Ambulatory management of secondary spontaneous pneumothorax: a randomised controlled trial

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Take home message

Ambulatory management with a flutter valve does not shorten overall length of stay in patients with secondary spontaneous pneumothoraces compared to standard management. This was due to increased risk of treatment failure with ambulatory management.

Introduction

Secondary spontaneous pneumothorax (SSP) is defined as a pneumothorax in the presence of known underlying lung disease. Many diffuse lung diseases are associated with SSP, with chronic obstructive pulmonary disease (COPD) present in approximately 70% of cases [1]. In the United Kingdom (UK), SSP is the leading cause of admission in patients with spontaneous pneumothorax, accounting for over 60% of admissions [2]. A French epidemiological study has demonstrated that the duration of hospitalisation in SSP is twice that of patients with primary spontaneous pneumothorax (PSP) [3]. The duration of air-leak is longer, and the in-hospital mortality greater when SSP and PSP are compared [4, 5]. Using a one-way flutter valve, rather than current standard management of a chest tube attached to an underwater seal chamber, may increase mobilisation and shorten hospital length of stay (LOS). The one-way flutter valve can either be attached to the end of a chest tube, as with the Atrium Pneumostat (Atrium Medical, Merrimack, New Hampshire, USA) chest tube valve, or integrated into an "all in one" ambulatory device that does not require prior chest tube insertion, such as the Pleural Vent (Rocket Medical PLC, Watford, UK). There are no published prospective studies describing use of flutter valves in patients with SSP. Pooled results from retrospective studies suggest that flutter valves may reduce hospital LOS in this patient cohort [6]. This study tested the hypothesis that ambulatory care with flutter valves in management of SSP shortens the length of hospitalisation compared with standard care.

Material and methods

Study design

This was a multi-centre open-label randomised controlled trial comparing ambulatory management with a flutter valve to standard care (chest tube attached to an underwater seal chamber) in patients with SSP. The trial was supported by an unrestricted research grant by Rocket Medical UK, who supplied Pleural Vents for study participants. Trial design, implementation, data collection, analysis and writing of the manuscript were performed by the trial investigators without commercial involvement.

Study subjects

The trial recruited patients with SSP from 13 secondary and tertiary care centres in the United Kingdom. SSP was defined as a pneumothorax in a patient with known underlying lung disease or in a patient older than 50 years old with a significant smoking history or CT scan evidence of smoking-related emphysema. Potential patients were identified on admission to hospital and eligible if they had a diagnosis of SSP confirmed by chest radiograph or CT scan, and if chest tube drainage was clinically indicated and technically possible as per BTS guidelines 2010 [7]. Patients were eligible if they had a chest tube placed for SSP within the last 36 hours and there was evidence of ongoing air-leak.

Exclusion criteria were iatrogenic or traumatic pneumothorax, a chest tube in situ, current or past tension pneumothorax, significant hydropneumothorax (≥25% lung field), bed-bound patients, patients age less than 18 years of age, contraindication to chest drain insertion, females who were pregnant or lactating, participants with no access to a phone, or were unable to comply with trial requirements or provide informed consent. All patients provided written informed consent. After enrolment, patients underwent randomization using a centralized, web-based system (RedPill, Sealed Envelope, Clerkenwell, UK). Trial-group assignments were made in a 1:1 ratio, in random permuted blocks [8]. Both participants and investigators were not blinded to trial assignment. North Bristol NHS Trust provided trial oversight, and ethics approval for recruitment was obtained from the South West - Exeter Research Ethics Committee (REC 16/SW/0023) The trial was prospectively registered with the

International Standard Randomised Clinical Trials Number (ISRCTN79956557). The study protocol is available in the appendix.

Procedures

Standard Care

Patients allocated to standard care underwent 12F Seldinger chest tube insertion and this was attached to an underwater seal. Resolution of pneumothorax was identified by full lung expansion on chest radiograph and cessation of bubbling of the underwater seal bottle. Decisions to remove chest tubes were made by the treating physician, with guidance that chest drains should be removed at the earliest opportunity following clarifying the absence of an ongoing air leak.

