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Original Article

Comparison between pleurodesis results by 50% glucose solution, versus Bleomycin pleurodesis in patients with malignant pleural effusion

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Abstract: Background: Following parapneumonic effusions, malignant pleural effusions (MPEs) stand as the second most common cause of exudative pleural effusions. These effusions typically remain unresponsive to systemic chemotherapy, necessitating novel therapeutic approaches. This study aims to ascertain the effectiveness of intrapleural injection with a 50% glucose solution and to compare it with intrapleural injection of Bleomycin sulfate in treating malignant pleural effusion. Methods: This prospective, double-blind, randomized clinical trial was conducted at Al-Zahra Hospital in Isfahan. The study protocol gained approval from the Iranian Registry of Clinical Trials (IRCT code: IRCT20201013049017N1) (https://en.irct.ir/trial/52739). The study population encompassed patients with malignant pleural effusion. Sampling occurred through a census approach from October 2019 to March 2020. The first group received a pleurodesis solution containing 12.5 cc of 2% lidocaine with Bleomycin, while the second group received a solution comprising 200 cc of 50% glucose solution (10 grams of glucose) and 12.5 ml of 2% lidocaine, within the same volume. These solutions were injected into the pleural space via the chest tube. Results: The complete response rate to treatment three months post-injection was 71.9% in the Bleomycin sulfate group and 65.6% in the 50% dextrose group. However, the difference between the two groups did not achieve statistical significance (P = 0.689). The incidence of post-injection fever and pain intensity exhibited comparability in both groups. Conclusion: The treatment involving a combination of 50% glucose solution with Bleomycin for pleurodesis in patients with malignant pleural effusion demonstrated outcomes akin to other treatment options.

Keywords: Bleomycin sulfate, malignant pleural effusion, glucose solution

Introduction

Malignant pleural effusion (MPE) constitutes a frequent complication of malignancies, correlating with a considerable mortality rate. Individuals afflicted with MPE encounter a decline in their quality of life, predominantly attributed to dyspnea. The intensity of dyspnea can escalate to a juncture where patients are incapacitated in performing fundamental self-care tasks autonomously, apprehensive of respiratory distress [1]. MPE arises from factors such as lymphatic artery and node invasion, direct malignant infiltration of the pleura, and biochemical mechanisms that heighten vascular permeability due to vasoactive agents generated by tumor cells. Usual indications of MPE encompass cough, dyspnea, lung heaviness, and chest pain. MPE is marked by distinct laboratory discoveries and clinical traits. Laboratory findings entail elevated protein levels, heightened lactate dehydrogenase (LDH), and the presence of tumor markers like carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) within the pleural fluid. Common clinical features observed in MPE patients encompass dyspnea (breathlessness), chest pain, cough, weight loss, and fatigue. Nevertheless, these findings and features are not exclusively exclusive to MPE and might manifest in other pleural effusions or medical conditions. The conclusive diagnosis of MPE hinges on the identification of malignant cells through cytological scrutiny of the pleural fluid [2].

Treatment options for Malignant Pleural Effusion (MPE) predominantly focus on palliative measures aimed at alleviating symptoms and enhancing quality of life. Swift diagnosis and treatment play a pivotal role in MPE management. Diverse therapeutic strategies have been employed to combat the notable recurrence rate of MPE. These encompass Pleurodesis employing diverse agents, placement of intrapleural catheters, repetitive thoracentesis, and foremost among them, Pleurodesis, which stands as the most frequently utilized approach. The principal therapeutic technique involves tube thoracotomy accompanied by Pleurodesis. A chest tube is commonly introduced as part of the Pleurodesis procedure [3, 4]. The diagnostic criteria for pleural fluid cytology in MPE diagnosis involve analyzing fluid acquired from a pleural tap to detect the presence of malignant cells. The central criterion revolves around the identification of malignant cells through cytological scrutiny. In certain instances, atypical or suspicious cells might manifest, warranting supplementary tests for confirmation [3].

