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Intrapleural Therapy for the Prevention of Recurrent Spontaneous Pneumothorax-A Randomized Comparative Evaluation of Bleomycin Pleurodesis & Autologous Blood Pleurodesis

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ABSTRACT: Background: *Pneumothorax is free to air in pleural space i.e. between visceral and parietal pleura. Among various treatment options for recurrent pneumothorax, one is chemical pleurodesis; intended to achieve a symphysis between parietal and visceral pleura, in order to prevent accumulation of air (pneumothorax) in the pleural space.*

Objective: *Our objectives in this study were to evaluate the efficacy of autologous blood pleurodesis in the management of persistent air leak in primary spontaneous recurrent pneumothorax and to compare the efficiency, side effects, cost and complications of autologous blood pleurodesis vis a vis bleomycin pleurodesis.*

Study Design: *It was a prospective randomized comparative evaluation of autologous blood & bleomycin pleurodesis involving patients with persistent air leak resulting due to primary spontaneous recurrent pneumothorax. We followed the patients for a period of 1-22 months with an average follow-up of 11.766 months.*

Methods: *The study entitled, "Intrapleural therapy for the prevention of recurrent spontaneous pneumothorax-A Randomized Comparative Evaluation of Bleomycin Pleurodesis & Autologous Blood Pleurodesis" was carried out in the Department of CVTS, SKIMS Srinagar Kashmir from May 2010 to Oct 2012. Total of thirty (30) patients with primary spontaneous recurrent pneumothorax were included in the study; 16 patients in Study Group (receiving autologous blood) & 14 patients in Control Group (receiving bleomycin). On an average 54.7ml (1ml/kg body weight) of peripheral venous blood taken from the patient's arm vein was immediately injected into the pleural cavity via the chest tube & chest tube was clamped for 1-2hrs. In bleomycin pleurodesis at 15 min after instillation of 20 ml of lidocaine 1%, about 55.7 units (1 iu/kg body wt.) of bleomycin in 100 ml of normal saline were instilled into the pleural cavity via the chest tube and the tube clamped for 1-2hrs.*

Results: *One (6.3%) patient in the Study group had a failure of cessation of air leak after blood patch pleurodesis. Hence the success rate of cessation of an air leak in Control group was 100% while as it is 93.7% in Study group (p-value=0.178, insignificant). In Study group 3(18.8%) patients had post-procedure pain but none had a fever; while as in Control group 13(92.9%) patients had post-procedure pain & 6(42.9%) patients had a fever. None of the patients from Study as well as Control groups had post-procedure empyema, tension pneumothorax, anaphylaxis, chest tube clogging or progressive respiratory failure. Per patient average cost of the procedure in Study group was Rs 53.13 (<1 dollar), while the average cost of procedure per patient in Control group was Rs1925.00 (about 30 dollars) (p-value ≤0.0001). After 1-22 months (average 11.76) follow up, in Study group 3(20%) out of 15 patients had a recurrence, and also in Control group 3(21.4%) out of 14 patients had a recurrence of pneumothorax.(p-value (0.44) insignificant).*

Conclusion: *The effectiveness of blood pleurodesis in the cessation of an air leak is approaching to that of bleomycin pleurodesis with similar recurrence rates in both groups. However, the incidence of immediate post-procedure pain and fever*

is much higher in patients of bleomycin pleurodesis. Also compared to bleomycin, the autologous blood pleurodesis is very much cost effective. Our limited experience indicates that pleurodesis with self-donated blood is an easy-to-perform, painless, convenient, rapid and inexpensive procedure that is moderately effective in the short and medium term.

INTRODUCTION

Pneumothorax (fig. 1) is the free air in pleural space i.e. between visceral and parietal pleura.[1] Etiologically pneumothorax is divided into three types i.e. Primary spontaneous pneumothorax, secondary spontaneous pneumothorax and traumatic pneumothorax. Various treatment options[2] for spontaneous pneumothorax include simple clinical observation or needle aspiration for mild asymptomatic pneumothorax, intercostal tube drainage, intrapleural suction and chemical pleurodesis for severe symptomatic or recurrent pneumothorax. However open thoracotomy and pleurectomy remain the procedure with the lowest recurrence rate for difficult or recurrent pneumothoraces. Minimally invasive procedures, thoracoscopy & VATS are all effective alternative strategies.

