Comparative efficacy of Doxycycline vs Povidone-iodine for pleurodesis: A Prospective analytical study

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Abstract

Background: Chemical pleurodesis is an effective intervention for managing malignant or recurrent pleural effusions. Both doxycycline and povidoneiodine are widely available, cheaper, but comparative data on pain and efficacy outcomes remain limited.

Methodology: A total of 100 patients with symptomatic pleural effusion requiring pleurodesis were included in the study either doxycycline (n=49) or povidoneiodine (n=51) through an intercostal drain. Pain scores were assessed using a visual analog scale (VAS) at preprocedure, 24 hours, and 48 hours postprocedure. Pleurodesis success, time to chesttube removal, complication rates, and followup outcomes were recorded.

Results: Baseline characteristics were well balanced between groups. Pain scores at 48 hours were significantly lower in the povidoneiodine group (median 4, IQR 4–5) compared to doxycycline (median 5, IQR 4–6; p=0.006), with a similar trend at 24 hours (p=0.039). Pleurodesis success rates were comparable (doxycycline 89.8% vs. povidoneiodine 84.3%; p=0.415). Median time to chesttube removal was 2 days in both groups (p=0.344). Complication rates and 1 month followup reeffusion outcomes did not differ significantly between groups (all p>0.05).

Conclusion: Povidoneiodine pleurodesis achieves comparable efficacy and safety to doxycycline while offering significantly better pain control at 48 hours postprocedure.

Keywords: Pleurodesis; doxycycline; povidoneiodine; betadine; malignant pleural effusion; chest tube

Background:

Pleurodesis is a medical procedure done to adhere parietal pleura and visceral pleura, to prevent recurrent pleural effusion or even pneumothorax. It is most commonly performed in patients with recurrent malignant pleural effusions, persistent pneumothorax, or chylothorax to improve symptoms and quality of life of patients.[1] It works by inducing inflammation in the pleura and inducing fibrosis. The irritant agent can be either chemical or mechanical, which triggers an inflammatory response, activating mesothelial cells and releasing cytokines like interleukin-8 and tumor necrosis factor-alpha (TNF-α). This leads to neutrophil recruitment, fibrin deposition, and subsequent fibroblast proliferation, resulting in permanent adhesions.[2]

Several chemical agents are explored for chemical pleurodesis including hypertonic glucose (50%), 0.5% silver nitrate, Talc, Doxycycline, Bleomycin, some bioactive bacterial agents and many more.[3,4]tetracycline, iodopovidone, etc. The ideal sclerosing agent should be highly effective, well-tolerated, widely available, and cost-effective while causing minimal complications.[4] Talc is considered the gold standard due to its high efficacy but it's not devoid of complications and can lead to talc pleuritis and Acute respiratory distress syndrome (ARDS). Therefore alternative agents such as doxycycline and betadine have been tried for safer outcomes.[5]

Doxycycline, a tetracycline antibiotic, is widely available, inexpensive, and relatively safe, making it a commonly used alternative with less complications as compared to talc.[6,7]and premedication with intravenous narcotic analgesics and intrapleural lidocaine 200 mg, the patients received doxycycline 1 g in 50 ml normal saline instilled through the

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chest tube. This was followed by instillation of 100-200 ml of air to facilitate dispersion. The chest tube was removed when the drainage was less than 150 ml/day. Twenty-three of 27 patients were evaluated at 30 days. Six (67% Furthermore, its antibiotic properties may offer an added advantage in preventing infections in patients with underlying pleural infections or malignancies.[9,10] Povidone-iodine has also been proven as a effective agent for pleurodesis due to its safety profile, cost-effectiveness, and antiseptic properties.[11,12] Studies have shown that betadine can achieve comparable pleurodesis success rates to talc and doxycycline, with fewer systemic side effects especially in a cases of malignant pleural effusion.[13,3]tetracycline, iodopovidone, etc. Likewise, its antimicrobial properties may provide an added benefit by reducing the risk of pleural infections, making it a suitable alternative, especially in immunocompromised patients or those with a history of pleural infections.[14]

Although literatures prove them efficacious and a lot has been done to compare their individual efficacy with talc limited comparative data exist regarding the efficacy and safety of doxycycline versus betadine for pleurodesis. Both doxycycline and iodopovidone are easy to administer via bedside chest tube as well as thoracoscopy.[15,16]

