# Intrapleural Minocyclin Instillation Vs Bleomycin in Management of Recurrent Pleural effusion

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## ABSTRACT

**Background:** Chemical pleurodesis was described to manage malignant pleural effusion, it is effective and associate with least morbidity and can be carried out as an outpatient procedure.

**Objectives:** To discuss uses of minocyclin as seclerosant agent to induce chemical pleurodesis in comparison to bleomycin from other studies regarding success rate, cost, side effects and acceptability.

**Methods:** A prospective study is carried out from February 2014 till April 2017 on 45 patients presented with recurrent pleural effusion, malignant in 29 patients (64.4%) and non malignant in 16 patients (35.6%) on an outpatient base.

**Results:** After 2-9 months follow up period (mean ±SD is 5 ±1.2). Intrapleural minocyclin instillation was successful in 39 patients (86.7%) as all over (successful result was reported when there was no recurrence of effusion within 30 days post instillation), no mortality reported. Reported side effects of minocyclin like chest pain in seven patients (15.5%), nausea and vomiting in five patients (11%), elevated serum bilirubin in two patients (4.4%). Recurrent effusion in six patients (13.3%).

**Conclusion:** Chemical pleurodesis using minocyclin instillation is safe and effective and can be carried out as an outpatient procedure. Minocyclin is one of the best materials available regarding lower side effect in comparison to bleomycin, cheap and acceptable by patients.

**Keywords: Recurrent pleural effusion, Chemical pleurodesis, Intrapleural minocyclin instillation.**

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Chemical pleurodesis was explained by Adler and Sayek in 1976 to manage malignant pleural effusion, it is effective and associate with least morbidity[1,2], and can be carried out as an outpatient management[1,3], nowadays it is used to manage other pleural conditions like non-malignant effusion, spontaneous pneumothorax and chylothorax[4-8].

Many articles support the use of sterile talc powder and minocyclin as the best two seclerosant agent with success rate of 91-92%[1,9] and 80%[9], consecutively. Sterile talc powder is not available in Iraq and nearby countries.

This study aimed to identify the seclerosant effect of minocyclin (in cases of recurrent malignant and non-malignant pleural effusion) to induce chemical pleurodesis in comparison to bleomycin from other studies regarding success, cost, side effects and acceptability from patients in cases of nonmalignant effusion.

## Methods

A prospective study is carried out from February 2014 till April 2017 on 45 patients presented with recurrent pleural effusion as an outpatient base, chest tube size (FG 28-34) was inserted under local infiltration of 10-15 ml of 2% Lidocaine to ensure evacuation of all pleural fluid and avoid the possibility of subsequent tube obstruction, and the patients were followed up till the daily amount of drained pleural fluid became less than 100 ml. Liver function tests were done for all to identify those with hepatic impairment as minocyclin is metabolized by liver.

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All patients were given slow intravenous metclopromide one ampoule as an anti-emetic and 500mg minocyclin was dissolved in 40 ml normal saline + 10 ml Lidocaine 2% and instilled into the pleural space and the chest tube was clamped, all patients were monitored for six hours post minocyclin instillation for the development of side effects, then they were discharged to home, all patients were educated to keep moving in bed 30 minute on each side and on back to spread the seclerosant agent on the whole surface of lung for 24 hours then the chest tube was declamped for another 48 hours to drain any remnant fluid which may be produced from the inflammatory effect of minocyclin then chest tube was removed.

## Results

Patients criterion involved in this study can be summarized in this table.

All patients were followed up for 2-9 months (mean+/- SD is 5 +/- 1.2), no mortality and the following immediate and long term adverse effects were reported, (Table 2).

Post instillation chest pain was started after 30 minutes, it was mild, self-limiting in most patients and only seven patients (15.5%) required pain killer. Nausea and vomiting were reported on day-one post instillation in five patients (11%) and was treated by Domperidon tab. three times daily and subsided within three days.

Simple allergic reactions like skin rash and itching were developed in four patients (8.8%) two hours post instillation and responded to 100mg intravenous Hydrocortisone. Elevated serum bilirubin was reported in two patients (4.4%), it was started on day-3 and it was self-limiting and subsided gradually within 10 days. Recurrent effusion was developed in six patients (13.3%) within one-month post instillation, all of them had malignant effusion and they refused to start chemotherapy, two of them (4.4%) were treated by another chest tube insertion while the other four refused more intervention and the author lost contact with them.

Intrapleural minocyclin was successful in 39 patients (86.7%) as all over (successful result was reported when there was no recurrent effusion within 30 days post instillation), and if we consider the cause of effusion, success rate was 79.3% in cases of malignant effusion (23 patients out of 29 patients got benefit) while 100% success was reported in nonmalignant conditions who complain from pleural effusion secondary to cardiac failure that fail to respond to full dose of drug therapy and repeated needle aspiration, table 3 summarize the difference between two study groups regarding their response to treatment, reported adverse effects, death and cure rate.