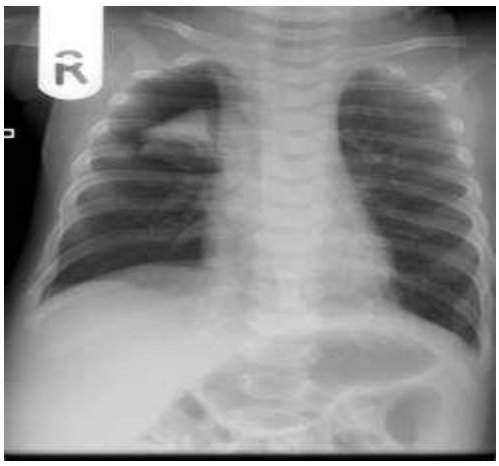

Fig 1: right pneumothorax with ipsilateral lung collapse

Pleurodesis (sclerotherapy), from the Greek pleura and designs (binding together), is intended to achieve a symphysis between parietal and visceral pleura, in order to prevent accumulation of either air (pneumothorax) or fluid (pleural effusion) in the pleural space. Depending upon the Type of inciting stimulus pleurodesis is of four type's i.e. mechanical pleurodesis, chemical pleurodesis, immunological stimuli and laser pleurodesis. A wide range of sclerosing agents has been used to achieve chemical pleurodesis. These sclerosing agents can be grouped into three categories like conventional agents (talc, tetracycline derivatives, corynebacterium parvum and bleomycin), agents used in the past (nitrogen mustard, radioactive colloidal gold, quinacrine, 50% glucose solution, saline water and iodised oil) and newer/under evaluation agents (Iodopovidone, TGF β-2, silver nitrate, sodium hydroxide and autologous blood). An ideal sclerosing agent should be highly effective, safe & virtually free of adverse effects causing no or little pain/discomfort, inexpensive, widely available, easy to handle & administer, easy to sterilize with low indices of pleural infection, minimal & easily controlled morbidity and null mortality. However, none of the agents presently used meet all of these criteria and the search for such an agent is still on. Contraindications to pleurodesis include the patients who are candidates for lung transplantation, known hypersensitivity to the sclerosing agent, the presence of bronchopleural fistula and trapped lung (prevention of lung re-expansion by narrowing of the lobar bronchus due to an extrinsic or intrinsic tumor, or by the encapsulated visceral pleura).

AIMS & OBJECTIVES

Our objectives in this study were to evaluate the efficacy of autologous blood pleurodesis in the management of recurrent primary spontaneous pneumothorax and to compare the efficiency, side effects, cost and complications of autologous blood pleurodesis vis a vis bleomycin pleurodesis.

MATERIAL & MATERIALS

We carried out the study at the Department of Cardiovascular & Thoracic Surgery, SKIMS Srinagar Kashmir from May 2010 to Nov 2012. It was a prospective randomised comparative evaluation of autologous blood & bleomycin pleurodesis involving patients of recurrent primary spontaneous pneumothorax. We had a total of 30 patients in our Study. The study group comprised of 16 patients who received intrapleural autologous blood @ 1ml/kg body wt.[3,4] Control group comprised of 14 patients who received intrapleural bleomycin @1unit/kg body wt. On an average 54.7ml (1ml/kg body weight) of peripheral venous blood taken from the patient's arm vein was immediately injected into the pleural cavity via the chest tube & chest tube was clamped for 1-2hrs. In bleomycin pleurodesis at 15 min after instillation of 20 ml of lidocaine 1%, about 55.7 units (1 iu/kg body wt.) of bleomycin in 100 ml of normal saline were instilled into the pleural cavity via the chest tube and the tube clamped for 1-2hrs. Patients were followed for a period of 1-22 months with an average follow-up of 11.77 months. Patients of all age groups and both sexes who had radiologically confirmed the primary type of significant pneumothorax with lungs having the ability of re-expansion and gave a valid consent for the procedure were included in the study. Patients who did not consent or having secondary & traumatic type of pneumothorax, bronchopleural fistula or with an active source of infection or with recent history of septicaemia and patients on corticosteroids or immunosuppressants were excluded from study.

