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Original Article

Does higher lavage height improve lavage effect for pulmonary alveolar proteinosis patients

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Abstract: Background: Many methods were used to improved lavage effect. Here we observed the influence of higher lavage height on the changes of hemodynamics and respiratory mechanics during whole lung lavage, and compared blood gas analysis, pulmonary function and chest radiograph after lavage, to evaluate the lavage effect. Method: Twenty pulmonary alveolar proteinosis patients were randomly allocated into two groups to receive whole lung lavage, respectively at the height of 100 cm (C group, n=10) or 150 cm (H group, n=10) above midaxillary line. Results: The lavage duration of H group is shorter than that of C group (P<0.05), but the other lavage parameters, CVP, SI, ITBVI, $PETCO_2$, Ppeak and VT had no difference between two groups during lavage (P>0.05). The values of gas exchange in two groups had no difference before lavage, three days and one week after lavage (P>0.05). Although the FVC, FEV1, FEV_1/FVC ratio, and DLCO had no difference in one week after lavage between two groups (P>0.05), the FVC, FEV_1 in H group were lower than those in C group in six months later (P<0.05). The results of chest radiograph had no significant difference between two groups after lavage (P>0.05). Conclusion: Whole lung lavage at higher lavage height can be tolerated by pulmonary alveolar proteinosis patients without causing unstable respiratory mechanics and hemodynamics changes, but higher lavage height cause no significant improvement in pulmonary function and chest radiograph after lavage.

Keywords: Pulmonary alveolar proteinosis, whole-lung lavage, respiratory mechanics, hemodynamic, lavage method, pulmonary function

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease which is characterized by the accumulation of surfactant-like material within the alveoli that results in progressive respiratory failure and gas exchange impairment [1-3]. It has been treated successfully since the early 1960s by whole-lung lavage (WLL), which remains the standard of therapy today [4-6]. There are many methods to improve the lavage effect [7-9]. Roger has modified previously published technique [10-12], such as large-volume (40-70 L per lung) for PAP lavage. Other modifications include manual percussion [13], vibration [14], chest compression and trypsin addition to the lavage fluid [15].

Among various techniques aim to enhance the lavage effect, increasing the lavage height has not been reported. Furthermore, there are many controversies about the optimal lavage height. The lavage height has been supposed to 30 cm [16-21], 50 cm [2], and 60-100 cm above midaxillary line [22, 23]. We conjecture that, if lavage pipe size remains unchanged, lower lavage height decreases lavage pressure, thus results in decreasing lavaged alveolar area and impairing lavage effect, and the consequent lower lavage pressure may decrease lavage solution absorption by alveolar capillary, therefore improves the recovery rate. Higher lavage height may be beneficial in that it increases lavage pressure, resulting in increasing lavaged alveolar area, which perhaps enhances the lavage effect. However, it may cause more solution absorption by alveolar capillary, thus the recovery rate decreases and unstable hemodynamics appears. Furthermore, raising lavage height may possibly incur pneumothorax and lavage leakage.

Our conjectures remain to be verified by evidence. So the present comparative and ran-

domized study mainly investigated the influence of lavage height on the changes of hemodynamics and respiratory mechanics during whole lung lavage, and compared pulmonary gas exchange, pulmonary function test, chest radiograph before and after lavage, to find out whether increasing lavage height was safety and effectiveness for whole lung lavage.

According to the data of Aquinaqa [23], the average arterial pressure (MAP) was normally distributed with standard deviation 9 (7.8%). We considered that blood pressure changed significantly when the MAP increased or decreased over by 20%. If the true difference in the experimental and control means is 20%, we will need to study 4 experimental subjects and 4 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) .8. The Type I error probability associated with this test of this null hypothesis is .05.