There may be altered pleural physiology in Nepalese population due to high prevalence of tuberculosis and other infectious diseases which leads to chronic pleural inflammation.[17]tuberculosis remains one of the most frequent causes of pleural effusions on a global scale, especially in developing countries. Tuberculous pleural effusion (TPE These differences may impact the effectiveness and safety of pleurodesis agents, necessitating region-specific research.This type of study has never been conducted in Nepal, and its findings will be highly beneficial for clinical use. This study aims to evaluate and compare the effectiveness of these two agents in achieving successful pleurodesis, their associated complications, and overall outcomes in patients requiring pleural space obliteration.

Methodology:

Study designs: This was a prospective comparative analytical cohort study conducted in Department of Surgical Oncology – Thoracic unit, B.P. koirala Memorial Cancer Hospital, to evaluate the efficacy and safety of two chemical pleurodesis agents: intrapleural Doxycycline versus intrapleural Povidone-Iodine (Betadine). The data collection time spanned from March 15 2025 to March 10 2026, with followup at 1 month for each enrolled patients.

Participants:

Total enumeration in the period of one year was done for first 100 eligible patients. Grouping was done on alternate basis . N = 100

- Group A: Doxycycline Pleurodesis (n = 49)
- Group B: Povidone-Iodine pleurodesis (n=51)

Inclusion Criteria:

- Age ≥18 years
- Symptomatic pleural effusion confirmed by chest radiography or ultrasonography
- Adequate lung expansion following intercostal tube drainage (no evidence of trapped lung)

Exclusion Criteria:

- Known hypersensitivity to doxycycline or povidoneiodine
- Pregnancy or lactation
- Empyema with systemic signs of sepsis
- Malignant pleural effusion with life expectancy <1 month
- Loss of follow up

Data Collection:

A total of 100 patients who met the inclusion criteria were included in the study. Patients were divided into two groups based on the sclerosant used for pleurodesis: the doxycycline group (Group A) and the povidone-iodine (betadine) group (Group B)**.**

All patients underwent detailed clinical evaluation and radiological assessment. Initial management included intercostal chest tube insertion for therapeutic drainage or video-assisted thoracoscopic surgery (VATS) biopsy, depending on the clinical indication. Pleurodesis was performed only after adequate drainage of pleural fluid and confirmation of complete lung expansion on standard chest radiography. Patients with non-expandable lung or contraindications to chemical pleurodesis were excluded from the study.

Following confirmation of lung expansion, chemical

pleurodesis was carried out using either povidone-iodine or doxycycline, based on the treating unit protocol. In the povidone-iodine group, 20 mL of 10% povidone-iodine was used, while in the doxycycline group, doxycycline at a dose of 7 mg/kg was administered. In both groups, the sclerosant was diluted with 50 mL of normal saline and 10 mL of 2% lignocaine and instilled into the pleural cavity through the existing chest tube. After instillation, the chest tube was clamped for two hours, following which it was reopened and connected to an underwater seal drainage system. Continuous negative suction of −10 cm of water was applied for 24 to 48 hours as needed to facilitate lung apposition and enhance pleurodesis efficacy.

Post-procedure, patients were monitored daily for chest tube output, clinical status, and complications. The chest tube was removed once the drainage decreased to less than 3-5 ml/kg/day with radiological evidence of sustained lung expansion. Patients were observed during the stay and next day for procedure-related complications including fever, pain, empyema, and pulmonary embolism. Pain severity was assessed using the Numeric Rating Scale (NRS), a validated 0–10 scale, where scores were categorized as mild (1–3), moderate (4–6), and severe (7–10), with severe pain indicating significant limitation of routine activities.

The primary outcome of the study was the success of pleurodesis, defined as the absence of recurrent pleural effusion requiring repeat therapeutic intervention during the follow-up period. Secondary outcomes included duration of chest tube drainage, length of hospital stay, and incidence of procedure-related complications. Patients were followed up clinically and radiologically using chest radiographs at 30 days to assess recurrence of pleural effusion and overall outcome.

Statistics

Normality of pain scores at pre-procedure, 24 hours, and 48 hours post-pleurodesis was assessed using the Shapiro–Wilk test. Comparisons were performed using the Mann–Whitney U test between the groups, while within-group changes over time were analyzed using the Friedman test. Post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction. A p-value < 0.05 was considered statistically significant.