When conducting Pleurodesis, particularly when utilizing talc, the use of a large-bore tube is recommended. The quest for an optimal sclerosing agent remains ongoing, necessitating the fulfillment of specific criteria, including safety, efficacy, affordability, accessibility, and patient tolerance without significant life-threatening adverse effects like acute respiratory distress syndrome. Each pleurodesis agent carries its own merits and drawbacks. Instances of these agents encompass talc, tetracycline, doxycycline, bleomycin, silver nitrate (SN), and povidone-iodine. The selection of an agent hinges on variables such as availability, cost, patient attributes, and the resources accessible at each treatment center [5, 6]. Bleomycin, an antibiotic agent, is frequently employed for pleurodesis in certain countries, such as Iran [7]. In a study, all cases attained cessation of air leakage, and no treatment-related deaths were recorded. The overall survival rates at 1, 2, and 3 years post-treatment stood at 83%, 74%, and 49%, respectively. Recurrence post-treatment emerged in six cases, four of which underwent pleurodesis using a 50% glucose solution. All instances of recurrence manifested within three months following pleurodesis. The efficacy and safety of pleurodesis with a 50% glucose solution have been established for pneumothorax patients. This procedure is applicable to both recurrent pneumothorax scenarios and patients encountering their initial pneumothorax episode with foreseen prolonged air leakage [8].

Hypertonic solution pleurotomy is a procedure employed for addressing secondary pneumothorax or chylothorax. It involves introducing a concentrated solution into the pleural space to induce pleurodesis, thereby preventing the accumulation of fluid or air. This procedure facilitates the adhesion between pleural layers, effectively sealing air leaks in pneumothorax and closing lymphatic leaks in chylothorax. Hypertonic solution pleurotomy has exhibited efficacy across various studies. The solution's provocation of irritation leads to inflammation and scarring, fostering the fusion of pleural layers. This mechanism aids in averting subsequent air or fluid buildup, offering a potential avenue for treating these conditions [4, 7].

Several studies have delved into utilizing Pleurodesis with a 20% glucose solution for patients grappling with spontaneous pneumothorax. These investigations have showcased that the 20% dextrose solution can proficiently curtail recurrence rates, aligning with alternative treatment modalities featured in preceding studies [9, 10]. However, the effectiveness and potential side effects of Pleurodesis via glucose solution have not been extensively explored in large-scale clinical trials. While reports have surfaced highlighting the efficacy of pleurodesis with hypertonic glucose solutions for conditions such as secondary pneumothorax or chylothorax [11], this represents the inaugural account comparing the outcomes of Pleurodesis treatment involving a 50% glucose solution versus Pleurodesis with bleomycin. Consequently, further research is imperative to appraise the effectiveness and plausible side effects of Pleurodesis utilizing glucose solutions, particularly in relation to other therapeutic alternatives.

Methods and material

Study design

The statistical population for this study consisted of patients with pleural effusion who visited the emergency department of Al-Zahra Hospital in Isfahan. The study was conducted from

October 2019 to March 2020. It was designed as a double-blind clinical trial, where informed consent was obtained from the participants. Comprehensive clinical history, physical examination, and routine tests such as complete blood count, kidney and thyroid function tests, and chest X-ray were performed to evaluate the location and severity of the pleural effusion. To assess the patients' condition during the pleurodesis surgery, additional tests including complete blood count, thyroid function tests (thyroid-stimulating hormone and thyroxine), and kidney function tests (blood creatinine and urea nitrogen levels) were conducted, particularly for patients undergoing chemotherapy.

Inclusion and exclusion criteria

The inclusion criteria for the study included a diagnosis of MPE based on pleural fluid cytology, symptomatic and recurrent disease, no history of Bleomycin allergy, and informed consent. Exclusion criteria encompassed a history of lung diseases such as COPD, patient dissatisfaction to continue the study, patient death before completion, Bleomycin allergy, previous pleurodesis history, recent systemic chemotherapy within the past two months, and malignant effusions caused by mesothelioma. Written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Helsinki Declaration.

