Simple aspiration and drainage and intrapleural minocycline pleurodesis versus simple aspiration and drainage for the initial treatment of primary spontaneous pneumothorax: an open-label, parallel-group, prospective, randomised, controlled trial

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Summary

Background Simple aspiration and drainage is a standard initial treatment for primary spontaneous pneumothorax, but the rate of pneumothorax recurrence is substantial. We investigated whether additional minocycline pleurodesis after simple aspiration and drainage reduces the rate of recurrence.

Methods In our open-label, parallel-group, prospective, randomised, controlled trial at two hospitals in Taiwan, patients were aged 15–40 years and had a first episode of primary spontaneous pneumothorax with a rim of air greater than 2 cm on chest radiographs, complete lung expansion without air leakage after pigtail catheter drainage, adequate haematological function, and normal renal and hepatic function. After simple aspiration and drainage via a pigtail catheter, patients were randomly assigned (1:1) to receive 300 mg of minocycline pleurodesis or no further treatment (control group). Randomisation was by computer-generated random numbers in sealed envelopes. Our primary endpoint was rate of pneumothorax recurrence at 1 year. This trial is registered with ClinicalTrials.gov (NCT00418392).

Findings Between Dec 31, 2006, and June 30, 2012, 214 patients were randomly assigned—106 to the minocycline group and 108 to the control group (intention-to-treat population). Treatment was unsuccessful within 7 days of randomisation in 14 patients in the minocycline group and 20 patients in the control group. At 1 year, pneumothoraces had recurred in 31 of 106 (29·2%) patients in the minocycline group compared with 53 of 108 (49·1%) in the control group (p=0·003). We noted no procedure-related complications in either group.

Interpretation Simple aspiration and drainage followed by minocycline pleurodesis is a safe and more effective treatment for primary spontaneous pneumothorax than is simple aspiration and drainage only. Minocycline pleurodesis should be an adjunct to standard treatment for primary spontaneous pneumothorax.

Introduction

Primary spontaneous pneumothorax most frequently occurs in men and boys aged 15–40 years. Rates of recurrence range from 16% to 52% after the first episode. These high rates have stimulated development of different treatment approaches, varying from simple aspiration to invasive strategies—eg, surgery.

Simple aspiration and chest-tube drainage are the most frequently used methods for the initial treatment of primary spontaneous pneumothorax. Compelling evidence shows that simple aspiration should be the primary treatment in uncomplicated cases because the procedure seems as effective as is chest-tube drainage but is associated with fewer hospital admissions and shorter hospital stays. Furthermore, insertion of an aspiration catheter is easier and safer than is that of a chest tube. Simple aspiration is the procedure recommended by the British Thoracic Society. However, the pneumothorax recurrence rate at 1 year for simple aspiration or chest-tube drainage is roughly 30% (range 16–52). Thus, standard treatment for primary spontaneous pneumothorax can be improved upon.

Intrapleural instillation of a chemical irritant (chemical pleurodesis) effectively reduces recurrence of spontaneous pneumothorax in surgical and non-surgical patients. Chemical pleurodesis is typically done through a chest tube or during thoracoscopy, and hospital admission is necessary. It is recommended only when the patient is unwilling or unable to have surgery, which is more effective. Use of chemical pleurodesis for outpatient treatment of primary spontaneous pneumothorax after simple aspiration with or without drainage through an intravenous needle and small-bore pigtail catheter is rare and its safety and efficacy remain unknown. We did a prospective, randomised controlled trial to investigate whether additional minocycline pleurodesis after simple aspiration and drainage would be safe and more effective than simple aspiration and drainage only for the treatment of primary spontaneous pneumothorax.
Methods
Study design and patients
We did a prospective, open-label, parallel-group, randomised, controlled trial between Dec 31, 2006, and June 30, 2012 (stopped recruiting patients July 1, 2011), at the National Taiwan University Hospital, Taipei, and Far Eastern Memorial Hospital, New Taipei City, both of which are in Taiwan. Patients were consecutively recruited by their primary physicians. Eligible patients were aged 15–40 years and had a first episode of primary spontaneous pneumothorax with a rim of air greater than 2 cm on chest radiographs. Other eligibility criteria were complete lung expansion without air leakage after pigtail catheter drainage, adequate haematological function (haemoglobin >100 g/L, absolute neutrophil count >1·5×10⁹/L, platelet count >100×10⁹/L), and normal renal and hepatic function (serum creatinine concentration <10·0 µmol/L, alanine aminotransferase and aspartate aminotransferase <2·5 times the upper limits of normal [ie, 40 U/L]).