RESULTS: In Study group 14 (87.5%) patients were males and 2 (12.5%) patients were females. In Control group 12 (85.7%) patients were males and 2 (14.3%) patients were females. The average age of patients in Study group was 37.69yrs, while the average age of patients in Control group was 29.93yrs. One (6.3%) patient in the Study group had a failure of cessation of air leak after blood patch pleurodesis. Hence the success rate of cessation of an air leak in Control group was 100% while as it is 93.8% in Study group. The majority of patients from both Study [9 (60%)] as well as Control groups [7(50%)] had a cessation of air leak within 24hrs. However, 4 (26.7%) patients from Study group & 6 patients from Control group attained cessation of air leak within 48hrs. In Study group 3(18.8%) patients had post-procedure pain; while as in Control group, 13(92.9%) patients had post-procedure pain. (p-value ≤0.0001, grossly significant difference). Also, the type of pain in blood patch pleurodesis group (Study group) was only dull aching type while as in bleomycin pleurodesis group (Control group) the post-procedure pain used to be severe & sometimes associated with nausea. *In the Study group, none of the patients out of 16 had a post-procedure fever, while as in Control group 6 (42.9%) patients had a post-procedure fever. (p-value ≤0.0001).* Per patient average cost of the procedure in Study group was Rs 53.13, while the average cost of procedure per patient in Control group was Rs 1925.00 (p-value ≤0.0001; grossly significant difference). After an average of 11.77months, follow-up in Study group 3(20%) patients had a recurrence, while as in Control group also 3(21.4%) patients had a recurrence. None of the patients from Study as well as Control groups had post-procedure empyema, anaphylaxis, tube clogging, tension pneumothorax or progressive respiratory failure.

DISCUSSION: It was Robinson [(5)] who first introduced blood pleurodesis for chronic spontaneous pneumothorax, followed by Dumire[(6)] some years later, who applied it for a persistent pulmonary air leak. Although fever, pleural effusion, and empyema have been reported with this method, there are several other reports that accent it as the safest method of pleurodesis in persistent air leak after pulmonary surgery and spontaneous pneumothorax. To our knowledge, ours is the first comparative prospective randomized trial to examine which agent i.e. bleomycin or autologous blood pleurodesis, is superior in terms of effectiveness, safety, complications, and cost.

We had 16 patients in Study group and 14 patients in Control group. Our group strength was consistent with previous studies in the literature. In the first study carried on autologous blood patch pleurodesis for the treatment of persistent air leak in patients with spontaneous pneumothorax, Robinson et al[(5)] (1987) took 25 patients. However, Dumire R. et al[(6)] reported only 2 cases of successful treatment with an autologous "blood patch" pleurodesis for a prolonged air leak. Alaa Gafar MD.[(7)] carried out a comparative study between autologous blood patch pleurodesis in 13 patients versus talc slurry pleurodesis in 16 patients with a persistent air leak. Ufuk Cobanoglu. et al[(8)] (2009) carried out Pleurodesis in 50 patients with persistent air leak resulting from primary and secondary spontaneous pneumothorax; using autologous blood in 20 patients, talc powder in 19 patients and tetracycline in 11 patients. However, in one of the largest series Manouchehr Aghajanzadeh, et al[(9)] (2009) performed autologous blood pleurodesis in 38 patients with a persistent air leak.

For pleurodesis in Study group, we used autologous blood (1ml/kg body wt.) taken from patients right or left antecubital vein. Heparin was not added and no sedative or analgesic was administered. The average quantity of blood used per patient was 54.69ml, with SD of 7.29. Minimum quantity of blood used in Study group was 45ml and maximum quantity was 70ml. The volume of blood used for pleurodesis is a controversial point among different authors. Ufuk Cobanoglu, et al[(8)] in 20 patients used a sample of 50 ml of blood (max. 1 ml/kg) taken from the patient and was injected immediately. Many perform the pleurodesis by instillation of 50 ml of blood,[(3,4,5)] while others use 120 ml[(10)] or 150 ml, thus introducing a completely different approach. We preferred the injection of autologous blood only once because minimal exposure of the patients to all infection risks resulting from tubing manipulations was our major concern. Robinson et al[(5)] in a series of 25 patients for the treatment of persistent air leak in patients with spontaneous pneumothorax used 1–3 injections of 50ml of blood in order to seal the air leak. Blanco Blanco I. et al[(11)] used bedside installations of 50 ml of autologous blood in all 14 adult patients with spontaneous pneumothorax except 1, who required a total volume of 120 ml. Athanassiadi K et al[(12)] carried out autologous blood pleurodesis with 60ml in 20 patients of persistent air leak (> 7 days). Ozpolat B.[(13)] (2010) evaluated the efficacy of autologous blood patch pleurodesis using venous blood @2mL/kg for a prolonged air leak.