**Table 1: Patient criterion involved in this study.**

| | | No. | % |
|---|---|---|---|
| Gender | Male | 26 | 57.8 |
| | Female | 19 | 42.2 |
| Side | Left | 21 | 46.7 |
| | Right | 20 | 44.4 |
| | Bilateral | 4 | 8.8 |
| Cause of pleural effusion Malignant | Secondary to bronchogenic, breast, GIT, GUT tumors, lymphoma | 29 | 64.4 |
| Non-Malignant | Secondary to heart failure not responding to drugs + aspiration | 16 | 35.6 |

**Table-2: Reported adverse effects from this study**.

| Adverse effect | Management | No. | % |
|---|---|---|---|
| Post instillation pain | Simple analgesia | 7 | 15.5 |
| Post instillation nausea & vomiting | Start on day-1 post instillation, subside within 3 days using anti-emetics | 5 | 11 |
| Simple allergy | 100 mg hydrocortisone intravenous | 4 | 8.8 |
| Elevated serum bilirubin to 6 mg/dl | Start on day- 3 post instillation and subside gradually within 10 days | 2 | 4.4 |
| Recurrent effusion within 30 days | Developed in patients with malignant effusion who refuse chemotherapy | 6 | 13.3 |

**Table 3: Involved study groups.**

| Outcome of patients (n= 45) | Malignant (n=29) | | Benign (n=16) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Total Patient number = 45 | 29 | 64.4 | 16 | 35.6 |
| Post instillation pain | 5 | 11.1 | 2 | 4.4 |
| Simple allergy | 2 | 4.4 | 2 | 4.4 |
| Elevated serum bilirubin level | 1 | 2.2 | 1 | 2.2 |
| Recurrent effusion within 30 days post instillation | 6 | 13.3 | Zero | Zero |
| Cure (success rate) | 23 | 79.3 | 16 | 100 |
| Death rate during follow up period (mortality) | Zero | Zero | Zero | Zero |

## Discussion

Pleural effusion leads to dyspnea whose severity is directly related to its volume, aspiration and pleurodesis reduce thoracic cavity dimensions enabling respiratory muscles to work on best part of length-tension relation. In our country chest surgeons, physicians and oncologist trend to use intrapleural bleomycin instillation as seclerosant agent, the author also tend to do the same till 2014 when he received 63-year-old female with history of recurrent malignant right-sided pleural effusion with failure of three trials of intrapleural bleomycin instillation.

Malignant pleural effusion is found in cases of advanced malignancy with limited life expectancy (3-9 months), here reduction of days of hospital admission is important to provide psychological support for patient by family[10], in general Seclerosant must be cheap, safe, free of side effects, available, induce pleurodesis[5]

Pleurodesis using minocyclin is safe, effective and can be done as an outpatient procedure[1-3], it associated with least morbidity[1,3], and can be used to manage different conditions in which pleural adhesion is required[4-8], in this study we use it to mange recurrent accumulation of pleural fluid for both malignant and non malignant conditions (heart failure that is not responding to full dose of drug therapy and thoracocentesis).

Post instillation chest Pain occurred in 15.5% of patients in this study is better than other studies (pain incidence post bleomycin instillation 20%[1,9], minocyclin instillation 38.7%[4], 20%[11], 23%[12], tetracyclin instillation 30%[1,9]).

Nausea and vomiting occurred in 11% of patients, it was better than what was reported with bleomycin 23%[1], 25%[9], it was self limiting and subside within 3 days.

Elevated serum bilirubin level was reported in 4.4% of patients, other studies did not report such side effect except in one study as elevated level of ALT liver enzyme was reported in 1.7%[12], this require further assessment, it may be partly due to systemic absorption of minocyclin from the pleural cavity, effect of heart failure that is known as cardiac cirrhosis, or the effect of

systemic chemotherapy in malignant conditions

Other side effects were reported in other studies with bleomycin like fever, hemoptysis as 45% of it is absorbed systemically[1,9], also hemothorax was reported with minocyclin[11] but did not encounter in this study.

Pleurodesis was successful in 86.7% of cases in this study (79.7% in patients with malignant effusion and 100% in cases of non malignant effusion), this is better than what was reported in other studies (bleomycin success rate 72%[1], 61%[9], 64%[13], tetracyclin success rate 65%[1,9] in dose of 1-1.5 gram or 20mg/kg, minocyclin success rate 80%[13] here failed cases were managed by repeated instillation of minocyclin[3,13] 2-5 times which was associated with more pain). Some studies talked about different factors which may affect the success rate, these factors are:

1. Chest tube size: some studies encourage use of wide bore tube, others prefer small bore tubes, the size of chest tube must be enough to ensure total evacuation of pleural fluid and avoid subsequent obstruction[1,10].
2. Total lung expansion and complete drainage of pleural fluid with daily drain amount less than 100 ml prior to instillation associated with best result[1,11-12].
3. High fibrinolytic activity in the pleural space and the use of systemic Corticosteroids decrease effectiveness of pleurodesis[1,13].
4. Two studies[14,15] stated that malignant cells in the pleural layers will metabolize glucose in the pleural fluid to $CO_2$ and lactic acid reducing the PH of the pleural fluid and this is associated with poor survive and increase failure rate of pleurodesis, this requires further studies and analysis of pleural fluid PH and if it is proved we may think about increasing PH of pleural space by adding $NaHCO_3$ solution to the instilled mixture to raise the success rate.

Regarding price minocyclin is cheaper than bleomycin[1,9-10] and also more acceptable by patients who had nonmalignant effusion who become afraid from bleomycin as it is a chemotherapeutic agent.

Regarding the follow up period for the patients in this study which is 2-9 months which seems to be short this is because most of the patients in this study have malignant effusion which is an end-stage condition and they usually not remain alive for long time[10] while for the benign conditions it is enough to prove successfulness of our management.

In conclusion; Chemical pleurodesis using minocyclin instillation is safe and effective and can be carried out as an outpatient procedure. Minocyclin is one of the best materials available regarding lower side effect in comparison to bleomycin, cheap and acceptable by patients.

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