Patients were excluded if they had underlying pulmonary disease, haemothoraces or tension pneumothoraces necessitating chest-tube insertion or surgery, history of ipsilateral thoracic surgery, or other serious concomitant illnesses or medical disorders, or if they were allergic to tetracycline or minocycline, pregnant, or lactating. The study protocol was approved by the hospitals’ institutional review boards.

Randomisation and masking
After simple aspiration and drainage, patients were randomly assigned (1:1) by a study nurse (who was masked to patients’ characteristics) to additional minocycline pleurodesis (minocycline group) or no further treatment (control group). Randomisation was done at each centre according to computer-generated random numbers, with a block size of four in sequentially numbered, sealed envelopes (appendix). The nurse opened the randomisation envelopes and did the randomisation after successful treatment of the pneumothorax by simple aspiration and drainage.

Procedures
All patients received simple aspiration and drainage with a small-bore pigtail catheter. For simple aspiration and drainage, patients were seated in semisupine positions. A small-bore pigtail catheter (8 Fr; Bioteque, I-Lan, Taiwan) was introduced to the second intercostal space at the midclavicular line. We manually aspirated until we noted resistance. We then connected the pigtail catheter to a water seal chest bottle. Chest radiography was done with the catheter in place. If there was no air leakage and the pneumothorax seemed resolved on the chest radiograph, then patients were randomly assigned.

Patients in the minocycline group were given 30 mL of 1% lidocaine hydrochloride (300 mg), followed by 30 mL of normal saline containing 300 mg of minocycline (Mirosin; Taiwan Panbiotic Laboratories, Kaohsiung, Taiwan) instilled into the pleural cavity through the pigtail catheter. Patients were repositioned every 30 min so that the minocycline could come into contact with all pleural surfaces. We noted any side-effects or complaints. Patients in both groups had chest radiographs taken 4–6 h after procedures. We removed catheters upon complete expansion of the lung in all cases.

We gave paracetamol for postprocedural pain. Intensity of the postprocedural pain was assessed with a visual analogue scale (0 represented no pain, 10 represented intractable pain). We did the first pain assessment 1 h after insertion of the pigtail catheter in the control group and 1 h after minocycline pleurodesis in the minocycline group, and the second 1 h after removal of the pigtail catheter in both groups. Intramuscular pethidine was given every 4 to 6 h according to patients’ requests when paracetamol did not relieve the pain. Chest radiographs were reviewed by the principal investigator and radiologists masked to treatment groups. Radiographic size of the pneumothorax was estimated by use of the Light formula.

We assessed residual pain at least 6 months after aspiration and drainage in patients who did not have

Figure 1: Trial profile
*Treatment failure within 7 days after randomisation.
recurrent pneumothoraces. We used a 0–5 pain scale (0=pain free, 1=occasional discomfort, 2=occasional use of analgesics, 3=regular use of non-opioid analgesics, 4=regular use of opioids, 5=severe and intractable pain) for these assessments.26 We measured forced vital capacity and forced expiratory volume in 1 s in patients who had no recurrence and were able to attend hospital outpatient clinics. We aimed to do pulmonary measurements at the 6 month follow-up visit, but timing could be delayed to accommodate patients.

We instructed patients to return to the clinic or emergency department if they developed chest pain, dyspnoea, or symptoms suggesting pneumothorax recurrence both in hospital and during follow-up visits.

Our primary endpoint was the 1 year pneumothorax recurrence rate. Pneumothorax recurrence was defined as the presence of an ipsilateral pneumothorax of any size during 1 year’s follow-up as diagnosed by chest radiography (appendix). Our secondary endpoints were rates of immediate treatment success, success at 1 week, complications, and hospital admission; length of hospital stay; postprocedure chest pain; and long-term pulmonary function results (and residual chest pain). We did post-hoc analyses of overall pneumothorax recurrence rates, duration of pigtail drainage, and subsequent thoracoscopic surgery outcomes.

Immediate success was defined as complete or nearly complete and persistent lung expansion at 24 h after aspiration, 1 week success as complete or nearly complete and persistent lung expansion 1 week after aspiration, overall pneumothorax recurrence as presence of ipsilateral pneumothorax of any size after randomisation, and hospital stay as the time from arrival at the emergency department to discharge (with or without admission).

### Statistical analysis
Details about estimation of sample size are in the appendix. We did intention-to-treat (all randomly assigned patients) analyses for the primary endpoint. Continuous variables are presented as means with SDs and categorical variables as frequencies with associated percentages. For two-group comparisons, we used the two-sample *t* test for continuous variables and Fisher’s exact test for categorical variables. We did the Wilcoxon rank-sum test to compare chest pain scores between groups. The Kaplan-Meier method was used to estimate the 1 year and overall pneumothorax recurrence and the log-rank test to test differences in recurrence between the groups. We used SAS (version 9.3) for all analyses. All tests were two sided; we deemed *p* values less than 0·05 to be significant. This trial is registered with ClinicalTrials.gov (number NCT00418392).