Ethical and clinical trial approval

The study protocol was approved by the Research Ethics Committees of the School of Medicine - Isfahan University of Medical Sciences, with the code IR.MUI.MED.REC.1398.712, on March 11, 2020. The study was also registered with the Iranian Registry of Clinical Trials (IRCT code: IRCT20201013049017N1) (https://en.irct.ir/trial/52739).

Participants

The samples were selected using convenient nonprobability sampling and 64 patients randomly assigned to two groups of 32 each.

Interventions

In this study, all participants had previously undergone initial treatment for Malignant Pleural Effusion (MPE), which entailed the insertion of a chest tube. Throughout the study duration, both therapists and patients were kept unaware of the administered treatment, rendering it a double-blind trial. Within the first group, a pleurodesis solution comprising 12.5 cc of 2% lidocaine with bleomycin (60 units of bleomycin dissolved in 150 cc of sterile normal saline solution) was introduced through the chest tube and then clamped for a duration of 2 hours. In the second group, a solution composed of 200 cc of 50% glucose solution and 12.5 ml of 2% lidocaine was instilled into the pleural cavity via the thoracic tube positioned between the ribs, maintaining the same volume. The thoracic tube was subsequently clamped for 2 hours.

Both groups were instructed to alter their positions every 15 minutes during the initial 2-hour period. Following this, all patients were connected to an Emerson device with negative pressure for 24 hours subsequent to the opening of the pleural effusion clamp. If the daily drainage fell below 150 to 200 cc post-pleurodesis, a chest X-ray (CXR) was conducted before the removal of the chest tube.

Data gathering

In the control group, patients received follow-up at outpatient clinics for a span of three months following the removal of the chest tube. During these visits, a comprehensive assessment was conducted for any clinical indications and symptoms linked to pleural effusion, encompassing shortness of breath, cough, chest pain, and lung sounds. Initial months after pleurodesis saw the performance of chest X-rays, contributing to an overall evaluation of patients' recovery progress. In this study, the Visual Analog Scale (VAS) was employed to gauge the patients' pain levels. The VAS entails a self-report scale utilized for measuring pain intensity. It takes the form of a 10 cm horizontal line, graded from 0 to 10. Additionally, facial pain depictions, comprising five emotive images, are incorporated. A VAS score of zero signifies the absence of pain symptoms, while a score of 10 corresponds to the utmost severity of the intended symptoms. The VAS serves as a straightforward tool for assessing the magnitude of a patient's pain, and its completion is easily managed by the patients themselves.

Table 1. Descriptive analysis of quantitative variables based on material type used for pleurodesis

Variable	Dextrose (Mean ± SD)	Bleomycin (Mean ± SD)	*P*-value*
Age	53.96±12.11	50.06±12.92	
Time required to hold the chest tube	3.34±0.48	3.28±0.52	

*Using independent T-test.

Table 2. Chest tube retention time and duration time of hospitalization in hospital based on type of material used in pleurodesis

Variable	Mann-Whitney U	*P*-value*
Time required to hold the chest tube	458.000	0.230
Hospitalization time	428.000	0.212
Pain after injection	443.000	0.215

*Using Mann-Whitney test.

Statistical analysis

The collected data was entered into SPSS software (version 24) for analysis. The Mann-Whitney U test was utilized to evaluate the results related to drainage volume. Fisher's exact test, chi-square test, and independent T-test were employed to analyze the remaining results. A statistical significance level of less than 0.05 ($P < 0.05$) was considered as the threshold for determining statistical significance.