Ambulatory Care

Patients allocated to ambulatory care received a flutter valve. Initially the flutter valve used for ambulatory care was the Pleural Vent (PV) (Rocket Medical, Watford, UK) (Figure 1a) (ambulatory pneumothorax device, 8F pig-tailed catheter mounted on an 18G needle, self-contained one-way valve and vent). The PV was cutaneously fixed in place with a hydrocolloid fixation device. After 12 months of recruitment, due to high proportions of potential eligible patients excluded from trial entry due to prior chest drain placement in the emergency room, an ethical amendment was submitted to allow the use of Atrium Pneumostat for patients with a chest tube already in situ. For these patients the Atrium Pneumostat chest tube valve (Atrium Medical, Merrimack, New Hampshire, USA) was attached to their 12F chest tube (one-way flutter valve which attaches to the end of a standard chest tube, 30 ml collection capacity chamber for secretions) (Figure 1b). The study exclusion criteria were changed to only exclude patients with a chest tube in situ for over 36 hours

Resolution of pneumothorax was confirmed by a chest radiograph and cessation of air-leak through the device. The decision to remove flutter valve device was decided by the treating physician, with guidance that device should be removed at the earliest opportunity following clarifying the absence of an ongoing air leak. Patients were able to be discharged from hospital with the ambulatory device in situ at the treating physician's discretion on the following criteria: 1) Patient deemed to be clinically stable (haemodynamic stability, stability of clinical observations and patients symptoms have returned to baseline level prior to pneumothorax); 2) the pneumothorax was stable (pneumothorax not increasing in size on imaging, functioning ambulatory device and no requirement for thoracic suction) and 3) the patient understood the care and function of ambulatory device and there was a responsible person at home able to assist patient or call for help if required.

Use of thoracic suction and referral for thoracic surgery was permitted in both treatment arms at the treating physician's discretion.

Patients were followed up until 26 weeks after randomization, or until death. Face to face follow-up consultations took place at 4 and 12 weeks, with a clinical assessment, chest radiograph, and a self-completed patient questionnaire. Spirometry was conducted at week eight. At week 26, the final follow up consultation was by telephone.

Analysis

Primary

The primary outcome was a patient's total number of hospital bed days due to SSP during the first 30 days from randomisation, including readmissions. Patients remaining in hospital overnight were

regarded as one day hospitalisation; for those discharged on the same day this was recorded as a zero days LOS. Otherwise partial days of hospitalisation were rounded up to the nearest complete day.

Secondary

Secondary outcomes included participant-related outcome measures with difference in daily breathless score and chest pain as assessed by visual analogue scale (VAS) over 28 days, with outcomes reported over the first seven and 28 days. The VAS breathlessness consists of a 100mm horizontal line, labelled from 0mm for "Not breathless at all' to 100mm for "Worst possible breathlessness", marked by the participant and measured by two assessors independently[9]. Quality of Life was assessed using the EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) questionnaire daily over first 14 days, and at four and 12 weeks after randomisation [10].

Hospital LOS was assessed for the patient's first admission, from admission date until discharge. Additionally, length of hospitalisation until classified medically fit for discharge, as based on pre-determined criteria, and length of hospitalisation from randomisation were recorded. Time from randomisation until pneumothorax resolution, drain removal and until further pleural intervention was recorded. Failure of initially randomised treatment, defined as requiring an additional pleural intervention, within the first week was recorded. The timing of any thoracic surgical intervention following the initial presentation with SSP was documented. The date of any ipsilateral pneumothorax recurrence within the first six months was recorded. Recurrence was recorded from randomisation to event. Recurrence was defined as an ipsilateral pneumothorax identified on a chest radiograph, after a chest radiograph had confirmed complete resolution for at least 24 h following the removal of any catheter or drain at the patient's initial presentation with SSP. Serious adverse events (SAE) and adverse events (AE) related to trial interventions were recorded.

A priori sub-group analysis was performed for the primary outcomes using an interaction test and considered statistically significant at the 5% level. Sub-group analysis was performed comparing Atrium Pneumostat with standard care and severity of COPD (as expressed by FEV_1).

Statistical analysis and power calculation

British Thoracic Society pleural disease audit data (2011, unpublished) for 115 patients with SSP showed a mean LOS of 12.3 days (SD=9.89) and median LOS of 8 days (IQR range: 4–17.5 days). Assuming 90% power and 5% significance, the sample size is determined by the coefficient of variation and the effect size. The coefficient of variation was 0.8. In order to detect an effect size of 0.5 with a coefficient of variation of 1 would require 30 patients per group [11]. The calculated coefficient of variation within the audit data was lower, suggesting a smaller sample size is necessary. However, a study size of 60 patients allows for a margin for error in relation to the effect size, including a 10% loss to follow up rate, suggesting a total required sample size of 66.