For pleurodesis in Control group, we used bleomycin @1IU/kg body wt. The average quantity of bleomycin used per patient for pleurodesis in Control group was 55.71 IU, with SD of 6.901. Minimum quantity of bleomycin used in Control group was 45IU and maximum quantity was 65IU. There is not sufficient data in the literature that suggests the dosage of bleomycin be used for pleurodesis in pneumothorax. However E. Martínez-Moragón. et al[(14)] performed a randomized study of tetracycline (1.5 g) versus bleomycin (60 iu) pleurodesis in malignant pleural effusions. Taking lead from this and other studies[(15,16)] we decided to use almost the same dose of bleomycin (@1 IU/kg) for pneumothorax as was used for pleurodesis in patients with malignant pleural effusion.

One patient (6.3%) in our Study group had a failure of cessation of air leak. Hence the success rate of cessation of an air leak in Control group was 100% while as it was 93.8% in Study group. However referring to the p-value (0.178) the difference is not statistically significant. Our results of blood patch pleurodesis were comparable to many studies. Robinson et al,[(5)] who first introduced blood pleurodesis for chronic spontaneous pneumothorax and reported an 85% success rate in a series of 25 patients. Blanco Blanco I et al[(11)] using autologous blood in 14 patients with spontaneous pneumothorax achieved closure of the fistula in 13 (92%) patients. Other studies[(6,9,12,13,17)] showed similar results. Alaa Gafar MD.[(7)] carried out a comparative study between autologous blood patch pleurodesis verses talc slurry pleurodesis in persistent air leak complicating lung resection, decortication or spontaneous pneumothorax with success rate of 92% with blood, 87% of talc slurry. Loic lang-lazdunski[(3)] studied 11 patients with persistent air leak following pulmonary resection, treated by autologous blood patch pleurodesis and reported a 100% success rate. Ufuk Cobanoglu. et al[(8)] carried out pleurodesis in 50 patients with persistent air leak resulting from primary and secondary spontaneous pneumothorax; using autologous blood in 20 (40.0%) patients, talc powder in 19 (38.0%) patients and tetracycline in 11 (22.0%) patients. They obtained a success rate of 75.0% using autologous blood, 84.2% using talc powder and 63.6% using

tetracycline. H. Ohta. et al[18] (2012) carried a retrospective review out of the medical records to compare chemical pleurodesis (11 patients) and autologous "blood patch" pleurodesis (9 patients) to evaluate the efficacy and safety of autologous "blood patch" pleurodesis for secondary spontaneous pneumothorax in severe underlying lung disease. The success rate (resolution of pneumothorax with no subsequent air leak or pneumothorax enlargement) was significantly better in autologous "blood patch" pleurodesis than chemical pleurodesis (100% vs. 54.5%; $p < 0.038$). Ali Asghar Alavi. et al[16] (2011) compare the belomycin with povidone-iodine pleurodesis on 39 patients presenting with symptomatic malignant pleural effusion. Authors reported complete response in 79% of belomycin group and 75% of the povidone-iodine group.

The majority of patients in the study from both Study [9 (60%)] as well as Control groups [7(50%)] had a resolution of pneumothorax within 24hrs. However, 4(26.7%) patients from Study group & 6 patients from Control group attained cessation of air leak within 48hrs. But overall there was not statistically significant difference in air leak cessation time between Study and Control groups, as p-value is 0.357. Our observation is consistent with most of the previous studies.[10,13]

Fever and pain were the only side-effects of pleurodesis in both groups. In Study group 3(18.8%) patients had post-procedure pain; while as in Control group 13(92.9%) patients had post-procedure pain (p-value=0.0001). Also, the type of pain Study group was only dull aching type while as in Control group the post-procedure pain used to be severe & sometimes associated with nausea. Our results of blood patch and bleomycin pleurodesis were comparable to many studies in the literature. Alaa Gafar MD.[7] carried out a comparative study between autologous blood patch pleurodesis verses talc slurry pleurodesis in persistent air leak & reported that chest pain occurred in 15% in case of blood and in 56% patients receiving talc slurry. Blanco Blanco I. et al[11] using autologous blood in 14 patients with spontaneous pneumothorax reported excellent tolerance, with no pain reported in any patient. Manouchehr Aghajanzadeh, et al[9] performed autologous blood pleurodesis in 38 patients with secondary spontaneous pneumothorax and reported that no patient experienced any pain.