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access to the data and participated in the decision to submit for publication. P-CY and W-KC had final responsibility for the decision to submit for publication.

Results
The trial lasted for 65 months. 253 patients with first episodes of primary spontaneous pneumothorax were enrolled (figure 1). 214 patients were randomly assigned; 106 to the minocycline group and 108 to the control group. Patients’ characteristics were similar in both groups (table 1). Mean follow-up was 19·3 months (range 12–65). No patients used steroids in the study. We recorded no procedure-related complications in either group.

Within 1 year, 31 (29.2%) patients in the minocycline pleurodesis group had a pneumothorax recurrence compared with 53 (49.1%) in the control group (p=0.003; table 2). Compared with the control group, minocycline pleurodesis significantly reduced the relative risk of overall pneumothorax recurrence from 56.3% (95% CI 42.9–70.6) to 32.9% (24.6–43.0; p=0.004; figure 2). Immediate success rate, success at 1 week, rate of hospital admission, and the mean durations of pigtail drainage and hospital stay did not differ significantly between groups (table 2).

34 patients in the minocycline group and 55 in the control group had pneumothorax recurrence. Significantly fewer patients in the minocycline group needed thoracoscopic surgery after randomisation than in the control group (31 [29.2%] vs 47 [43.5%]; p=0.034). Of the remaining 11 patients with recurrences, three underwent tube thoracostomies and eight chose observation because they did not want surgery or had small recurrent pneumothoraces.

Chest pain was more common in the minocycline than in the control group. 72 (67.9%) patients in the minocycline group requested pethidine compared with 21 (19.4%) in the control group (p<0.0001); the mean pethidine dose was also significantly higher in the minocycline group (table 3). Patients in the minocycline group reported significantly more pain than did those in the control group in the first visual analogue scale measurement, but less pain than did those in the control group in the second measurement—ie, after removal of the pigtail catheter (table 3). Most patients had no residual chest pain 6 months after treatment, and pain scores were similar in both groups (appendix).

Findings from subsequent thoracoscopic surgery showed that pleural adhesions were more common in the minocycline than in the control group (p=0.007); mean blood loss, operation duration, and postoperative stay, and the frequency of postoperative pneumothorax recurrence did not differ significantly between groups (table 4). The pleural adhesions noted were scant and loose, and mainly located in the anterior superior pleural cavity where the pigtail catheter was inserted (data not shown). The adhesions were easily freed with endoscopic instruments and did not significantly affect thoracoscopic procedures or outcomes (data not shown).

47 patients in the minocycline group and 33 in the control group were available for spirometric measurements at a median of 7 months (IQR 6–10) after treatment (table 5). Neither mean forced vital capacity nor mean forced expiratory volume in 1 s differed significantly between groups (table 5). No patients reported restrictive pulmonary dysfunction throughout the duration of this study (data not shown).

Discussion
Our study is the first prospective, randomised, controlled study to investigate the use of minocycline pleurodesis after simple aspiration and drainage for the treatment of primary spontaneous pneumothorax. We noted that the addition of minocycline pleurodesis after simple aspiration and drainage is safe and more effective than is simple aspiration and drainage without pleurodesis and significantly reduced the frequency of pneumothorax recurrence and subsequent thoracic surgery (panel).

The 1 year recurrence rates recorded in the control group by intention-to-treat analysis in this study seem higher than those reported in the medical literature (mean 30% [range 16–52]).7–9,14,15 However, most previous
Minocycline pleurodesis has been used to reduce the recurrence of primary or secondary spontaneous pneumothorax. Light and colleagues did a randomised trial that showed that tetracycline pleurodesis decreased the pneumothorax recurrence rate from 41% to 25% during 5 years in patients who were admitted to hospital and treated with tube thoracostomies compared with those given chest-tube drainage only. Another randomised trial of chest-tube drainage showed that tetracycline pleurodesis reduced the rate of pneumothorax recurrence from 36% to 13% compared with drainage only during 7 years. We noted similar therapeutic effects with minocycline pleurodesis in our trial, suggesting that minocycline-based or tetracycline-based pleurodesis is effective when given via chest tube or small-bore pigtail catheter.

We chose to use minocycline (a tetracycline derivative) because tetracycline is no longer available. Minocycline is widely available, safe, and inexpensive, and the efficacy of minocycline pleurodesis is similar to that of tetracycline pleurodesis in animal experiments. Additionally, minocycline is more convenient than talc because it can be easily administered through small-bore aspiration catheters and hospital admission is not necessary.