Analyses were performed using IBM SPSS, Version 23.0 (SPSS Inc. Chicago, IL). The primary analysis for each outcome was intention-to-treat, meaning that all patients in whom an outcome was available were included in analysis, and were analysed according to their randomized treatment group. Descriptive statistics were used to summarise patient characteristics and clinical data. Medians (IQR) were calculated for hospital LOS. Continuous non-parametric variables were analysed using Mann-Whitney test and categorical data was analysed using Chi-squared test. All tests were two-sided and considered statistically significant at the 5% level.

Urgent Safety Review

In January 2019, 22 months after the first patient was enrolled, an urgent safety review was conducted by the Trial Steering Committee (TSC), due to reports from Trial Investigators of SAE in patients receiving ambulatory care. On TSC review, a majority of SAE appeared to be causally related to use of the PV. Six of 13 (46%) patients managed with this device required an additional chest tube insertion within the first week due to treatment failure. The TSC felt this was an unacceptably high risk of device failure, and stopped use of the PV, but continued use of the Atrium Pneumostat in those randomized to ambulatory care.

Results

Recruitment and Population Characteristics

Recruitment and follow-up of participants took place from March 2017 to March 2020. Of potential participants, 186 were screened/recruited and 41 were randomised (Figure 2). Of these, 21 were randomised to ambulatory care and 20 to standard care. Of patients receiving ambulatory care, 13 were managed with a PV and 8 with a Pneumostat. The two groups were well matched at baseline (Table 1). All patients were included in the primary analysis. The study did not reach the target sample size of 66 in the pre-defined study period due to slower than anticipated recruitment.

	Ambulatory care (N=21)	Standard care (N=20)
Age – mean (SD), years	63.4 (12.6)	68.1 (9.2)
Male – no. (%)	14 (67)	17 (85)
Side of pneumothorax - no. (%)		
Right	10 (48)	11 (55)
Size of pneumothorax at presentation		
Interpleural distance at hilar point (cm)	3.1 (2.0)	4.8 (2.8)
Size ≥2cm at hilum. No (%)	15 (71)	17 (85)
Smoking status No. (%)		
Current smoker	8 (38)	5 (25)
Ex-smoker	11 (52)	15 (75)
Never-smoker	2 (10)	0
Pack-year history. Mean (SD)	30.9 (12.8)	37.6 (15.9)
Previous pneumothorax No (%)	6 (29)	8 (40)

Respiratory history No (%)		
COPD	15 (71)	12 (60)
Asthma	3 (14)	4 (20)
Interstitial Lung Disease	1 (5)	0
Non-CF Bronchiectasis	0	0
Lung Cancer	0	2 (10)
Intercurrent pulmonary infection	0	1 (5)

Table 1: Baseline characteristics by treatment allocation

COPD, Chronic obstructive pulmonary disease; CF, Cystic fibrosis

Primary analysis

Total hospitalisation in the first 30 days was 6 days (IQR 1-15.5) in those who received ambulatory care and 6 days (IQR 2.25-15.5) in those who received standard care (p =0.77) (Table 2).

	Ambulatory care (flutter valve)				Standard care (Chest tube)				
	N	Mean	Median	IQR	N	Mean	Median	IQR	P value
Length of Hospital stay	21	11.57	6.00	1.00-15.50	20	8.70	6.00	2.25 - 15.50	0.77

Table 2: Primary outcome by prespecified sub-group analysis

Secondary analysis

The hospital LOS for the initial admission was 1 day (IQR 1-14) for ambulatory care versus 3.5 days (IQR 2-7) for standard care (p =0.122). The median time until medically fit for hospital discharge in those who received ambulatory care was 1 day (IQR 1-1), versus 2 days (IQR 2-6) in those who received standard care (p =0.001). The time to chest tube removal was 3 days (IQR 1.5-9) for ambulatory care, versus two days (IQR 1-6) for standard care (p =0.36). Failure of initial treatment within the first week occurred in 6 (28%) of the 21 patients receiving ambulatory care versus 3 (15%) of the 20 patients receiving standard care (p =0.29). Of those 21 patients receiving ambulatory care, 8 (38%) required an additional pleural procedure within three months from randomisation, compared with 6 (30%) of the 20 patients who received standard care (p = 0.59).