Results

Total of 100 patients were enrolled in the study. Distribution of patients in two groups was non-significant in terms of gender (P = 0.686).

In the doxycycline pleurodesis group (n=49), 57.1% of patients had no comorbidities. Among those with comorbidities, hypertension (14.3%), diabetes (8.2%), and their combination (10.2%) were most frequently observed; other conditions accounted for 10.2%. In the betadine group (n=51), 20 patients (39.2%) had no comorbidities, while 31 (60.8%) had comorbidities: hypertension (29.4%), diabetes (5.9%), both conditions (13.7%), or other (11.8%).

The overall comorbidity distribution was not statistically different between groups (p = 0.115). However, hypertension was more prevalent in the betadine group (29.4% vs. 14.3% in doxycycline), while other comorbidity categories showed comparable frequencies.

Table 1: Different Demographic statistics distributed as per two groups of intervention

	Doxycycline	Povidone-Iodine
Male	23(46.9%)	26 (51%)
Female	26(53.1%)	25(49%)
Youngest (Age)	23	24
Oldest (Age)	81	82
BMI (Mean +- SD)	22.02 +- 2.73	22.30 +- 2.30
Smoker	35 (71.4%)	30(58.8%)
Right Pleural effusion	31(63.3%)	26(51%)
Left Pleural effusion	18(36.7%)	25 (49%)

Our cohort (N=100) was predominantly composed of malignant effusions (80%), with lung adenocarcinoma representing the most frequent underlying pathology (56%). This high proportion of malignancy is consistent with populations typically referred for pleurodesis.Pleural fluid cytology results for the overall cohort showed that 45 patients (45.0%) had cytology negative for malignancy, 29 patients (29.0%) had suspicious cytology, and 26 patients (26.0%) had cytology positive for malignancy.

As pain scores showed non-normal ($p < 0.05$), non-parametric statistical tests were used. MannWhitney U test showed no significant baseline difference in pain (U=1230, p=0.886). At 24 hours postprocedure,

pain scores differed between groups with a trend toward significance (U = 958.5, p = 0.039), though this did not survive Bonferroni correction for multiple comparisons (adjusted α = 0.0167). At 48 hours postprocedure, pain scores differed significantly between groups (U = 861.5, p = 0.006), surviving Bonferroni correction for multiple comparisons,

Friedman tests revealed significant overall changes in pain scores over time in both groups (doxycycline: χ^2=68.37, p<0.001; betadine: χ^2=61.38, p<0.001). Posthoc Wilcoxon signedrank tests with Bonferroni correction (adjusted α=0.0167) showed that pain increased significantly from preprocedure to both 24 h (doxycycline p<0.001; betadine: p<0.001) and 48 h (doxycycline: Z= p<0.001; betadine: Z=p<0.001) in both groups. However, pain scores between 24 h and 48 h did not differ significantly in either group after correction (both p>0.05).

Median time to chesttube removal was 2.0 days in both groups, with no significant difference in distribution (MannWhitney *U* = 1076, p = 0.344). Most tubes were removed within two days: 71.4% (35/49) in the doxycycline group and 85.7% (42/49) in the betadine group. A minority required longer drainage (doxycycline: 28.6% at 3–5 days; betadine: 14.3% at 3–4 days).

The overall pleurodesis failure rate, at one month was 13% (13/100). Failure occurred in 10.2% (5/49) of doxycycline-treated patients and 15.7% (8/51) of Povidone-Iodine treated patients. This difference was not statistically significant (χ^2=0.664, p=0.415). Both agents demonstrated high rates of complete response at followup (doxycycline: 89.8%, betadine: 84.3%). Recurrence requiring intervention was numerically more frequent with betadine (9.8% vs. 4.1%), but the difference was not statistically significant (Fisher's exact test, p = 0.552).

