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# Comparison of the effects of doxycycline and povidone iodine in treatment of pleural effusion; an open label randomized clinical trial

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## Abstract

**Introduction:** Doxycycline is commonly used in treating pleural effusion. Povidone-iodine is another agent that has been used for treating pleural effusion.
**Objectives:** We aimed to compare the effects of doxycycline and povidone iodine in treating pleural effusion.
**Patients and Methods:** Forty-one patients with pleural effusion were enrolled and randomly divided into two groups. After insertion of the chest tube, pleurodesis was performed in the first group with povidone iodine and doxycycline in the second group. The chest tube clamped and opened one hour later. Then, connected to the suction through a double chest bottle. By decreasing of drainage to less than 50 cc per day, the chest tube was removed and the patients were evaluated three days later for pain, fever, empyema, recurrent effusion and long-term side effects at 7th, 30th, 60th and 90th day.
**Results:** The pain intensity was not different between two groups ($P > 0.05$). None of the patients had empyema and other side effects including hemothorax or pneumothorax were not seen too. In a 90-day follow-up, 47.6% of doxycycline recipients and 25% of povidone iodine recipients experienced the recurrent effusion ($P=0.133$). Three patients had fever (one on the first day and two on the second day) in the doxycycline group, while fever was not observed in povidone iodine recipients. The cost of treatment in both groups was almost the same.
**Conclusion:** Side effects of pleurodesis include pain, fever, recurrent effusion, cost in the two groups is almost equal, and both agents can be used as an effective drug for treating pleural effusion.
**Trial Registration:** The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT2015052918168N3; https://en.irct.ir/trial/16560, ethical code; IR.SEMUMS.REC.1394.91).

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## Introduction

The pleural cavity is composed of two pleura layers known as visceral and parietal layer. By imposing a negative pressure, it keeps the lungs expanded (1). There is only 0.1 to 0.2 mL/kg of fluid in, which allows the pleurae to slide effortlessly against each other during respiratory movements (1, 2).

The imbalance between the pleural fluid secretion and its reabsorption leads to pleural effusion (PE), which is observed as transudates or exudative forms. The main causes of transudative PE include congestive heart failure (CHF), hypoalbuminemia, fluid accumulation in the abdomen and renal failure, while the main causes of exudative PE are infections, malignancies, embolism and lung infarction, collagen vascular disease and trauma (1). Malignant effusion is the second leading cause of exudative effusion, which is common in lung carcinoma and breast cancers. The accumulation of pleural fluid in malignancies can be attributed to the infiltration of the pleurae by malignant cells and impaired fluid reabsorption.

**Key point**

The management of recurrent pleural effusion or pneumothorax has always been a cause for serious concern among chest physicians. Among the wide variety of agents that are available for pleurodesis, povidone iodine is now perhaps the most sought after agent as it is cheap, easily available, effective and safe.

Pleurodesis is proposed as one of the treatments for malignant effusion and recurrent non-malignant effusion (1, 2). In this method, a chemical that produces inflammation is injected into the pleural cavity. By doing this, the layers become irritated and attach together. Consequently, they prevent accumulation of the fluid and the effusion. Commonly used inflammatory

chemicals include cyclines (such as tetracycline), talc and bleomycin (3).

The success rate of these substances varies (91% for talc, 68% for cyclines (tetracycline, minocycline and doxycycline) and 52% for bleomycin), which indicates that talc outperforms other compounds (3).

Although talc is considered as a safe drug, it sometimes causes severe side effects such as respiratory failure and death in which talc crystals seen in broncho-alveolar fluid lavage. They were also observed in the lung and other organs during autopsy. Since 1958, more than 5000 pleurodesis have been reported and the prevalence of acute respiratory failure has been less than 1% (3).

Side effects of tetracycline are severe pain and fever. However, no fever was reported in talc pleurodesis. It should be pointed out that the fever starts 4 to 12 hours after the injection and continues until the next day (3).

The advantages of cyclines include appropriate, fast and uniform distribution throughout the pleural cavity without the need for patient to move. The cost of these drugs and compounds varies significantly. Talc is the cheapest and preferred compound that costs $1 per gram (3). Although talc is cheap and has a high success rate, it is associated with the risk of pulmonary edema and death or severe pain in the administration of tetracycline (3-5). It is also associated with high recurrence rate in cases of pleurodesis with bleomycin, as well as empyema, which is known commonly related to pleurodesis. More research is needed to achieve a more reliable and effective substance. In some studies, povidone-iodine (5-9) or a combination of drugs such as tetracycline and bleomycin are used for pleurodesis (4).