There was no difference in the percentage of patients who required thoracic surgery (ambulatory care: 6/21 (29%), standard care 6/20 (30%)) between the two groups. There was no difference in the percentage of patients who received medical pleurodesis (ambulatory care: 2/21 (10%), standard care 2/20 (10%)) between the two groups, nor was there a difference in 6-month recurrence rates (ambulatory care: 4/21 (19%), standard care 4/20 (20%)).

In patients receiving ambulatory care, the hospital LOS in the first 30 days was 1.5 days (IQR 1-24.8) for those managed with the Atrium Pneumostat, and nine days (IQR 2-15.5) for those managed with a PV (p =0.374) (Table 3). In the first week after randomisation there were no treatment failures with the Pneumostat, but there were 6/13 (46%) failures with the PV (p =0.046).

	Atrium Pneumostat			Pleural Vent			
	N	Median	IQR	N	Median	IQR	P value
Length of Hospital stay (1st 30 days)	8	1.5	1.00-24.75	13	9.0	2.00-15.50	0.37

Table 3: **Length of stay of Atrium Pneumostat versus Pleural Vent**

Mean breathlessness and pain VAS scores improved during the first 30 days in both groups (Figure 4). Whilst there was no difference in overall VAS breathlessness between standard care and ambulatory care, the trend over time for VAS breathlessness was group dependent (p <0.05). In those who received ambulatory care there was progressive improvement in VAS breathless, whilst for those who received standard care there was an initial sharp decrease. There was no significant difference In VAS pain scores between study group using the linear mixed model (p =0.093).

Quality of life scores improved throughout the study in both patients receiving ambulatory and standard care, with significant improvement in both mean EQ-5D-5L and EQ5D VAS (Figure 5). Mean EQ5D VAS improved between baseline and week four (p <0.001) in both groups and did not differ between groups at baseline (p=0.10), at week four (p =0.48), or week 12 (p =0.21). Mean EQ-5D-5L improved between baseline and week four (p =0.02 and 0.01, respectively) in both randomised arms and then did not differ between groups at baseline (p =0.85), at week four (p =0.44), or week 12 (p =0.50).

Adverse events

Ambulatory care accounted for 33 (56%) of the total 59 AEs. Patients in standard care arm had 26 (44%) of the total 59 AEs (Table 4). Rates of treatment failure were high in those treated with the PV, with six patients requiring an additional chest tube within the first week at a median time of two days from randomisation. These six cases included three instances where the pneumothorax increased in size and two instances where the PV blocked resulting in subcutaneous emphysema (SE). There were

two cases where the PV was dislodged, one where the vent was attached to a suction device due to SE, with the resultant increased pull on drain leading to dislodgement, and another case where it was accidentally dislodged overnight.

Event	Ambulatory care (N=21)	Ambulatory care- Pleural Vent (N=13)	Ambulatory care- Atrium Pneumostat (N=8)	Standard care (N=20)	Total (N=41)
Chest pain					
Related to insertion of device	0	0	0	1	1
While device in-situ	3	1	2	1	4
Subcutaneous emphysema	6	6	0	3	9
Infection					
Pleural	2	1	1	2	4
Subcutaneous	0		0	1	1
Pneumonia/chest infection	7	3	4	1	8
Device dislodgement	2	2	0	1	3
Device blockage/enlarging pneumothorax	4	4	0	1	5
Death due to underlying respiratory disease	1	1	0	0	1
Death due to pneumothorax	0	0	0	1	1
Readmission due to Pneumothorax	5	3	2	7	12
Other	3	2	1	7	10
Total AEs	33	23	10	26	59

Table 4: Adverse events

Discussion

This randomised controlled trial compared ambulatory management using two types of flutter valves with standard care using a chest tube attached to an underwater seal chamber, in patients with SSP. The trial found no difference in total length of hospitalisation, including readmissions, in the first 30 days after randomisation between the two groups. While the length of hospitalisation for the initial admission was non-significantly shorter in those receiving ambulatory care, high rates of early treatment failure in this group, with subsequent readmission, increased the overall LOS. This, combined with a lower than anticipated length of hospital stay for participants who received standard care, at less than a third of that observed in epidemiological studies, likely contributed to the similar LOS in the two groups in the present study [2].