Table 2: Statistical analysis between pain before and after procedure in two groups

Time points	Doxycycline (n=49) Median VAS (IQR)*	Betadine (n=51) Median VAS (IQR)	P-Value
Pre procedure pain	3 (3-4)	3(3-4)	0.886
Post Procedure pain (24 hours)	6 (5-6)	5(4-6)	0.039
Post procedure (48 hours)	5 (4-6)	4(4-5)	0.006
Within-group	χ^2=68.37, p<0.001	χ^2=61.38, p<0.001	

IQR – Interquartile range

Table 3: Overall Pleurodesis success at one month follow up

Groups	Complete Response	Pleural effusion in follow up		P value
		Needing Intervention	No intervention	
Doxycyline	44 (89.8)	2 (4.1)	3 (6.1)	0.552*
Betadine	43 (84.3)	5 (9.8)	3 (5.9)	

* *FisherFreemanHalton exact test*

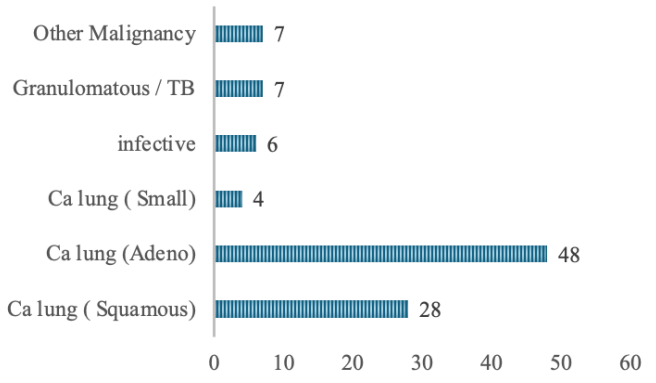
Table 4: Various Complication as per two different groups

Complications	Doxycycline (Frequency)	Povidone Iodine (Frequency)	P – Value *
Fever	6 (12.2%)	2 (3.9%)	0.125
Re- Drainage	5(10.2%)	15.7(%)	0.415
Respiratory difficulty	6 (12.2%)	3(5.9%)	0.154
Hypotension	0(2%)	1(2%)	0.325
Arrhythmia	3 (6.1%)	0	0.073

* Chi-square test used to calculate statistical significance

Complication rates did not differ significantly between groups, with fever (12.2% vs. 3.9%, p=0.125), redrainage (10.2% vs. 15.7%, p=0.415), and respiratory difficulty (12.2% vs. 5.9%, p=0.154) showing no statistically significant differences.

Of the histopathology confirmed cases, the most common finding was adenocarcinoma of the lung, identified in 48 patients (40%). Followed by Squamous cell carcinoma of lung and then few cases of small cell carcinoma and other malignancies.



*Note: TB – Tuberculosis ; Ca lung (Small) – Small Cell Carcinoma of lung; Ca lung (Adeno) – Adenocarcinoma of lung

Figure1: Bar chart showing different final histopathological results

Discussion

A total of 100 patients with symptomatic pleural effusion requiring pleurodesis with or without undergoing VATS biopsy, were included in the study, with 49 assigned to doxycycline and 51 to

povidoneiodine group. The cohort had a mean age spanning 23–82 years and a mean BMI of 22.16 ± 2.15 kg/m². This age group reflects similar demographic groups as per the study of Hemmati et al.[15]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 Our study had heterogenous etiology and thus the age distribution span was also wide. Sex distribution was balanced (doxycycline: 46.9% male; betadine: 51% male) and the distribution among two groups were nonsignificant.Smoking was prevalent in 65% of patients overall, and effusions were slightly more common on the right side (57%). No statistically significant differences were observed between the comorbidities and two groups however, hypertension was more prevalent in the betadine group (29.4% vs. 14.3% in doxycycline), while other comorbidity categories showed comparable frequencies.

Our study demonstrates a reduced pain score in betadine group over doxycycline pleurodesis. At 48 h postprocedure, pain scores were significantly lower in the betadine group (median VAS 4, IQR 4–5) compared to doxycycline (median VAS 5, IQR 4–6; p = 0.006). In a study of Ibrahim et al., povidoneiodine and talc demonstrated comparable postpleurodesis pain profiles (p=0.291), with 83.3% and 100% of patients reporting no or only minor pain, respectively.[12]In contrast to our finding of higher pain with doxycycline at 48h, one study reported nearly identical median pain scores (0.00) for both agents at 48h (p=0.940), suggesting variability in pain experience across different populations or protocols.[15]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

The median time to chesttube removal was 2 days in both groups, with >70% of patients having tubes removed within 48 h. This is notably shorter than the 3–7 days frequently cited for talc slurry (Dresler et al., 2005) and suggests that both doxycycline and betadine induce a rapid inflammatory response that permits early discontinuation of drainage.[18] Damaraju et al. reported similarly rapid tube removal (mean 1.5–1.9 days), closely matching our median of 2.0 days in both groups.[16]chest pain (assessed using visual analog scale [VAS] Early removal may reduce hospital stay and infection risk, a practical advantage in resourceconstrained settings and any of pleurodesis agent shows similar time to removal.

