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Comparison of the Efficacy of Autologous Blood and Tetracycline for Pleurodesis in Malignant Pleural Effusions in Zaria

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Abstract

Introduction: The presence of malignant pleural effusion signifies an advanced malignancy, and the aim of management is palliative, including palliation of dyspnea. This can be achieved by tube thoracostomy and drainage, with subsequent pleurodesis. Several sclerosants have been used to achieve pleurodesis in malignant pleural effusions, including the use of tetracycline. Autologous blood pleurodesis has commonly been used for spontaneous pneumothorax, but less commonly for malignant pleural effusion. This study sought to compare the efficacy of autologous blood and tetracycline for pleurodesis in patients with malignant pleural effusions presenting to Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Nigeria.

Materials and Methods: A prospective randomized comparative study of adults with symptomatic malignant pleural effusion requiring drainage, being managed at the Ahmadu Bello University Teaching Hospital (ABUTH), Zaria within the twelve-month study period was conducted. Fifty patients were used for this study and were divided into two groups of 25 each *viz.*: Patients who received autologous blood pleurodesis, and those who received tetracycline pleurodesis during the study period. The duration between pleurodesis and tube removal, need for repeat pleurodesis, pain score, the incidence of complications, and a 30-day review of a plain chest radiograph [according to the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement on the definitions of success or failure of pleurodesis in the management of malignant pleural effusions] were recorded.

Results: Autologous blood pleurodesis was associated with significantly reduced pain at 5 min (1.60 *vs.* 5.04; p-value <0.01), and 6 h (0.04 *vs.* 1.12; p-value <0.01) after pleurodesis, but not at 24 h (0.20 *vs.* 0.40; p-value 0.13) after pleurodesis, compared to tetracycline pleurodesis. The mean duration between pleurodesis and removal of chest tube was significantly reduced in those who had autologous blood pleurodesis compared to those who had tetracycline pleurodesis (1.32 *vs.* 2.40 days: p-value 0.02). The success rate and need for repeat pleurodesis for both pleural sclerosants were comparable to each other with no statistically significant difference. Only one patient who had tetracycline pleurodesis had a fever as a complication.

Conclusion: The efficacy of autologous blood as a pleural sclerosant is comparable to tetracycline and only better in terms of reduced pain scores. Autologous blood is thus, a readily available alternative for use for pleurodesis when tetracycline or lignocaine is unavailable or contraindicated.

Keywords: Malignant pleural effusion; Pleurodesis; Autologous blood; Tetracycline

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Introduction

Malignant pleural effusion is defined as any pleural effusion with malignant cells isolated on pleural fluid cytology or positive pleural biopsy. They usually occurs secondary to advanced malignancies of any origin. Lymphomas and cancers of the lung, breast, and ovaries, are among the most common underlying tumors, accounting for 75% of cases [1]. Optimal management requires pleural drainage and pleurodesis (symphysis between the visceral and parietal pleurae). This can be achieved via mechanical (pleural abrasion), chemical (pleural sclerosants), or biological means

[2]. Although the use of a pleuroperitoneal shunt has the advantage of preventing loss of pleural fluid proteins and nutrients, its use in malignant pleural effusions is froth with the risk of tumour seeding the peritoneal cavity. Autologous blood has been used to achieve pleurodesis in patients with malignant pleural effusion, but very few studies have compared its effectiveness with the commonly used tetracycline [3,4].

Materials and Methods

This study was conducted on all adult patients with symptomatic malignant pleural effusion (cytologically confirmed) requiring drainage and pleurodesis in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Kaduna State, Nigeria within the twelve-month study period (December 2018 to November 2019). The patients were randomized into two groups. The first group consisted of patients who underwent autologous blood pleurodesis, and the second group consisted of those who underwent tetracycline pleurodesis. The following category of patients was excluded from the study:

1. Patients diagnosed with active pleural (i.e. positive pleural fluid microbiology) or systemic infection as infection may alter the outcome.

2. Patients whose chest X-ray showed a trapped lung after pleural drainage or those with significant lung parenchymal disease or bronchial obstruction limiting lung re-expansion.