Results

Study population

A total of 64 patients were recruited from Educational and Medical centers of Isfahan University of Medical Sciences from September 2019 to February 2020. The mean ± SD age of groups I and II were 53.96±12.11, and 50.06±12.92. 38 cases were males (59.4% male of Dextrose group, 62.5% male of Bleomycin group), 26 were females (43.8% female of Dextrose group, 37.5% male of Bleomycin group).

Surgery information

The chest tube retention time for both groups was 2-4 days. The treatment failure rates were 29% in the Dextrose group (Group 2) and 35% in the Bleomycin group (Group 1). The recurrence rate was 65% in the Dextrose group and 71% in the Bleomycin group, with no statistically significant difference between the two groups. **Table 1** displays the descriptive analysis of quantitative variables, including age, chest tube retention time, hospitalization time after drug injection, and chest pain after a few hours of long-term injection. The mean chest tube retention time in the Bleomycin group was significantly higher compared to the Dextrose group. However, for variables such as age, duration of hospitalization after drug injection, and chest pain after a few hours of injection, the prolongation observed in the Bleomycin group did not demonstrate a significant difference, possibly due to the smaller sample size of 32 individuals. Regarding side effects, no fever was detected, and chest pain was only present at the time of injection. The pain subsided within a few hours and did not persist [12].

Chest tube retention time

Based on the Mann-Whitney test outcomes, which yielded a value of 458 and a significance value (Sig) of 0.230, it can be deduced that, at a significance level of 0.05, the hypothesis of equivalence in chest tube retention time is upheld. This suggests the absence of a notable distinction between the two groups. Likewise, the Mann-Whitney test findings, displaying a value of 428 and a significance value (Sig) of 0.212, lead to the conclusion that, at a significance level of 0.05, the presumption of comparability in hospitalization duration subsequent to drug administration is validated, implying no marked contrast between the two groups. Moreover, as depicted in **Table 2**, the t-value (-1.486) alongside the significance value (0.143) indicates that despite the lower secretion volume in the dextrose drug group compared to the bleomycin group, this variance lacks statistical significance at the 0.05 significance level.

Side effects

According to the results presented in **Table 3**, it is observed that the type of drug agent used did

Table 3. The created side effects based on type of material used in pleurodesis

Variable	Dextrose N (%)	Bleomycin N (%)	*P*-value*
No side effects	21 (65.6)	25 (78.1)	0.479
Cough	2 (6.3)	2 (6.3)	
Shortness of breath	2 (6.3)	2 (6.3)	
Increase blood glucose	3 (9.4)	0 (0)	
Increased fever (37.5°C and 38.3°C)	4 (12.5)	3 (9.4)	
No recurrence of the disease	21 (65.6)	23 (71.9)	
Early failure rate	4 (12.5)	2 (6.3)	
Late failure rate	7 (21.9)	7 (21.9)	

*Using Chi Square test.

Table 4. Comparison of mean and standard deviation on type of material used in pleurodesis discharge after medication

Variable	Dextrose (Mean ± SD)	Bleomycin (Mean ± SD)	*P*-value*
Discharge after medication	115.12±42.05	131.04±43.73	0.899

*Using independent T-test.

not have a significant effect on the occurrence of side effects. Only in one case, there was a significant difference in the increase of hyperglycemia, which can be attributed to the presence of glucose in the dextrose drug. Based on the Chi-square value of 3.491 and a significance value of 0.479, it can be concluded that there is no significant difference between the two groups in terms of the number of complications after using the two drugs.

Frequency of recurrence or non-recurrence

Based on the results presented in **Table 4**, it can be observed that the type of drug used does not have a significant effect on the frequency of recurrence or non-recurrence of the disease during the follow-up period after the 3 months. The frequencies of recurrence and non-recurrence are reported to be similar between the two groups. Early failure was defined as a discharge of more than 200 cc per day (3 cc/kg/day) for 5 days, while late failure after 3 months was defined as fluid accumulation and symptomatic patients during this period. Considering the Chi-square value of 0.160 and a significance value of 0.689, as well as the Fisher's Exact Test value of 1.00, it can be concluded that there is no significant difference between the two groups in terms of the number of recurrences or non-recurrence of the disease after using the two drugs.