This is the first randomised study to investigate ambulatory management strategies in SSP. In 2015, a systematic review of ambulatory treatment in management of pneumothorax identified 16 non-randomised studies, seven of which included patients with SSP. No study looked exclusively at SSP, and this patient group formed only 10% of the review population [6]. The review cited high rates of success in patients with SSP, defined as use of a flutter valve with a chest tube to manage pneumothorax. A subsequently published prospective case series of a selected cohort of patients with SSP reported that 65% (32/49) were successfully managed with the AP attached to a 12F chest drain [12]. However, non-randomised case-series are subject to high risk of selection bias, with sick and

complex patients at greater risk of exclusion. Three randomised controlled trials have examined use of flutter valves in patients with primary spontaneous pneumothorax (PSP) with reported success [13-15]. The most recent, and largest, randomised 236 patients with PSP to either a chest drain attached to under water seal or to ambulatory management using the Rocket PV. It found significantly shorter LOS in patients managed with the PV compared to standard care [15]. Patients with a PV were, however, at higher risk of serious adverse events, with the ambulatory cohort experiencing all 14 SAEs. Whilst, 21% patients in the PV arm required a further pleural procedure, the early failure rate seen in our trial was rare in PSP. Only 3% of the 117 patients receiving PV for PSP had an enlarging pneumothorax at outpatient review requiring chest tube insertion and only two (2%) patients with PSP suffered a device malfunction.

In this study of SSP patients, rates of treatment failure with the PV, presenting as either increasing pneumothorax size or surgical emphysema, were higher, with more than half requiring an additional chest tube within the first week for pneumothorax management. This difference in success of the PV in PSP and SSP likely reflects their distinct disease processes, with SSP associated with higher rates of persistent air-leak and broncho-pleural fistula formation than PSP[16]. Patients with SSP, typically also have poorer respiratory reserve and therefore less able to tolerate an undrained pneumothorax. Interestingly, results from this trial suggest this high failure rate in ambulatory care may be device specific, with large differences in hospital LOS and rates of complications seen in patients who received the two types of flutter valves. In contrast with the high treatment failure rates in patients with a PV, there were no early treatment failures and a trend towards a shorter LOS in those managed with the Atrium Pneumostat. A plausible explanation for the observed increased failure rate with the PV is its smaller 8F gauge catheter, compared with the larger 12F used with the Pneumostat. The 8F catheter may potentially not be of sufficient calibre to manage the large volume air-leak that can occur with SSP or may be at a higher risk of partial or complete obstruction from luminal secretions.

This is the first study to demonstrate that pleural intervention in SSP improves patient related outcomes, with early and maintained improvements in breathlessness, chest pain and quality of life in both ambulatory and standard care. Ambulatory care, however, did not demonstrate superiority over standard care in these patient related outcomes. This is similar to the results in the recent trial of the PV in patients with PSP, which found no differences in VAS pain or breathlessness scores between ambulatory and standard care [15].

Long-term follow up at six-months after presentation with SSP showed pneumothorax recurrence rates slightly lower than rates in previous publications [2, 3, 17-19]. This likely reflects the high rates of surgical and medical pleurodesis in this study and the duration of follow-up.

There are limitations to our trial. The trial did not meet the intended recruitment target and the failure to reject the null hypothesis may be a result of the small sample size. Under recruitment was primarily due to high numbers excluded due to urgent treatment being required before randomisation could be performed. It was not feasible to blind the study participants and clinicians to the study intervention, therefore a primary end-point was selected that was easily measurable and objective.

In conclusion there was no difference in LOS between patients managed with ambulatory care compared to chest drain attached to underwater seal. This may be related to high rates of treatment failure with the PV and a shorter LOS in the standard arm than previously cited. We do not advise use of PV in patients with SSP, and the encouraging results with PV in PSP are not translatable to this population. Our study has, however, shown early supportive evidence of safety in the attachment of an Atrium Pneumostat to an existing chest drain to ambulate patients with SSP. A dedicated trial using this device is now warranted.

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