Our study demonstrates comparable pleurodesis success rates between doxycycline (89.8%) and betadine (84.3%), a finding consistent with the recent randomized trial by Damaraju et al., which reported similar success (complete response: 82.7% vs. 79.3%; p = 0.3).[16]chest pain (assessed using visual analog scale [VAS] However, important differences in study populations must be noted. While Damaraju et al. exclusively enrolled patients with malignant pleural effusions (MPE), predominantly from lung cancer (≥60%), our cohort included a mixed etiology: only 55% of patients had either suspicious or positive cytology for malignancy, and final diagnoses encompassed infective (6%), granulomatous/TB (7%), and other nonmalignant causes (7%). This suggests that both agents retain comparable or even high efficacy even in populations with a substantial proportion of nonmalignant effusions—a clinically relevant extension of previous evidences.

Povidoneiodine demonstrated comparable efficacy to talc, whereas doxycycline was associated with a 50% failure rate in a recent cohort of malignant pleural effusion patients (Kathamuthu et al.).[19]chest pain, cough and prevents recurrent pleural collections which require repeated thoracentesis. Pleurodesis improves the quality of life as a minimally invasive procedure. Chemical pleurodesis is preferred through tube thoracostomy in limited resource settings. The ideal sclerosing agent should be

easily administered, safe, inexpensive, and widely available. The commonly used agents in tertiary care hospitals are talc (10 mg/kg Ibrahim et al. reported similar recurrence rates requiring intervention (4 vs. 5 patients) even though statistically non-significant and concluded that povidoneiodine is a costeffective, safe, and repeatable alternative.[20]leading to a significant reduction in quality of life with progressive dyspnea, dry cough, chest pain and reduced physical activity. This study was conducted to compare the efficacy, safety, and outcome of Talc Powder Pleurodesis (TPP Park et al. reported that doxycycline was associated with higher recurrence compared to talc in spontaneous pneumothorax (p=0.033).[21] Our study even though demonstrates comparable efficacy in terms of pleurodesis but povidone iodine seems to show analgesic advantage and its substantially cheaper, which shows that betadine can be opted as a good pleurodesis agent in resource limited setting for heterogenous etiologies.

However, the numerical trend toward higher reeffusion requiring intervention in the betadine group (9.8% vs. 4.1%) warrants attention in larger studies.

Clinical Implications and Recommendation

In clinical practice, betadine may be considered the agent of choice for patients in whom post-procedural pain is a significant concern, such as the elderly or those with reduced physiological reserve. Where betadine is not feasible, doxycycline represents an effective alternative, albeit with an expectation of greater analgesic requirements. However, future multicenter randomized trials with standardized analgesic protocols and longer followup are needed to confirm these findings.

Limitations

Our study has several limitations, first off, its nonrandomized, singlecenter design may limit generalizability. Second, the sample size may be underpowered for secondary endpoints such as individual complications. Third, pain assessment was not standardized with a fixed analgesic protocol, which could account for some of the variability when compared with other studies. Furthermore, followup was shortterm; longer observation is needed to evaluate the durability of pleurodesis. Finally, the inclusion of both malignant and nonmalignant effusions, while reflective of realworld practice, adds etiological heterogeneity that may influence outcomes. Future multicenter randomized trials with standardized analgesia and longer followup are warranted to confirm these findings.

Conclusion

This study demonstrates that both doxycycline and povidoneiodine are effective agents for chemical pleurodesis, with high overall success rates (>84%) and comparable safety profiles.Despite differing inflammatory mechanisms, no significant differences were observed in pleurodesis failure, complication rates, or longterm reeffusion outcomes, underscoring their clinical equivalence in efficacy and safety, but betadine may offer a tolerability advantage in the first 48 hours after pleurodesis.

In resourcelimited settings, both doxycycline and betadine represent viable, lowcost alternatives; however, when postprocedural analgesia is a priority, betadine appears preferable.

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