The results of the study indicate that the time of discharge after drug injection is not significantly different between the two groups. Furthermore, there is no significant difference in the incidence of complications following the injection of both drugs or in terms of long-term hospitalization.

Discussion

Malignant pleural effusion (MPE) stands as a prevalent complication of malignancies, often culminating in progressive dyspnea that significantly disrupts patients' daily activities. The recurrence of MPE and its associated poor 6-month survival rates contribute to heightened patient distress. Pleurodesis has gained widespread acceptance as a palliative intervention for MPE [13]. Within this study, we undertook a comparison between the outcomes of pleurodesis utilizing a 50% glucose solution and pleurodesis involving Bleomycin. The selection of the 50% glucose solution was predicated on its cost-effectiveness, accessibility, simplicity, and established efficacy. We constrained the maximum dosage of dextrose injection, while the Bleomycin injection rate was lower than that of dextrose. At the one-month follow-up juncture, 89% of patients attained a complete clinical response, signifying an absence of pleural space fluid retention, as indicated by chest X-rays. Notably, the success rate for Bleomycin treatment reached 90.6%, while the success rate for 50% glucose treatment stood at 87.5% within this study. Thus, pleurodesis employing a 50% glucose solution showcased efficacy on par with that of Bleomycin in individuals with MPE. However, the occurrence of a few cases marked by postoperative recurrence suggests the potential inadequacy of intra-pleural instillation of hypertonic glucose solution [14, 15].

Bleomycin, produced by Streptomyces verticillus, is an anticancer antibiotic commonly used in pleurodesis. Previous studies have shown a treatment success rate of around 70% in MPE

patients treated with Bleomycin sulfate [16]. Nikbakhsh et al. observed that 66% of MPE patients undergoing chemical pleurodesis with Bleomycin did not experience any complications [17]. Another study by Zakariyah et al. investigated the effectiveness and safety of intrapleural Bleomycin for pleurodesis and found that 70% of patients did not experience significant adverse effects, indicating positive results for MPE treatment [17].

While several studies have explored pleurodesis with a 50% glucose solution and Bleomycin, no major clinical trials have directly compared these two treatments. However, previous studies have demonstrated the feasibility and safety of pleurodesis using a 50% glucose solution. The mechanism of action is believed to involve osmotic damage and inflammation caused by the hypertonic glucose solution, which may lead to effective prophylaxis [12, 18]. Fujino et al. confirmed the efficacy, safety, and ease of pleurodesis with a 50% glucose solution, making it a viable treatment option [12]. Chen et al. successfully used a 50% glucose solution for the treatment of chylothorax [19]. The precise method of injecting high-concentration glucose solution is still unknown. One hypothesis suggests that hyperosmotic tension triggers pleural mesothelial cells and resident pleural macrophages to secrete growth factors into the pleural effusion [16]. However, differences in screening criteria, pleurodesis procedures, and success rate criteria across various trials make it challenging to assess and compare the success rates of different sclerosants used for MPE pleurodesis [20, 21].

The analysis outcomes suggest that the recurrence of pleural effusion following three months of pleurodesis surgery with a 50% glucose solution is akin to that observed with Bleomycin. This study holds a distinctiveness due to its focus on success rates assessed through radiological recurrence one-month post-pleurodesis, diverging from the conventional approach that spans the entire follow-up period, which could diverge based on malignancy prognosis and patient adherence to follow-up. Given the contrast in injection volumes-50 cc for Bleomycin and 200 cc for injectable dextrose-the drainage of dextrose concluded more swiftly compared to Bleomycin. The mean fluid quantity drained post-pleurodesis surgery using a 50% glucose solution surpassed that of pleurodesis with Bleomycin among MPE patients. Notably, no instances of dehydration necessitating supplemental infusion solution administration were encountered.