Although chemical pleurodesis effectively reduces the frequency of recurrence, published guidelines do not recommend it as the initial treatment for primary spontaneous pneumothorax. That tetracycline pleurodesis can induce plural adhesions that can cause restrictive pulmonary dysfunction or interfere with subsequent surgery (in the event of recurrence) might be of concern. However, tetracycline pleurodesis has been done in thousands of patients worldwide for many years and no such cases of plural adhesions have been reported.

Surgery remains the standard of care for patients with recurrent primary spontaneous pneumothoraces. We noted that plural adhesions from minocycline pleurodesis did not interfere with subsequent surgery for recurrence. Of the 31 patients in the minocycline group who underwent thoracoscopic bullectomy and mechanical pleurodesis for pneumothorax recurrence had scant, loose adhesions, which did not affect the procedures or outcomes. Mean operation time, blood loss, postoperative hospital stay, and postoperative pneumothorax recurrence were similar in both the treatment and control groups. A possible explanation for this finding is that minocycline pleurodesis might induce different degrees of plural adhesions in patients. Minocycline pleurodesis theoretically induced dense plural adhesions, which can prevent pneumothorax recurrence. All patients with pneumothorax recurrence in the minocycline group had no or scant adhesions during subsequent thoracoscopic surgery; thus, we postulated that minocycline pleurodesis might induce different degrees of plural adhesions in patients. Only patients with suboptimum or no plural adhesions after minocycline pleurodesis present with pneumothorax recurrence. Closely similar spirometry results in the minocycline and control groups suggest that minocycline pleurodesis had no long-term adverse effects on pulmonary function.

Immediate chest pain was the most common complaint associated with minocycline pleurodesis. Despite 300 mg of intrapleural lidocaine before pleurodesis, most patients had immediate chest pains of short duration, which were controllable by pethidine. We suggest that

Panel: Research in context

Systematic review

We searched PubMed, Medline, and Google Scholar with the terms “spontaneous pneumothorax”, “pleurodesis”, “clinical trial”, and “treatment” for papers published in English before July 25, 2012. We also searched the reference lists of relevant papers identified. Prospective randomised trials about the initial treatment of spontaneous pneumothorax with chemical pleurodesis were given preference. We did not limit our search by publication date. In the four studies identified (appendix), tetracycline or talc pleurodesis was instilled via chest tube in hospital inpatients with primary or secondary spontaneous pneumothorax. All four studies showed a significant reduction in pneumothorax recurrence with tetracycline or talc pleurodesis and chest-tube drainage compared with chest-tube drainage alone. No trials of outpatient treatment of primary spontaneous pneumothorax with chemical pleurodesis after simple aspiration and drainage through an intravenous-needle and small-bore pigtail catheter in patients aged 15–40 years were identified, and thus the safety and efficacy of the treatment remains unknown.

Interpretation

In a prospective randomised trial of 214 participants, we showed that minocycline pleurodesis after simple aspiration and drainage is safe and more effective than simple aspiration and drainage alone for primary spontaneous pneumothorax with chemical pleurodesis after simple aspiration and drainage through an intravenous-needle and small-bore pigtail catheter in patients aged 15–40 years were identified, and thus the safety and efficacy of the treatment remains unknown.

Figure 3: Suggested algorithm for the treatment of primary spontaneous pneumothorax

Modified from Henry et al.29
in patients with primary spontaneous pneumothoraces who have high recurrence risks after simple drainage.30

Our study has some limitations. First, the trial was not double-blind; however, we tried to minimise bias by masking the independent radiologists who reviewed patients’ chest radiographs to allocated treatment. Second, our study population is small because primary spontaneous pneumothorax is not a common disease. Patients are often treated by their primary care doctors without referral to medical centres, and thus clinical trials of primary spontaneous pneumothorax are difficult to do. Third, only a small number of patients underwent long-term pulmonary function tests and the follow-up time was short, and thus evidence of restrictive pulmonary dysfunction after minocycline pleurodesis could be weak. However, no restrictive pulmonary dysfunction was reported after minocycline pleurodesis during more than 5 years. Finally, the role of minocycline pleurodesis remains unclear in patients older than 40 years and in those with secondary spontaneous pneumothorax.

Contributors
J-SC was the principal investigators of this study (after January, 2011). P-CY conceived and designed the study. J-SC conceived and designed the study, analysed and interpreted the data, and drafted and submitted the Article for publication. H-SI conceived and designed the study, enrolled patients, and provided treatment. K-TT and H-HH did the medical literature search, gathered data, enrolled patients, and provided treatment. AY and W-JC collected data, enrolled patients, and provided treatment. W-KC drafted the Article and submitted the paper for publication.

Conflicts of interest
We declare that we have no conflicts of interest.

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