Material and methods

Patients

There were twenty PAP patients scheduled for whole lung lavage from January 1, 2014 to December 30, 2014. This was a double blinded clinical trial. By randomly allocated (computer-generated lists), patients were lavaged in sequence, initially the left lung, then the right lung, with isotonic saline solution suspended at the height of 100 cm (C group, n=10) or 150 cm (H group, n=10) above midaxillary line. The study protocol was approved by the China Clinical Trials Registry Center (registration number: ChiCTR-TRC-13004074), and all participants provided written informed consent. The selected patients were ASA physical status II-III, aged 20-60 years, and pulmonary alveolar proteinosis was confirmed by bronchoscopic biopsy. The criteria of exclusion were known allergies to any used anesthetic drug, a history of malignant hyperthermia; significant renal or hepatic dysfunction; body mass index ≥ 30; serious cardiovascular disease; additionally, patients who had been exposed to whole lung lavage in last two years were excluded.

Whole lung lavage

The procedure was performed in the supine position. Warmed normal saline solution (37°C) in 1-L aliquots was infused into the lung, then the inlet tube was clamped off. With the aid of suction, the protein effluent was drained out. The sequence was repeated until the effluent became clear. Two-lung ventilation (TLV) was commenced at the end of the procedure. Once circulation and respiration attained stabilization, the patient was transferred to the intensive care unit for ventilation support and extubated in the next day. All patients were followed up one week and six months after lavage.

Heart rate (HR), invasive mean arterial pressure (MAP), saturation of peripheral oxygen (SPO_2) were recorded before anesthesia, at the beginning of left-lung lavage, the fifth left-lung lavage, the end of left-lung lavage, at the beginning of right-lung lavage, the fifth right-lung lavage, at the end of right-lung lavage, and 10min after resuming two-lung ventilation. 5 patients in C group and 8 patients in H group also received pulse indicator continuous cadiac output (PICCO) (Oximetry PA catheter, 7.5 F. Pulsion Medical Systems Inc, Germany) to measure hemodynamic values. Central venous pressure (CVP), cardiac output index (C.I.), stroke volume index (SI), peripheral vascular resistance index (SVRI), extravascular lung water index (EVLWI), intrathoracic blood volume index (ITBVI) were recorded. All above measurements were performed after the lavage fluid was sucked out.

Inspired oxygen concentration (FiO_2), end-tidal carbon dioxide tension ($PETCO_2$), peak-airway pressure (Ppeak) and tidal volume (VT) were recorded after anesthesia, at the beginning of left-lung lavage, the fifth left-lung lavage, the end of left-lung lavage, at the beginning of right-lung lavage, the fifth right-lung lavage, at the end of right-lung lavage, and 10 min after resuming two-lung ventilation.

Dopamine or atropine was used to maintain stable hemodynamics in the event of low blood pressure (systolic blood pressure below 70 mmHg) or low heart rate (heart rate below 50 bpm). Intravenous mannitol and furosemide were given if CVP increased to over 15 mmHg. The lavage volume, return volume, lavage duration, anesthesia time, extubation time and side effects were recorded.

A serial blood-gas determination was recorded before lavage, at the end of lavage, three days after lavage, and one week after lavage.

Table 1. Patients' demographic data ($\bar{x}$±s) (n=10)

Parameter	C group	H group
Age (years)	42.4±12.03	40.9±10.88
Male/Female (ratio)	5/5	6/4
BMI	23.39±4.80	24.27±4.25
Once lavaged (n)	2	3
Combined disease (n)		
Hypertension	1	1
Diabetes	0	1
Thrombocytopenia	1	0

Data are represented as mean ± SD. No significant differences between groups were detected.

Pulmonary function test and chest radiograph were performed before lavage, one week after lavage and 6 months after lavage. The results of chest radiograph were divided into no change, improvement, significant improvement and worsen when compared with the results before lavage. Pulmonary function test and chest radiograph were performed by respiratory physician and radiologist who were blinded to the randomized groups.

Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences for windows (SPSS 13.0.1; SPSS Inc; Chicago, Il, USA). A power analysis with a pilot study revealed a sample size of 4 patients per group would be enough to achieve a type-I error of 5%. Quantitative variables were expressed as means ± SD and categorical variables as number (%). Unpaired t-test was used to compare values between groups. One-way analysis of variance was used to detect differences at different lavage time point in each group. Repeated measures ANOVA analysis was used to compare variables of different groups at different time point. Differences in categorical variables between groups were analyzed by two-independent samples test when appropriate. P<0.05 was considered statistically significant.