In some patients who received pleurodesis with a 50% glucose solution, the Chest Tube was kept in place for zero to 24 hours longer than in the case of Bleomycin. This was due to patients' lack of proper cooperation in changing their positions, leading to inadequate drainage. Similarly, in some patients receiving pleurodesis with Bleomycin, the Chest Tube was kept in place for up to 1 day after injection, with a smaller number of patients requiring re-injection of Bleomycin. However, once the Chest Tube was removed, patients who were eligible for discharge showed signs of good health. This shortened hospital stay is beneficial for patients with limited life expectancy, provides support to the patients, and results in cost savings for the healthcare system. Goodman's study revealed that the decision to remove the drain after pleurodesis is predominantly based on drainage volume criteria and/or absence of fluid on chest radiograph, rather than on a specific time frame after chemical instillation [22].

In this study, complications related to pleurodesis were observed in 28% of patients. These side effects with 50% glucose were higher than Bleomycin. In all diabetic and non-diabetic patients, before and after injection at 1, 3, and 6 hours' glucose of patients were received and recorded with a glucometer and a small number most diabetics were involved with hyperglycemia above 350 in the first 1 hour, which was controlled with ten units of regular insulin. Only seven patients were involved to fever of 38 degrees at variable times in the first 24 hours, which was controlled by injection of 1 gram of Apotel. Before glucose injection, 50% of patients' fever was detected and recorded and if there was a patient's fever, it was controlled by the relevant service, and after 24 hours after the last patient's fever without taking Apotel, the injection protocol was started. None of the patients couldn't experience chest pain for a long time (i.e., more than three days) after the injection. Also, the amount of pain of Bleomycin injection was more than dextrose injection.

The most common side effects of traditional pleurodesis are pain and fever. Shortness of breath, cough, and fever were observed as side

effects of Bleomycin, but they were manageable and alleviated with antipyretics. The study by Fujino et al. reported a blood glucose level of 250 mg/dL or higher in 43.5% of patients one hour after the injection of 200 mL of a 50% glucose solution [13].

Various sclerosing agents, such as tetracycline and its equivalents, talc, Bleomycin, and OK-432 (Picibanil), have been used in clinical trials as alternatives to the 50% glucose solution for pleurodesis. These agents are generally considered safe and convenient. However, it is important to note that all of these agents, including the ones mentioned in this article, carry the risk of severe complications such as empyema, acute respiratory distress syndrome (ARDS), and anaphylactic reactions [23]. The choice of a specific pleurodesis agent is influenced by the practitioner and should take into consideration factors such as the patient's symptoms and comorbidities. Further research is needed to determine which sclerosing agents are most suitable for individual patients based on their specific characteristics and needs. The goal is to identify agents that provide effective pleurodesis while minimizing the risk of adverse events.

The limitations of this study include a small sample size of patients with pleural effusion from a single hospital, which may limit the generalizability of the findings. Nonprobability sampling introduces potential selection bias, and the lack of blinding for participants may impact outcome assessment. The absence of a control group hinders the ability to determine treatment effects and relative efficacy. The three-month follow-up period may not capture long-term outcomes, while subjective outcome measures and potential unmeasured confounding variables pose challenges in establishing causality. Being a single-center study, the findings may not be applicable to other settings. The study also lacks information on adverse events and could benefit from a more comprehensive statistical analysis.

Conclusions

Based on the results obtained from our study, revealing a lack of substantial disparity between the two therapeutic approaches, we advocate for the utilization of a 50% glucose solution as an alternative sclerosing agent in place of Bleomycin. Several factors underscore this recommendation. Primarily, when weighed against Bleomycin, the cost of the 50% glucose solution is notably lower, rendering it a more economically viable choice. Furthermore, existing literature has presented instances associating Bleomycin with mortality, thereby prompting concerns regarding its safety profile.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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