The efficacy and safety of povidone-iodine in pleurodesis in patients with malignant PE has been shown in some studies. Accordingly, the intensity of pain was lower and the prevalence of empyema was zero, compared to tetracycline (10).

## Objectives

In this study, the effect of povidone-iodine has been studied in terms of cost, success, and pain, prevalence of fever and empyema and recurrence, compared to doxycycline, a common chemical compound for the treatment of PE.

## Patients and Methods

### *Study design*

In a randomized clinical trial, 41 patients with PE (including recurrent or malignant cases) who were referred to Semnan Kosar hospital randomly were divided into two groups (Figure 1). The procedure was described for patients and they underwent pleurodesis after informed consent. After insertion of the chest tube into pleural

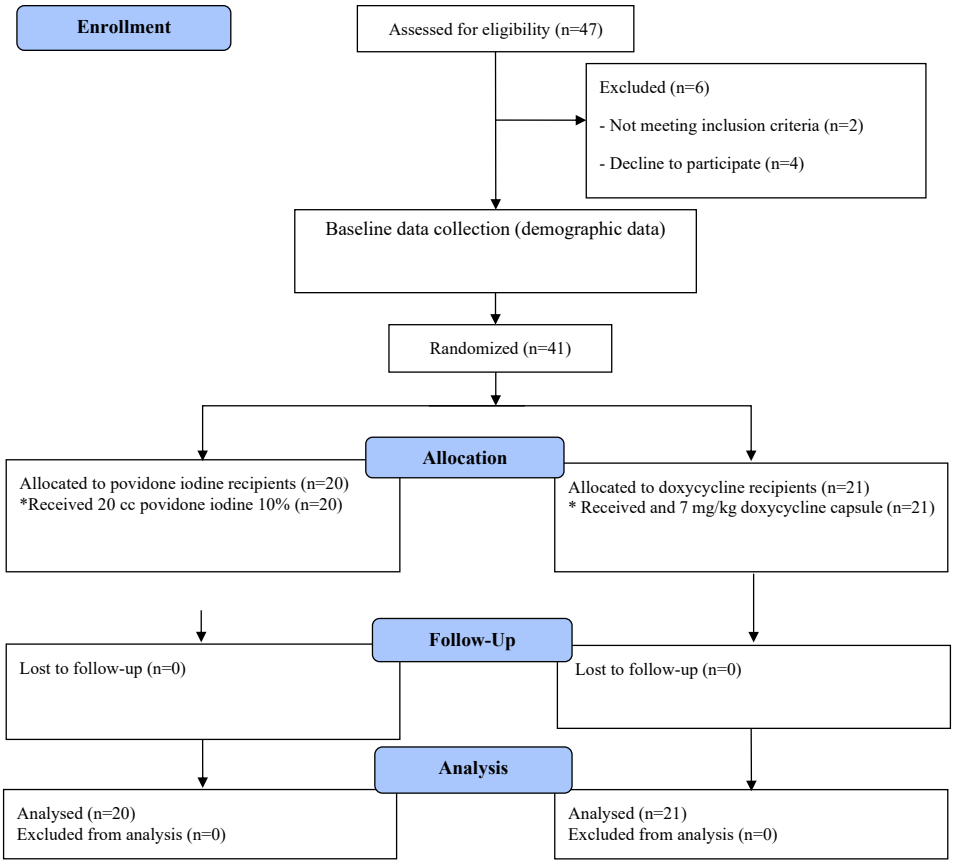


**Figure 1.** Flow diagram of the study.

cavity and drainage the fluid, a standard chest radiography was performed to ensure complete lung expansion, then pleurodesis was conducted with 20 cc povidone-iodine 10% in the first group and 7 mg/kg doxycycline capsule in the second group. Both agents were diluted with 50 cc of normal saline and 10 cc lidocaine 2% and injected into the pleural cavity through the chest tube. The chest tube then clamped and opened one hour later and the chest tube connected to the chest bottle. The system attached to a -10 cm of water suction machine for 48 to 72 hours to help with lung expansion.

