Efficacy and analgesic use during the therapy of iatrogenic pneumothorax using Pleuralvent™ and Chest Tube (ASPIRATE): A randomised controlled trial protocol

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Background. Iatrogenic pneumothorax is a common complication of various diagnostic and therapeutic procedures such as transbronchial lung biopsies. The classical mode of treatment is chest tube insertion. Pneumothorax devices are now available on the market but there is a dearth of data on their efficacy to treat iatrogenic pneumothorax. It is important to provide such data as the pathophysiology of iatrogenic pneumothorax is different in comparison with spontaneous pneumothorax for which some data is available.

Methods. This is a randomized, non-blinded, actively controlled trial of effectivity of iatrogenic pneumothorax treatment using the Pleuralvent™ device and chest tube insertion (16F). The secondary aim is to compare the overall pain level and the need for analgesic treatment in both treatment arms. We are planning to enrol 126 patients (63 in each treatment arm).

Discussion. Preliminary results showed similar effectivity of the Pleuralvent™ system compared to large bore chest tube insertion. This randomized clinical trial should confirm these results and prove that the Pleuralvent™ system is an effective way of treatment of patients with iatrogenic pneumothorax. If Pleuralvent™ proves to have the same level of efficacy, it may become the standard of care of patients with iatrogenic pneumothorax.

Trial registration: ClinicalTrials.gov Identifier: NCT03700554

Key words: iatrogenic pneumothorax, Pleuralvent™, chest tube

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BACKGROUND

Pneumothorax is a common complication of different diagnostic and therapeutic procedures and usually requires invasive treatment as observation alone is inappropriate for symptomatic patients and for those with a large pneumothorax. The incidence of iatrogenic pneumothorax differs for various procedures and patient cohorts (e.g. 6.6% in the case of transbronchial lung biopsy) (ref.¹). Classical treatment methods include needle aspiration (14–16 G needles) and chest tube insertion (16+ F catheters) (ref.²). A third option is the insertion of small-bore catheters (<16F), which appear to be equivalent according to some studies^{3,4}. Small-bore catheters have the same success rate and according to some studies, this treatment is less painful^{5,6}. Heimlich valves, developed by the American thoracic surgeon Henry Heimlich in 1965 (ref.⁷), were designed for use as a drainage tool to obviate intrapleural suction. These valves were used as an outpatient treatment for pneumothorax in different types of patients⁸ and for the treatment of pneumothorax in wounded soldiers in armed conflicts⁹. The greatest

advantage in comparison with underwater seal drainage is the full mobility of patients and the small size of the devices. However, there is still a need for the insertion of a classic chest tube and this stimulated the development of systems that combine small bore catheters and Heimlich valves into one compact device. These are now available and have become an integral part of advanced medical interventions in pleural diseases (according to the European Respiratory Review) (ref.¹⁰). Valves are designed for easy insertion (typically in the 2nd intercostal space in the mid-clavicular line) by puncture technique and they offer the possibility of full outpatient treatment. As it contains an 8F catheter (together with the aforementioned puncture technique without the need of tube channel preparation), we assume less trauma to the intercostal soft tissue and thus greater patient tolerability and less pain. However, as there are currently no data available in the literature to support this statement and due to the higher cost of this treatment (approximately 10 times higher), it is necessary to provide evidence of the advantages of these ambulatory devices for national healthcare system authorities.

Although the Pleuralvent™ system is currently available on the market, there is not much data regarding its efficacy, cost-effectiveness and overall tolerability. This randomized clinical trial should answer these questions and compare it with standard treatment with a large bore chest tube – 16F. We are planning to show whether the Pleuralvent™ system is comparable, superior or inferior to standard pneumothorax treatment in the Czech Republic.

METHODS

Study design and objectives

ASPIRATE is a multicentric, randomised, non-blinded, actively controlled clinical trial. The study will be carried out in tertiary care hospitals (Department of Respiratory Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic and Department of Respiratory Medicine, 1st Faculty of Medicine Charles University in Prague, Thomayer-Hospital, Prague) in accordance with the protocol of Good Clinical Practice and the legislation of the Czech Republic. The University Hospital Olomouc Ethics Committee approved the ASPIRATE clinical trial on the 20th of August 2018 (Reference number 129/18). The trial will be conducted in accordance with the ethical principles outlined in the latest Declaration of Helsinki and the informed consent will be obtained prior to enrolment. The trial is registered in the international registry of clinical trials ClinicalTrials.gov as NCT03700554.