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of ABUTH, Zaria, Kaduna State, Nigeria. For those scheduled to have tetracycline pleurodesis, the fluid for pleurodesis consisted of 12.5 ml of 2% lignocaine made up to 50 ml with normal saline. Tetracycline powder obtained from tetracycline capsules (35 mg/kg body weight) was added to this fluid. The mixture was drawn into a 50 ml syringe and then instilled into the pleural cavity through the chest tube [5]. For those scheduled to have autologous blood pleurodesis, 1 ml/kg of autologous venous blood without anticoagulant was obtained from each patient's forearm using 20 ml syringes. As fast as possible, the blood was instilled into the pleural cavity *via* the chest tube using sterile techniques (without intrapleural lignocaine injection) and followed by 30 ml of sterile normal saline to prevent blood from clotting in the chest tube [4]. The patients were monitored during and after phlebotomy to ensure hemodynamic stability. The chest tubes were clamped for two hours and subsequently connected to the underwater seal drainage system [3,5]. If the post-pleurodesis drainage was <100 ml in 24 h, the tube was removed. If the post-pleurodesis drainage was >300 ml in 24 h pleurodesis was repeated. If the post-pleurodesis drainage was 100 ml to 300 ml in 24 h, drainage was continued until it was reduced to <100 ml in 24 h (and the tube subsequently removed). If it increased to >300 ml in 24 h, pleurodesis was repeated. If the drainage after pleurodesis remained 100 ml to 300 ml per day after 3 days, pleurodesis was considered to have failed, and it was repeated. Pain score was recorded at 5 min before, 5 min after, 6 h after, and 24 h after pleurodesis using a numeric scale with 0 depicting "no pain" and 10 depicting the "worst kind of pain imaginable". The clinical response was evaluated using a plain chest radiograph done at 30 days post-pleurodesis according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) consensus statement on the definitions of success or failure of pleurodesis in the management of malignant pleural effusions [6].

Complete success

Long-term relief of symptoms related to the effusion, with the absence of fluid re-accumulation on chest radiographs after 30 days.

Partial success

Diminution of dyspnea related to the effusion, with only partial re-accumulation of fluid (radiographic evidence of <50% of the initial fluid), with no further therapeutic thoracentesis required during the follow-up.

Failed pleurodesis

Lack of success as it is defined above. The data so obtained for each patient was entered into a spreadsheet and analyzed using the Statistical Package for Social Science (SPSS) version 20 software (IBM Corp. Released in 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

A total of 50 patients were randomized into two groups of 25 each (autologous blood pleurodesis and tetracycline pleurodesis groups). Both groups had similar characteristics in terms of age, gender, and underlying malignancy. All the patients were undergoing adjuvant chemotherapy before and during the study period.

The results obtained are as follows:

Patients who had autologous blood pleurodesis had statistically significantly decreased pain felt at 5 min and 6 h. There was no statistically significant difference in the level of pain felt at 24 h at a p-value of <0.05. Four patients in the tetracycline group and 1 patient in the autologous blood group required repeat pleurodesis. This was not statistically significant (p-value =0.349). On the 30-day assessment of the success of pleurodesis, complete success/partial success/failed pleurodesis was 13/10/2 for the tetracycline group and

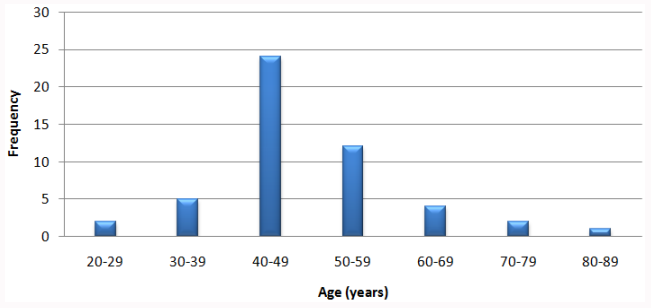


Figure 1: Age distribution.
The mean age of patients was 48.02 years, SD=11.71. The majority were between the ages of 40-49 years.

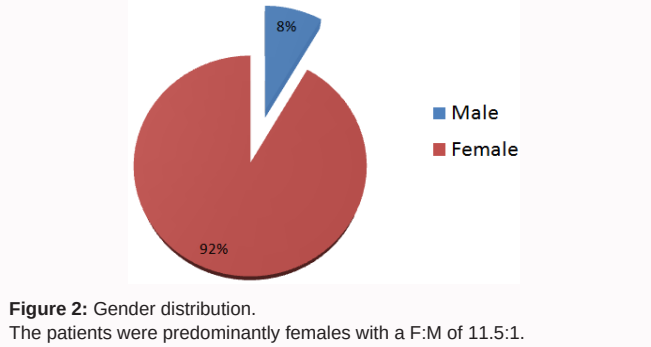


Figure 2: Gender distribution.
The patients were predominantly females with a F:M of 11.5:1.