Following the reduction of drainage from the chest tube to less than 50 mL/d, the chest tube was removed and the patients were evaluated during next three days for fever, pain, empyema and PE. The patients were also evaluated for recurrence on days 30$^{th}$, 60$^{th}$ and 90$^{th}$ by chest X-ray.

Numeric rating scale (NRS) is a variation of the visual analog scale that uses a scalar numbering system to objectify a patient's pain. Most NRSs use a 10- cm line with tick marks spaced 1 cm apart. The leftmost mark labeled "0" and has the notation "No Pain" rightmost mark is labeled "10" and notation "Worst Pain imaginable". The patient was asked to indicate where on the continuum he or she would rate the current intensity of pain. In order, scores of zero interpreted as "painlessness", 1-3 "mild pain", 4-6 "moderate pain" and 7-10 "severe pain". In severe pain, the patient is incapable of even ordinary work and finds it hard to deal with routine activities (11).

### *Statistical analysis*

The data were analyzed by Shapiro-Wilk, *t* test Mann-Whitney U, chi-square and Fisher's exact tests in SPSS software version 18. Additionally, *P* value less than 0.05 is considered statistically significant.

## Results

Forty-one patients were enrolled in the study (21 patients in the doxycycline recipient group and 20 in the povidone-iodine group). Distribution of patients in two groups was normal in terms of gender ($P = 0.412$) and age ($P = 0.813$).

The youngest and oldest subjects in the doxycycline recipient group were 35 and 93 years old, respectively. However, the youngest and oldest subjects in the povidone-iodine group were 37 and 84 years old, respectively.

The mean ± standard deviation of pain intensity in two groups was not significantly different in all phases of the pain assessment periods (Table 1).

Empyema was not diagnosed in any patients. The chest X-ray of the two groups in the acute phase (the pre-discharge phase) was normal and no side effects were observed, including hemothorax or pneumothorax.

Accordingly, seven days after discharge, five patients (19%) in the doxycycline recipient group and one (5%) patient in povidone-iodine recipient group suffered from recurrent effusion which was not significantly different ($P = 0.089$; Table 2).

Patients were re-examined after 30 days. By excluding patients who had recurrence or died on the seventh-day evaluation, it was shown that one (5.9%) patient in the doxycycline recipient group and four (23.5%) patients in povidone-iodine recipient group suffered from recurrent effusion ($P = 0.168$; Table 3).

Patients were re-examined after 60 days. On 60$^{th}$ day, by excluding patients, who had recurrent effusion or died, 15 patients in the doxycycline recipient group and 11 patients in the povidone-iodine group were evaluated. In the doxycycline recipient group, four patients (26.7%) had recurrent effusion, while none of patients in povidone-iodine recipient group had recurrent effusion ($P = 0.091$) which was not significantly different (Table 4).

On 90$^{th}$ day of follow up, the patients who had recurrent effusion or died excluded again. In addition, 10 patients in the doxycycline recipient group and 10 patients in the povidone-iodine group were evaluated. Only one of the patients in the doxycycline recipient group had recurrent effusion, while no one in the povidone-iodine group had

**Table 1.** Mean, standard deviation, median, and interquartile range for the intensity of pain in the two groups of patients in three evaluation periods

| Evaluation periods | Groups | | | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | Doxycycline | | | | Povidone Iodine | | | | |
| | Mean | SD | Median | Interquartile Range | Mean | SD | Median | Interquartile Range | |
| 24 hours after intervention | 2.81 | 2.68 | 3 | 5 | 3.05 | 3.15 | 1.50 | 7 | 0.786 |
| 48 hours after intervention | 0.52 | 1.21 | 0.00 | 0.00 | 0.50 | 1.23 | 0.00 | 0.00 | 0.940 |
| 72 hours after intervention | 0.00 | 0.00 | - | - | 0.20 | 0.52 | 0.00 | 0.00 | 0.069 |

**Table 2.** Recurrence in patients on the 7th day after discharge

| Result | Groups | | | | P value |
|---|---|---|---|---|---|
| | Doxycycline | | Povidone iodine | | |
| | No. | % | No. | % | |
| Normal | 17 | 81 | 17 | 85 | 0.187 |
| Recurrence | 4 | 19 | 1 | 5 | |
| Death | 0 | 0 | 2 | 10 | |
| Total | 21 | 100 | 20 | 100 | |