Results

No severe complications were observed during lavage. Baseline demographic data was comparable between groups (**Table 1**). The lavage parameters had no difference between two groups except for the lavage duration (**Table 2**). The lavage duration of H group is shorter than that of C group (P<0.05).

Hemodynamic changes during lavage

The repeated measures ANOVA analysis showed that HR, CI, SI and ITBVI of each group had interaction with lavage time (P<0.05), but MAP, SPO_2, CVP, SVRI and EVLWI had no interaction with time (P>0.05).

The trends of MAP and SPO_2 in H group had similar changes with those in C group, but when compared with values in C group, HR was higher at the end of left-lung lavage and right-lung lavage (P<0.05) , MAP was lower at the beginning of right-lung lavage (P<0.01) (**Figure 1**).

The trends of CVP, EVLWI, ITBVI increased gradually after the beginning of left-lung lavage in both groups, especially CVP increased significantly after the beginning of right-lung lavage in H group (P<0.05). The CVP, SI, ITBVI had no difference between groups (P>0.05) (**Figure 2**). The values of CI, SVRI, EVLWI in H group were higher than those in C group, especially at the beginning of left-lung lavage (P<0.05), but had no difference after that point (P>0.05) (**Figure 2**).

Changes of respiratory mechanics during lavage

The repeated measures ANOVA analysis showed that FiO_2, $PETCO_2$, Ppeak and VT had no interaction with lavage time (P>0.05). Ppeak increased significantly after anesthesia and VT decreased gradually in both groups (P<0.05). The values of $PETCO_2$, Ppeak, VT had no difference between groups (P>0.05) (**Figure 3**).

Gas exchange

The repeated measures ANOVA analysis showed that pH, $PaCO_2$ and SaO_2 of each group had no interaction with time (P>0.05), but PaO_2 had interaction with time (P<0.05).

When compared with values before lavage, pH, $PaCO_2$ in C group and $PaCO_2$ in H group had no difference (P>0.05), but PaO_2 and SaO_2 in C group improved at the end of lavage, three days after lavage (P<0.05), and PaO_2 and SaO_2 in H group improved at the end of lavage, one week after lavage (P<0.05). The values in two groups had no difference before lavage, at end of

Table 2. Patients' lavage parameters ($\bar{x}\pm s$) (n=10)

Parameters	C group	H group	*P* value
Total lavage volume (ml)	18302±4613	22227±6118	0.123
Return volume (ml)	16268±4290	19877±6130	0.145
Return rate (%)	86.8±6.0%	88.7±5.0%	0.968
Total urine volume (ml)	3523±1357	3273±820	0.625
Volume of transfusion (ml)	1305±414	1339±307	0.836
Lavage duration (hour)	4.83±1.56	3.67±0.77	0.049#
Anesthesia time (hour)	7.05±2.21	5.69±0.83	0.083
Extubation time after lavage (hour)	17.0±4.78	20.30±3.23	0.087
Dosage of furosemide (mg)	83.33±108.25	175.0±120.76	0.783
Dosage of mannitol (mg)	200.0±68.47	187.5±115.73	0.101
Use of vasoactive drugs			
Dopamine	1 case	1 case	
Atropine	None	1 case	
Side effects			
Pneumothorax	None	None	
Lavage leakage	None	1	
Hospitalization after lavage (day)	10.80±9.48	10.20±7.90	0.880

Data are represented as mean ± SD, n (%). When compared with values between groups, #*P*<0.05. Lavage time was the time from the beginning of first lavage to the end of lavage. Anesthesia time refered the patient began from anesthesia to leave the operation room.

lavage, three days and one week after lavage (P>0.05) (**Figure 4**).