In the Study group, none of the patients out of 16 had a post-procedure fever, while as in Control group 6(42.9%) patients had a post-procedure fever (p-value ≤ 0.0001). Manouchehr Aghajanzadeh, et al[9] performed autologous blood pleurodesis in 38 patients with secondary spontaneous pneumothorax and reported that no patient had a fever. Loic lang-lazdunski[3] studied 11 patients with persistent air leak following pulmonary resection, treated by autologous blood patch pleurodesis and reported that two patients developed a fever. E. Martínez-Moragón. et al[14] (1997) performed a randomized study of tetracycline versus bleomycin Pleurodesis in malignant pleural effusions. Authors reported fever was a more common complication in bleomycin-treated patients (p=0.024).

None of the patients from Study as well as Control groups had post-procedure empyema, tension pneumothorax, anaphylaxis, chest tube clogging or progressive respiratory failure. Fever, pleural effusion, and empyema are reported with autologous blood pleurodesis. Robinson[5] found pleural infection in 4% of patients treated with autologous blood in his study. Blanco Blanco I. et al[11] using autologous blood in 14 patients with spontaneous pneumothorax reported excellent tolerance except for one case of infectious pleural effusion of unknown etiology which was treated by evacuation and antibiotics. Ufuk Cobanoglu. et al[8] reported empyema after tetracycline pleurodesis in one case and in one patient after blood pleurodesis. We preferred to use a single injection of about 50 ml of blood to prevent the accumulation of contaminated bacteria necessary for infecting the pleural space. Strict aseptic conditions were accomplished during the procedures. Strict adhesion to contra-indications and a single injection of a limited volume of blood (50ml) may minimize the risk of serious infectious complication such as empyema. One potential complication of the blood patch pleurodesis technique is tension pneumothorax due to blood clotting in the chest tube. We didn't observe this complication in our study. We flushed the tube with 10ml of normal saline in all patients to prevent this complication. Similar results were reported by Manouchehr Aghajanzadeh, et al[9] (2009).

Per patient average cost of the procedure in Study group was Rs53.13 (<1dollar) with SD of 12.30, while the average cost of procedure per patient in Control group was Rs1925.00 (about 30dollar), with SD of 233.13. Referring to the p-value (≤ 0.0001) as compared to the bleomycin pleurodesis, autologous blood pleurodesis is very much cost effective.

One patient from Study group failed to attain cessation of air leak, so out of 16 patients in Study group, only 15 were followed on long term basis. And we followed the patients for a period of 1-22 months with an average follow-up of 11.766 months. In Study group 3(20%) patients had recurrence, while as in Control group 3(21.4%) patients had recurrence (p-value =0.44). Blanco Blanco I et al[11] showed recurrence rate of 71.4%. Cagirici U. et al[17] and Athanassiadi K. et al[12] after successful autologous blood pleurodesis observed no recurrences. Alaa Gafar MD.[7] (2009) reported recurrence rate of 8% in blood pleurodesis group and 13% in talc slurry group.

CONCLUSION

Our limited experience indicates that pleurodesis with autologous blood is an easy-to-perform, painless, convenient, rapid and inexpensive procedure that is moderately effective in the short and medium term with no need of analgesia nor sedation during pleurodesis. However strict asepsis is mandatory to avoid infectious complications. Main drawbacks of autologous blood pleurodesis are the lack of consensus on certain technical considerations, such as the optimum amount of blood to be installed, the number of installations to perform and if multiple installations are carried out, what should be the interval between them.

Last words: Further randomized clinical studies are needed to confirm or discount our results and to determine the place this technique (autologous blood pleurodesis) may have in the clinical management of primary recurrent spontaneous pneumothorax.

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