**Table 3**. Recurrence in patients on the 30th Day after Discharge

| Result | Groups | | | | *P* value |
|---|---|---|---|---|---|
| | Doxycycline | | Povidone iodine | | |
| | No. | % | No. | % | |
| Normal | 15 | 88.2 | 11 | 64.7 | 0.168 |
| Recurrence | 1 | 5.9 | 4 | 23.5 | |
| Death | 1 | 5.9 | 2 | 11.8 | |
| Total | 17 | 100 | 17 | 100 | |

**Table 4**. Recurrence in patients on the 60th Day after Discharge

| Result | Groups | | | | *P* value |
|---|---|---|---|---|---|
| | Doxycycline | | Povidone iodine | | |
| | No. | % | No. | % | |
| Normal | 10 | 66.7 | 10 | 90.9 | 0.168 |
| Recurrence | 4 | 26.7 | 0 | 0 | |
| Death | 1 | 6.7 | 1 | 9.1 | |
| Total | 15 | 100 | 11 | 100 | |

recurrent effusion. Moreover, none of the patients died in the two groups. At this phase, the recurrent effusion was not significantly different in two groups ($P=0.500$)

Recurrence of effusion occurred at 10 patients (47.6%) in doxycycline recipients and five patients (25%) in povidone-iodine recipients, which was not significantly different ($P=0.133$).

The mean ± SD of the body temperature in the doxycycline recipients and povidone-iodine recipients was 36.77 ± 0.43°C and 36.70 ± 0.43°C, respectively, while difference was not significant ($P=0.0911$). On the first day, only 4.8% (one person) in the doxycycline recipient group had fever (above 37.7) and fever not reported in the povidone-iodine group. On the second day, 9.5% (two people) of the doxycycline recipients had fever, while no signs of fever were reported in the povidone-iodine group. On the third day, none of the patients in the two groups suffered from fever.

The cost of treatment was similar in two groups. In addition, both drugs were quite common and available.

## Discussion

In this study, 41 patients with PE were randomly assigned and investigated in two groups. There was no significant difference in intensity of pain in patients in both groups ($P>0.05$). No empyema was reported in any of the patients. The chest radiography of all patients in the two groups during the acute phase (before drainage) was normal and no side effects were observed, including hemothorax and pneumothorax. Evaluation on the 30$^{th}$ 60th and 90$^{th}$ days indicated that in a 90-day follow-up, 47.6% of doxycycline recipients and 25% of povidone-iodine recipients had recurrent effusion ($P=0.133$). In general, fever was observed in three subjects (one on the first day and two on the second day) in the doxycycline recipient group, while no one suffered from fever in the povidone-iodine recipient group. In both groups, the cost was almost the same.

The overall success rate in our study in the pleurodesis with doxycycline and povidone-iodine was 81.5% and 85.1%, respectively, which is similar to other studies (11-14). In this study, patients were evaluated on days 7, 30, 60 and 90, and 47.7% in doxycycline recipients and 25% in povidone-iodine recipients had recurrent effusion for a total of 90-day follow-up, which was not significantly different ($P=0.133$). Therefore, the present study supports the findings of the study by Herrington et al conducted in 1996 on 27 patients under pleurodesis, during which 67% of patients suffering from malignant effusion fully responded to the treatment. In addition, 16.5% responded to treatment comparatively and 16.5% needed pleurodesis. The results of studies in which povidone-iodine was used for pleurodesis are supported by this study. For example, Agarwal et al performed a study on 64 patients. Accordingly, 86.5% of patients treated and no longer required pleurodesis (11).

In the study by Bakr et al, 40 patients with MPE (malignant PE) underwent medical pleurodesis using bleomycin, doxycycline, povidone-iodine and 5-fluorouracil and the final reported success rates were 70% for bleomycin, 80% for doxycycline, 80% for povidone-iodine, and only 50% for 5 fluorouracil which was the lowest success rate (10).

In the study by Kelly-Garcia et al, in which he compared bleomycin and povidone-iodine in 22 patients for pleurodesis, 64.2% of povidone-iodine recipients and 87.5% of bleomycin recipients responded to the treatment completely (15).