Pulmonary function tests

Three cases of values missed in 6 months after lavage in each group. The repeated measures ANOVA analysis showed that FVC, FEV_1, FEV_1/FVC ratio, and DLCO had no interaction with time (P>0.05).

The FEV_1/FVC ratio in H group was lower than that in C group before lavage (P<0.05). The FVC, FEV_1, FEV_1/FVC ratio, and DLCO had no difference in one week after lavage between two groups (P>0.05). The FVC, FEV_1 in H group were lower than those in C group in 6 months after lavage (P<0.05) (**Table 3**).

The FVC, FEV_1 and Vt of C group increased significantly in 6 months after lavage when compared with values before lavage (P<0.01) (**Table 3**).

Radiographic features

There were seven and ten patients' results of chest radiograph improved respectively in C group and H group (70% vs 100%) in one week after lavage. In 6 months after lavage, there were six and seven patients' results of chest radiograph improved respectively in C group and H group (60% vs 70%) (**Table 4**; **Figure 5**).

Discussion

In our observation, although the lavage duration was shorter in H group, there were no significant difference in other lavage parameters, gas exchange, CVP, SI, ITBVI, $PETCO_2$, Ppeak and VT. The values of pulmonary function had no difference in one week after lavage. The results of chest radiograph also had no difference between groups. These results were contrary to the hypothesis. Higher lavage height did not cause much more adverse effects on respiratory mechanics and hemodynamics, but also did not improve significant lavage effects.

Since Whole-lung lavage was first described by Ramirez in 1967 [4], it is often performed as the first line therapy for pulmonary alveolar proteinosis [2, 24]. In the past decade, our institution has gained experience in anesthetic management of nearly 75 successful whole-lung lavages in 68 adult patients. We have tried many methods to improve the lavage effect, including using different ventilation methods, chest percussion and raising lavage height.

The infusion of large volumes of saline into the lung can be associated with significant hemodynamic disturbances. Hypotension [22], increased central venous pressure [23, 25-27] and changes in arterial oxygenation [25] have all been reported. Both in two groups, the trends of MAP, C.I. and SI decreased, but the trends of CVP, EVLWI, ITBVI increased after the beginning of left-lung lavage. This meaned that the hemodynamic changes had similar trends in two groups. Left ventricular filling may decrease when the lung is fluid-filled [18]. These are due to intrathoracic pressure