Following the completion of the initial screening (fulfilling of both inclusion and exclusion criteria) and the signing of informed consent, a patient with iatrogenic pneumothorax (PNO) will be treated, according to randomisation using the sealed envelope system, with either the Pleuralvent™ system or a large bore chest tube – 16F. A control chest X-ray will be performed immediately after the introduction of the therapeutic method and the following 3 days of therapy. For the treatment of pain, only metamizole or tramadol will be used. This limitation is due to the need for homogenisation of the study group for further interpretation of the results. These analgesics have been chosen as they are widely used currently, providing good analgesia with few side effects.

If no signs of PNO are present, the therapy will be terminated. In cases where the lung is not completely expanded, the control X-ray will be repeated on the 5th, 7th and 10th day of therapy. If following this, the PNO persists without resolution, the therapy will be declared non-effective and other therapy modes will be used (conversion to large bore chest drainage in the Pleuralvent™ group and surgical treatment in the chest drainage group).

A 4-year period until the completion of the planned number of patients is foreseen.

Study participants and recruitment

Patients with iatrogenic pneumothorax indicated for invasive treatment will be enrolled in this trial. Exclusion

criteria will be chronic analgesic therapy, contraindications for Pleuralvent™ use, non-compliance of patients, clinically significant hepatopathy (alanine aminotransferase or aspartate aminotransferase > 3 times normal values), clinically significant renal insufficiency (glomerular filtration < 0.5 mL/kg/min), and allergy to metamizole/tramadol.

For the study, we plan to enrol 126 patients, 63 for each arm of the clinical trial. The patient has the right to discontinue participation in the trial at any time. Patients will immediately inform the trial staff about such a decision.

Clinical follow-up

After the end of the clinical trial, patients will be followed up in the standard way according to basic diagnosis.

Statistical analysis

The statistical analysis will be performed using Statistica software (ver. 12, Statsoft CZ, Prague, Czech Republic). Kaplan-Meier plots will be used to compare the duration of hospitalization. Success rates will be assessed with the chi-squared test or Fisher's exact test when appropriate.

Description of the "discontinuation rules" and "discontinuation criteria" for individual subjects and the entire study will be included.

Endpoints

As a primary endpoint, the treatment efficiency, defined as a condition with no need for further therapy modes will be followed-up. As secondary endpoints, the use of analgesic, the overall quality of life, the time to lung re-expansion, and the subjective pain perception according to the visual analogue scale in both arms will be compared.

DISCUSSION

There is a dearth of data on the efficacy, tolerability and cost effectivity of the Pleuralvent™ device. To the best of our knowledge, this is the first randomized trial of iatrogenic pneumothorax treatment using the Pleuralvent™ device in comparison with chest tube insertion.

Our preliminary results clearly show that the use of the Pleuralvent™ device is associated with a statistically significant shorter period of hospitalization than the standard chest tube. The duration of treatment, as well as hospitalization, were a third longer in patients undergoing standard chest drainage than that in the Pleuralvent™ arm. To compare the use of the analgesics, a method using Defined Daily Doses of analgesics was used. Preliminary results showed a significant decrease in analgesic use in patients treated with the Pleuralvent™ device.

Although the Pleuralvent™ device is more expensive than the standard chest tube, it may provide significant savings in healthcare due to shorter hospitalization periods and lower analgesic consumption. The potential

reduction in pain and the increase in quality of life may outweigh the higher economic burden of these new treatment strategies.

Implications of findings

If this study confirms that Pleuralvent™ treatment has the same efficacy in the treatment of iatrogenic pneumothorax and the overall quality of life and pain level is comparable and possibly better, Pleuralvent™ could become the new standard in the treatment of pneumothorax. Hypothetically, the ambulatory treatment of out-patients using this device may be feasible.

Trial status

Patients are currently being enrolled into this trial in both centres.

Author contribution: MS, MP: conceptualization, literature search and manuscript writing; SG, PJ, JZ, MV, LS, PZ, AGA: conceptualization and literature search; VK, KU: critical reading and manuscript revision.

Conflict of interest statement: The authors declare no conflicts of interest.

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