In the study by Makkar et al, the response to the treatment was 79% and there was no periprocedural mortality. In addition, 8% of the patients had fever and 10% had pain after procedure (14). Moreover, 5 out of 18 patients suffered from recurrent effusion in treatment of povidone-iodine in a study by Ibrahim et al (16), while three out of 20 patients suffered from recurrent effusion in

a study by Mohsen et al (12).

The results of the clinical trial of Bakr et al, suggest that although bleomycin is as effective as povidone-iodine and doxycycline, the latter two are cheaper and more available which are also regarded as a better alternative (10). Therefore, given the fact that the overall success rate in doxycycline and the povidone-iodine groups was 81.5% and 85.1%, respectively; it can be implied that they were equally effective; both are recommended due to availability and affordability. Moreover, one is not preferred to another in terms of cost.

In a study by Agarwal et al, 64 patients had pleurodesis with povidone-iodine. An empyema was reported after the procedure (11). In our study, none of the patients had empyema.

The radiological evaluation of our patients in the acute phase (the previous phase of discharge) was normal and there was no hemothorax or pneumothorax, so it indicates that povidone-iodine and doxycycline are equally effective in pleurodesis. Patz et al showed that short-term outcomes after pleurodesis with doxycycline and bleomycin are not different (17).

In the present study, patients were evaluated for fever. Accordingly, only three (14%) out of 21 patients receiving doxycycline had fever which in Herrington et al, occurrence of fever was reported 11% (13). On the other hand, in our study, the povidone-iodine group did not suffer from fever that is not similar to previous studies. For example, in a study by Agarwal et al, 10.9% of the patients had fever (11). Ibrahim et al, compared povidone-iodine and talc powder in which four patients povidone-iodine recipients and four patients in talc powder recipients had fever after the procedure (16).

In our study, we evaluated the pain intensity with the NSR (numerical rating scale) system. There was no significant difference in pain intensity in any of evaluation days. In both groups, the intensity of pain reduced over time. None of the pain evaluations was based on the NSR system. However, other various methods, including the visual analogue scale, have been used to evaluate the pain.

In a study by Agarwal et al, 64 patients underwent pleurodesis with povidone-iodine. In this study, the patients were evaluated for pain after the procedure, which was mild to severe, based on visual analogue scale ranging from 10 to 95 and median equal to 50.5 (4).

In a study by Mohsen et al, 42 patients underwent pleurodesis. Accordingly, 22 patients received talc, while 20 patients received povidone-iodine. In this study, 18% of the patients in the talc group had to take analgesics after the procedure; while none of the patients in the povidone-iodine group received analgesics (12).

In the study by Makkar et al, on 104 patients with malignant effusion after a mean follow-up of 7.8 months 79% of patients did not show any re-accumulation of fluid and there was no periprocedural mortality, 8 patients had severe pain; 11 patients had fever and one patient had arrhythmia (14).

Song et al studied 77 patients of whom 40 patients received doxycycline and 37 patients underwent pleurodesis with *Viscum album*. Overall, 42.1% of patients in the doxycycline group and 13.5% of patients in the viscum album group suffered from severe pain (5).

Herrington et al studied 27 patients who underwent pleurodesis with doxycycline. Accordingly, 81% of patients complained of post-procedure pain. The pain intensity remained unknown (13).

One of the limitations of our study was the small sample size. Therefore, a study with a larger sample size could reach the results that are more reliable in the future.

The results showed that pleurodesis with povidone-iodine and doxycycline were not significantly different in terms of pain, cost, fever, and recurrence and povidone-iodine was as effective as doxycycline. This drug can be used in patients with PE as an efficient alternative.

## Limitations of the study

Given some of the limitations of our study, such as the lack of cooperation of some patients, it is recommended to conduct studies with more samples size and multiple centers to obtain results with more reliability.