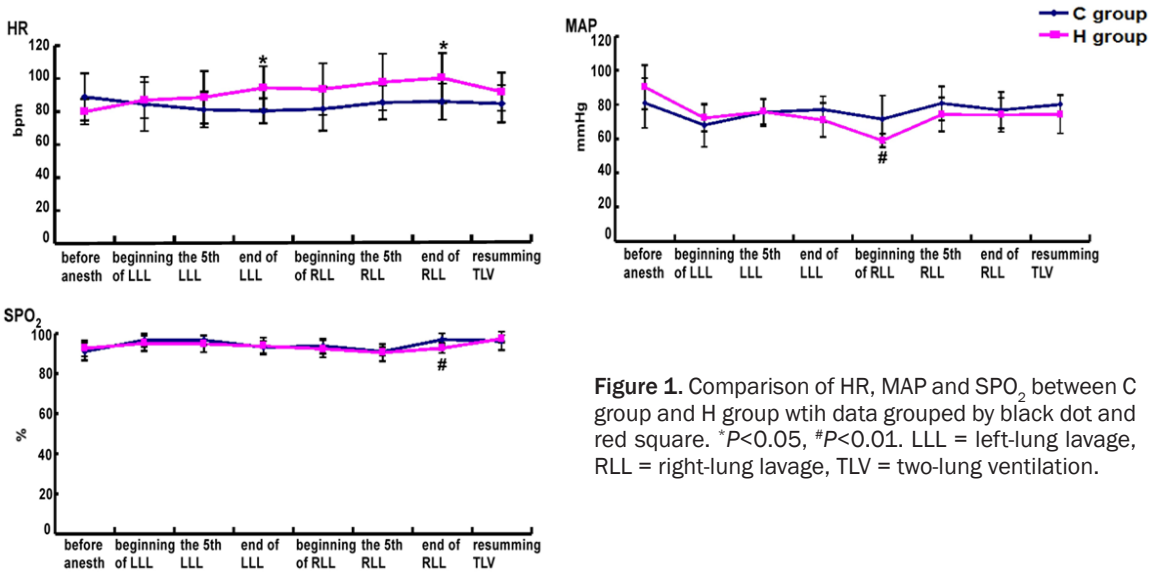

Figure 1. Comparison of HR, MAP and SPO_2 between C group and H group wtih data grouped by black dot and red square. $^{*}P<0.05$, $^{\#}P<0.01$. LLL = left-lung lavage, RLL = right-lung lavage, TLV = two-lung ventilation.

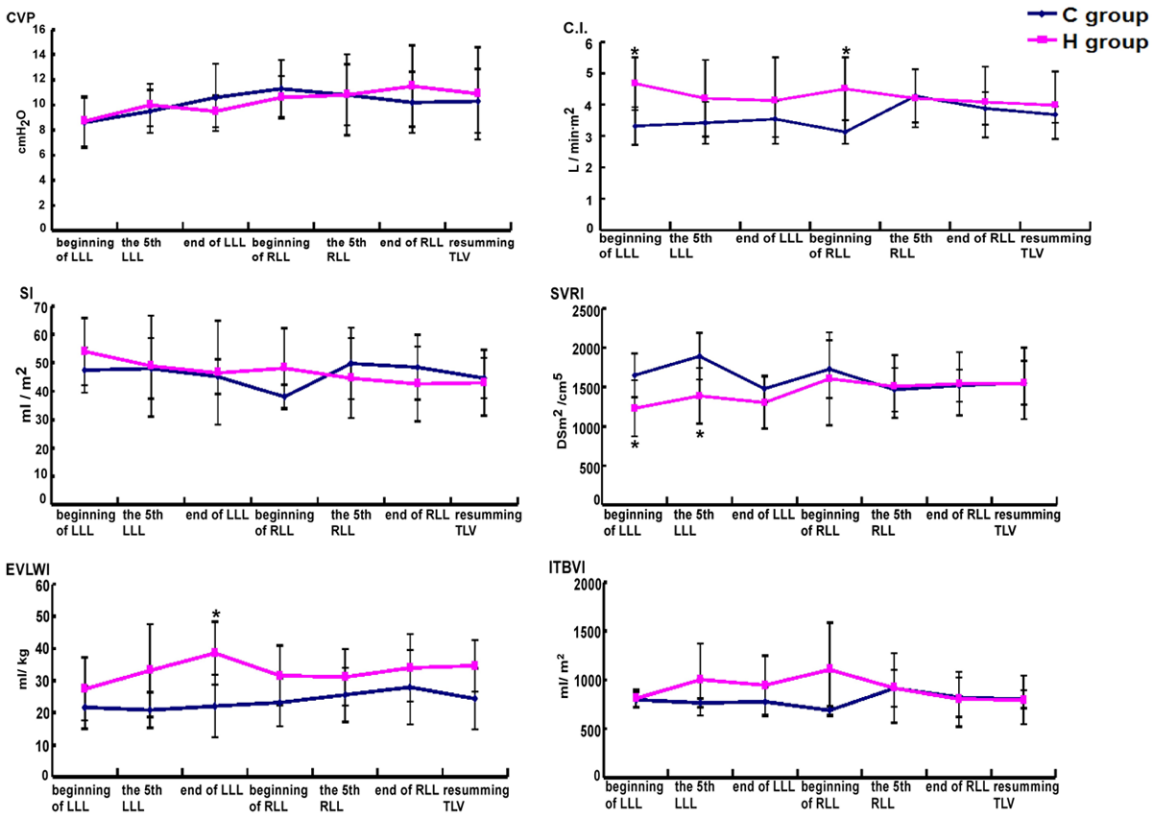

Figure 2. Comparison of PICCO values between C group and H group wtih data grouped by black dot and red square. $^{*}P<0.05$. LLL = left-lung lavage, RLL = right-lung lavage, TLV = two-lung ventilation.

