications					
None	28 [62.0]	13 [28.9]	4 [8.9]	45 [100]	P=0.31+
Present	2 [33.3]	3 [50.0]	1 [16.7]	6 [100]	

Table 2b: Comparison of the 2 groups at each level of outcome of tetracycline pleurodesis in respondents

Variables	Responses to Tetracycline Pleurodesis			Total n (%)	Statistical test and values
	Complete	Partial	None		
Position					
Rotated	18 [60.0]	5 [31.3]	2 [40.0]	25 [49.0]	P=0.175+
Supine	12 [40.0]	11 [68.7]	3 [60.0]	26 [51.0]	
Age group					
Less than 47	8 [26.7]	11 [68.8]	4 [80.0]	23 [45.1]	P=0.005+
47 and above	22 [73.3]	5 [31.2]	1 [20.0]	28 [54.9]	
Sex					
Males	6 [20.0]	4 [25.0]	2 [40.0]	12 [23.5]	P=0.627+
Females	24 [80.0]	12 [75.0]	3 [60.0]	39 [76.5]	
Complications					
None	28 [93.3]	13 [81.3]	4 [80.0]	45 [88.2]	P=0.31+
Had	2 [6.7]	3 [18.7]	1 [20.0]	6 [11.8]	

+Fishers Exact. The position of the respondents, their sex and presence of complications were not significantly associated with the outcome of tetracycline pleurodesis [P=0.175, 0.627 and 0.31 respectively]. Age of respondents was significantly associated with their response to tetracycline pleurodesis [P=0.005]

The outcomes showed that 30 patients (58.8%) achieved complete response, 16 patients (31.4%) had partial response while 5 patients (9.8%) had failed response. Cancers of the breast, lung and ovary were the top 3 common cancers with resultant malignant pleural effusion among the respondents while cancer of the ileum contributed the least. The duration of admission ranged from 9-14 days with a median of 12 days for rotated group and 11 days for supine group. There was no significant difference between the 2 arms of the study (P = 0.726).

Twenty five patients (49.0%) were in rotated arm while 26 patients (51.0%) were in the supine group of the study. Table 2a shows that in the rotated arm, 18 (72.0%) achieved complete response, 5 (20.0%) had partial success while 2 (8.0%) had failed response. In the supine group, 12 (46.2%) achieved complete response, 11 (42.3%) had partial response and 3 (11.5%) had failed response.

Table 2b shows that out of 30 patients that achieved complete response, 18(60%) were in the rotated group and 12 (40.0%) were in the supine arm. Similarly, of the 16 patients who had partial response, 5(31.3%) were in the rotated group while 11 (68.7%) were in the supine arm of the study. Failed response seen in 5 patients was recorded in 2 patients (40.0%) in the rotated group and 3 patients (60%) in the supine group. The outcome of tetracycline pleurodesis was not significantly affected by the position (P = 0.175).

Discussion

It has been shown that after intrapleural instillation of parenteral form of tetracycline to achieve chemical pleurodesis, tetracycline is distributed completely throughout the pleural space within seconds, and the distribution is not enhanced by patient's rotation. However, parenteral tetracycline which is highly water soluble, had long been withdrawn from the market and the use of powder from tetracycline capsule which is incompletely soluble in water, is now commonly used. Response to tetracycline pleurodesis was evaluated according to Paladine's criteria.[6]

- Complete response when there was no evidence of pleural fluid re-accumulation within 30 days after removal of chest tube.

- Partial response when there was evidence of minimal pleural fluid re-accumulation and no intervention was required.
- Failed response when the re-accumulated pleural fluid requires pleural aspiration or tube thoracostomy.

Successful outcome in this study and in another study[2] was both complete and partial response.

In this study, 30 (58.8%) respondents had complete response, 16 (31.4%) had partial response, and 5 (9.8%) had failed response giving a successful outcome of 90.2%. In a related study at Korle Bu in Ghana[6] which used 35mg/kg of the powder from tetracycline capsule, a similar complete response rate of 61% as well as a successful response of 77% was achieved; however, there was disparity in partial response and failed response as 16% and 23% had partial response and failed response, respectively. A previous study in Uyo showed a similar result in successful outcome of 80%[19] using 1g of tetracycline as the sclerosant and all the patients were rotated. The result also showed a similar pattern in a study in Egypt in which a success rate of 60% was achieved using parenteral tetracycline.[5] This further opined that the use of powder from tetracycline showed similar efficacy to that of parenteral tetracycline.

Though parenteral tetracycline had long been withdrawn from the market, the powder from tetracycline capsule is a reliable alternative to parenteral tetracycline in pleurodesis.

Similar successful response (complete response and partial response) was seen in both groups (rotation and supine groups). Twenty three patients (92%) in the rotated group had successful response and 23 patients (88.5%) in the supine group also had successful response. Pioneer works to assess the effect of rotation to the success of tetracycline pleurodesis by Dryzer et al[14] also demonstrated similar successful outcome among the 2 groups as 73% and 61.9% of patients achieved successful response for the rotated and non-rotated groups, respectively. The higher response rate in the index study may be attributed to the use of higher dose of tetracycline (2,000mg for all patients) compared to the use of 20mg/kg[14] (1,400mg for a 70kg patient) in the other study. It has also be shown that the efficacy of tetracycline is dose dependent; the higher the dose, the better the outcome.[10]

In a previous related study in the centre comparing the outcome of 2 sclerosants, and in which all the patients were rotated, a success rate of 80% was achieved using 1gm of tetracycline.[19] In the index study, a success of 90% was achieved for all the groups using 2g of tetracycline. Perhaps the marginal difference of the success rate might be attributed to the difference in dosage of tetracycline. Similar successful outcome of 77% was noted in another study in Ghana in which all the patients were not rotated. From these studies, it can be inferred that position of the patient during tetracycline pleurodesis does not have a significant contribution to the outcome of tetracycline pleurodesis.

Pioneer works utilized parenteral form of tetracycline which is very water soluble but all recent studies utilize the powder from tetracycline capsule because the parenteral form of tetracycline had been withdrawn from the market since 1991 due to quality control issues. The powder from tetracycline capsule is very slightly soluble in water and its solution in water is turbid on standing due to precipitation of tetracycline.[20,21]

Conclusion

This study has shown that rotation of patients does not add any therapeutic benefit and does not lower complication rate. However, rotation increases nurses' workload and is an additional stress to these patients who are already burdened by advanced malignancies. It has also shown that even though the powder from tetracycline capsule is slightly soluble in water, it gives a comparable outcome with rotation or non-rotation of patients to the use of parenteral form of tetracycline which has higher solubility in water.

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