### Authors' contribution

HRH, FM and AH were the principal investigators of the study. HRH, FM, SS, RG and MZ were included in preparing the concept and design. HRH and MZ revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy and integrity of any part of the work.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research was conducted in accordance with the tents of the Declaration of Helsinki. The ethics committee of Semnan University of Medical Sciences approved this study. The institutional ethical committee at Semnan university of medical sciences accepted all study protocols (IR.SEMUMS.REC.1394.91). Accordingly, written informed consent was taken from all participants before any intervention. The study was extracted from M.D., thesis of Armin Hadjizadeh at this university. The trial protocol was approved in the Iranian registry of clinical trial (#IRCT2015052918168N3; https://en.irct.ir/trial/16560). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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### References

1. Peek GJ, Morcos S, Cooper G. The pleural cavity. BMJ. 2000;320:1318-21. doi: 10.136/bmj.320.7245.1318.
2. Charalampidis C, Youroukou A, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, et al. Physiology of the pleural

space. J Thorac Dis. 2015;7:S33-S7. doi: 10.3978/j.issn.2072-1439.2014.12.48.
3. Yu H. Management of pleural effusion, empyema, and lung abscess. Semin Intervent Radiol. 2011;28:75-86. doi: 10.1055/s-0031-1273942.
4. Agarwal R, Khan A, Aggarwal AN, Gupta D. Efficacy & safety of iodopovidone pleurodesis: a systematic review & meta-analysis. Indian J Med Res. 2012;135:297-304.
5. Song KS, Keum D, Kim JB. Chemical Pleurodesis using doxycycline and viscum album extract. Korean J Thorac Cardiovasc Surg. 2017;50:281-6. doi: 10.5090/kjtcs.2017.50.4.281.
6. Ferreiro L, Suárez-Antelo J, Álvarez-Dobaño JM, Toubes ME, Riveiro V, Valdés L. Malignant Pleural Effusion: Diagnosis and Management. Can Respir J. 2020;2020:2950751. doi: 10.1155/2020/2950751.
7. Tettey M, Sereboe L, Edwin F, Frimpong-Boateng K. Tetracycline Pleurodesis for Malignant Pleural Effusion-A Review of 38 Cases. Ghana Med J. 2005;39:128-31.
8. Das SK, Saha SK, Das A, Halder AK, Banerjee SN, Chakraborty M. A study of comparison of efficacy and safety of talc and povidone-iodine for pleurodesis of malignant pleural effusions. J Indian Med Assoc. 2008;106:589-90, 92.
9. Neto JD, de Oliveira SF, Vianna SP, Terra RM. Efficacy and safety of iodopovidone pleurodesis in malignant pleural effusions. Respirology (Carlton, Vic). 2010;15:115-8. doi: 10.1111/j.440-843.2009.01663.x.
10. Bakr RM, El-Mahalawy II, Abdel-Aal GA, Mabrouk AA, Ali AA. Pleurodesis using different agents in malignant pleural effusion. Egyptian Journal of Chest Diseases and Tuberculosis. 2012;61:399-404. doi:10.1016/j.ejcdt.2012.07.005.
11. Agarwal R, Aggarwal AN, Gupta D. Efficacy and safety of iodopovidone pleurodesis through tube thoracostomy. Respirology (Carlton, Vic). 2006;11(1):105-8. doi: 10.1111/j.440-843.2006.00792.x.
12. Mohsen TA, Zeid AA, Meshref M, Tawfeek N, Redmond K, Ananiadou OG, et al. Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial. Eur J Cardiothorac Surg. 2011;40:282-6. doi: 10.1016/j.ejcts.2010.09.005.
13. Herrington JD, Gora-Harper ML, Salley RK. Chemical Pleurodesis With Doxycycline 1 g. Pharmacotherapy. 1996;16:280-5. doi:10.1002/j.875-9114.1996.tb02946.x.
14. Makkar A, Patni S, Joad AK, Lakhera KK. An observational study on safety and efficacy of povidone-iodine for pleurodesis in cancer patients. South Asian J Cancer. 2017;6:79-80. doi: 10.4103/2278-330X.208849.
15. Kelly-Garcia J, Roman-Berumen JF, Ibarra-Perez C. Iodopovidone and bleomycin pleurodesis for effusions due to malignant epithelial neoplasms. Arch Med Res. 1997;28:583-5.
16. Ibrahim IM, Dokhan AL, El-Sessy AA, Eltaweel MF. Povidone-iodine pleurodesis versus talc pleurodesis in preventing recurrence of malignant pleural effusion. J Cardiothorac Surg. 2015;10:64. doi: 10.1186/s13019-015-0270-5.
17. Patz EF, Jr., McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Gilkeson RC, et al. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. Chest. 1998;113:1305-11. doi: 10.78/chest.113.5.