increase, mediastinum shift, shunt between ventilated lung and lavaged lung. The rapid expansion of lavaged lung also constricts the diastole, resulting in lower cardiac output. Lavage solution absorption increased extravascular lung water content which increased EVLWI especially in higher lavage height group. Diuretic drugs were commonly used in the later stage of left-lung lavage and right-lung lavage. This may effectively maintained the circulatory sta-

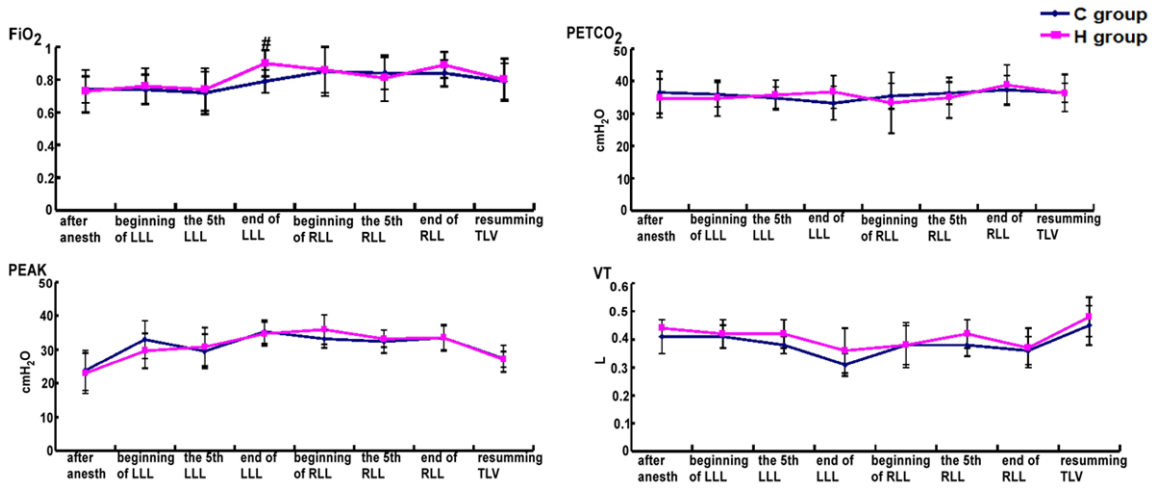

Figure 3. Comparison of ventilation values between C group and H group wtih data grouped by black dot and red square. $^{*}P<0.05$, $^{\#}P<0.01$. LLL = left-lung lavage, RLL = right-lung lavage, TLV = two-lung ventilation.