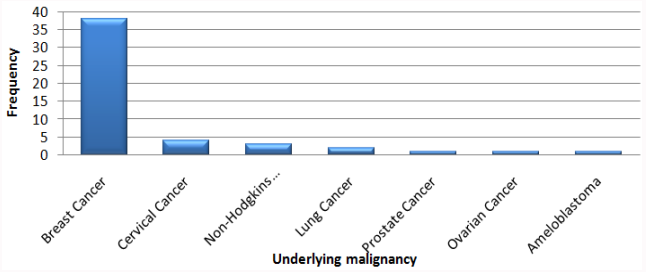
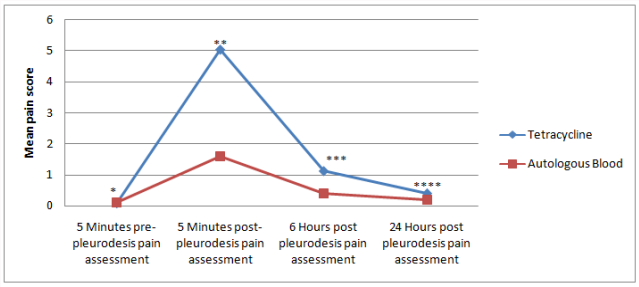


Figure 3: Underlying malignancy.



*p-value 0.65
**p-value <0.01 (statistically significant)
***p-value <0.01 (statistically significant)
****p-value 0.13

Figure 4: Mean pain scores.

19/5/1 for the autologous blood group respectively, and this was not statistically significant at a p-value of 0.210. For the complications, only one patient who had tetracycline pleurodesis had a fever.

Discussion

Successful pleurodesis requires a complete apposition of both pleurae. It, therefore, requires a compliant lung, free from infiltrative disease or restricted by any pleural inflammatory process. With the administration of an appropriate sclerosant, diffuse inflammation, fibrin deposition, and subsequent fibrous tissue deposition by proliferating fibroblasts (which also produce collagen) are findings following pleurodesis. Although talc is generally accepted as the sclerosant associated with a high success of pleurodesis, its side effects and toxicity has favored the use of other agents with fewer side effects and toxicity, and which also possess acceptable efficacy when used for pleurodesis. Tetracycline is a widely used alternative with comparable efficacy. However, the pain and hypersensitivity (in susceptible patients) make it short of an ideal sclerosant for pleurodesis. Although the use of autologous blood has been well established as a sclerosant for pleurodesis following pneumothorax, there are limited studies that have compared its efficacy for pleurodesis in malignant pleural effusions against the use of tetracycline [4,7]. In comparison to a previous study in our sub-region by Tettey et al. [5] this study population was demographically similar to their study in terms of age, gender, and diagnosis. Most patients were middle-aged females, with breast and other gynecologic-related malignancies. Breast cancer was the most common underlying malignancy due to its proximity to the chest and pleura, with similar draining lymphatic channels; and since breast cancer was commoner in females, malignant pleural effusion was commoner in the same gender. In a study by Cobanoglu et al. [10], the use of autologous blood for pleurodesis in persistent air leak was associated with no pain or other complications when compared

Table 1: T-test comparing the duration between pleurodesis and tube removal.

The duration between pleurodesis and tube removal (days)	Tetracycline	Autologous Blood	Total
1	7	20	27
2	10	3	13
3	3	1	4
4	3	1	4
5	1	0	1
7	1	0	1
Total	25	25	50
Mean duration	2.40 days	1.32 days	p-value = 0.02

with talc or tetracycline. Similar to a study by Warangkana et al. [4] where the efficacy of the same agents was compared for use in malignant pleural effusions, the use of autologous blood in this study was associated with a statistically significant decrease in 5 min and 6 h pain scores. However, in contrast, this study did not find a statistically significant difference in the pain scores at 24 h after pleurodesis. In another comparison between talc and autologous blood for pleurodesis, Warangkana et al. [11] found the latter to be associated with a statistically significant decrease in pain scores at 5 min, 6 h, and 24 h post-pleurodesis. The pain associated with tetracycline pleurodesis is due to the significant pleural inflammation induced by tetracycline. This inflammation is much reduced with the use of autologous blood [4]. Autologous blood in itself contains fibrinogen, fibroblasts, and other inflammatory mediators [12] implicated in pleurodesis (which could become activated following the process of contact with the inner lining of the syringe used for aspiration, the contact with the inner lining of the chest tube *via* which it is instilled, and contact with the pleural surface). Coagulation, the complement system, and inflammatory cells have been found to be activated following contact of blood with synthetic surfaces [12-14]. This could probably reduce the need for significant inflammation (and pain) and inflammatory cell exudation (since the instilled autologous blood contains the required inflammatory mediators which have been possibly activated as earlier discussed). In contrast, instilled tetracycline in the pleural space causes pleural irritation increased capillary permeability, and release of similar inflammatory mediators, which might appear to be the convergent point of both agents when used for pleurodesis (i.e. the conversion of fibrinogen to fibrin, and subsequent production of fibrous tissue between both pleural surfaces). In this study, the mean duration between pleurodesis and tube removal was significantly shorter in patients who had autologous blood pleurodesis (1.32 *vs.* 2.40 days, p-value 0.02). This is so because tetracycline is associated with significant pleural inflammation, increased capillary permeability, and exudation of fibrin-rich fluids, before the subsequent organization of the fibrin to fibrous tissue in the pleural space. This causes some production and drainage of pleural effusion in the immediate post-instillation-of-tetracycline period [4]. This accounts for the increased duration of drainage before the commencement of the organization of fibrin and subsequent tube removal. However, the use of autologous blood is not associated with significant inflammation, and thus, a less profound increase in capillary permeability. It is found to induce pleural symphysis by the formation of fibrinous pleuritis, without significant exudation of fibrin-rich fluid [4]. Similar to our findings above, Cobanoglu et al. found that in patients with persistent air

leaks, the mean air leak termination interval was significantly shorter ($p<0.001$) in patients who had pleurodesis using autologous blood in comparison to talc powder and tetracycline [10]. This underscores the fact that autologous blood initiates the onset of pleurodesis faster than tetracycline and talc, thus reducing the number of days of having the pleural drain *in-situ*, and by extension, length of hospital stay for the pleural collection. In this study, the 30-day success of pleurodesis was similar in both groups with no statistically significant difference (p-value 0.21). This was similar to an earlier report by Warangkana et al. The pleural mesothelial lining plays a major role in the success of pleurodesis. Mesothelial cells are involved in the elaboration of several mediators like interleukin-8, transforming growth factor-β, and basic fibroblast growth factor. These mediators are involved in the recruitment and proliferation of fibroblasts, which produce the needed fibrous tissue and collagen for successful pleural symphysis. With extensive tumour infiltration of the pleurae, there is a significant reduction in the quantity of normal pleural mesothelial cells, with a consequent reduction in the success of pleurodesis following the instillation of sclerosants [15]. This could account for the few failed pleurodesis encountered in this study (tetracycline - 2; autologous blood - 1). Rodriguez-Panadero et al. had identified an increase in pleural fibrinolysis as a cause of failure of pleurodesis [16]. In our study, a pleural biopsy would have been recommended to identify the cause of the recorded failures, but this lies outside the scope of this research. However, this difference in failure rates between the two studied groups was not statistically significant. Although the success rate of use of tetracycline powder for pleurodesis in our study (complete response plus partial response) seemed to be higher than a previous study in our sub-region by Tettey, et al. [5] (92% *vs.* 77%), it is worthy of note that the criteria used for the 30-day assessment were slightly different, especially in the definition of partial response. They used the Paladine's criteria, while we used the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement on the definitions of success or failure of pleurodesis in the management of malignant pleural effusions, which is a modification of the Paladine's criteria [5,6]. Despite the above difference in the definition of partial response, the complete response rates for tetracycline powder were similar in both studies (52% in this study *vs.* 61% in Tettey's study).

Conclusion

Autologous blood pleurodesis is associated with significantly reduced pain at 5 min, and 6 h after pleurodesis. The duration between pleurodesis and removal of the chest tube is significantly reduced in those who had autologous blood pleurodesis, compared to those who had tetracycline pleurodesis. The success rates and the need for repeat pleurodesis were comparable.

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