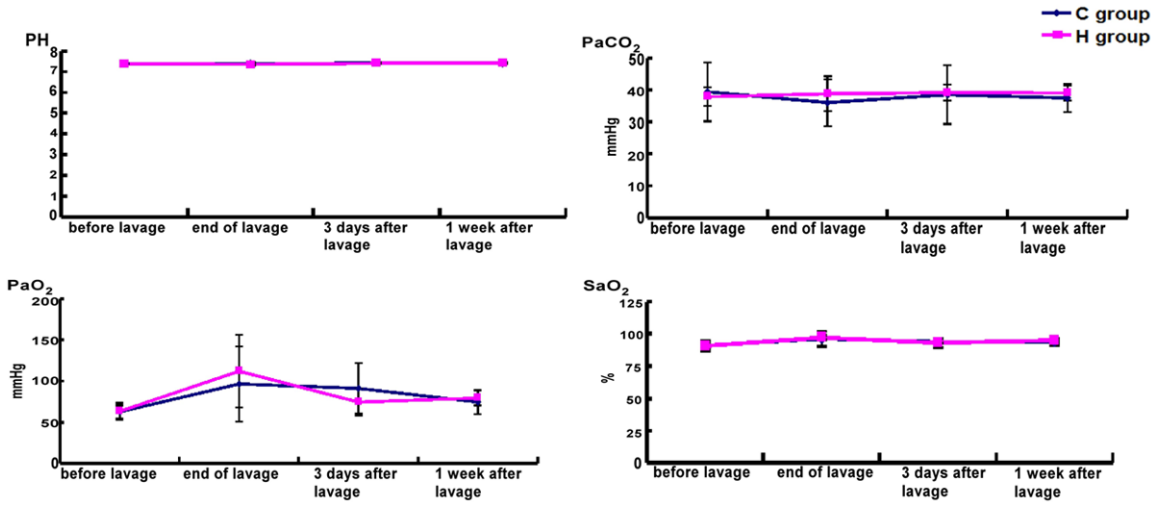

Figure 4. Comparison of blood gas analysis between C group and H group wtih data grouped by black dot and red square. No significant differences between groups were detected.

bility during lavage. Thus, higher lavage height did not produce significant hemodynamic changes. This result implied that higher lavage height did not impose much effect on hemodynamics changes during lavage. Although all of our observation was conducted after lavage solution vacuum suction, we also did not observe significant hemodynamic fluctuation in higher lavage height when solution instillation.

As the lavage duration prolonged, the lung water increased, resulting in increasing airway resistance, thus the Ppeak increased significantly after anesthesia and VT decreased gradually in both groups. The trends of FiO_2, $PETCO_2$, Ppeak, VT had similar changes in C group and H group during lavage. These implied that high-suspended lavage had no much effect on respiratory mechanics during lavage. Respiratory mechanic parameters are reported to improve after 6 whole-lung lavage procedures for a single patient [28]. Our observation was the change of respiratory mechanics during a single whole-lung lavage, which may be more credible in comparison, reflecting the change of respiratory mechanics in left and right lung lavage in different lavage height.

Higher lavage height shortened the instillation time, thus reduced solution retention in the alveoli and capillaries. Therefore, the lavage solution absorption by alveolar capillary did not

Table 3. Pulmonary function tests before lavage, 1 week and 6 months after lavage ($\bar{x}\pm s$)

Time	Group	FVC (% Pred)	FEV_1 (% Pred)	FEV_1/FVC (% Pred)	DLCO (ml/min/mmHg)	Vt (L)
Before lavage	C group (n=8)	61.93±7.28	66.11±8.95	108.64±9.35	46.13±12.12	0.45±0.20
	H group (n=10)	68.17±15.69	65.72±19.79	93.16±13.19$^{\gamma}$	43.84±17.25	0.49±0.23
1 week after lavage	C group (n=9)	63.30±4.18	66.77±4.91	107.45±8.01	48.03±14.12	0.37±0.09
	H group (n=9)	70.68±15.70	66.65±17.79	97.66±13.13	50.21±19.32	0.51±0.13$^{\gamma}$
6 months after lavage	C group (n=7)	76.60±9.55$^{\#\#}$	77.56±6.56$^{\#\#}$	103.46±10.10	50.04±7.24	0.75±0.22$^{\#\#}$
	H group (n=7)	58.81±14.24$^{\gamma}$	59.41±9.60$^{\gamma\gamma}$	106.09±10.66$^{\Delta}$	48.09±15.54	0.65±0.24

$^{\#}$indicated statistically significant difference when compared with values before lavage in C group; $^{\Delta}$indicated statistically significant difference when compared with values before lavage in H group. When compared with values between two groups, $^{\gamma}P<0.05$; $^{\gamma\gamma}P<0.01$.

Table 4. The results of chest radiograph after lavage (n=10)

Compared with results before lavage	1 w after lavage C group/H group	6 m after lavage C group/H group
No change (n, %)	2 (20%)/0	1 (10%)/2 (20%)
improvement (n, %)	5 (50%)/9 (90%)	5 (50%)/7 (70%)
Significant improvement (n, %)	2 (20%)/1 (10%)	1 (10%)/0
Worsen (n, %)	1 (10%)/0	3 (30%)/1 (10%)
P value	*P*=0.783	*P*=0.196

No significant differences between groups were detected.

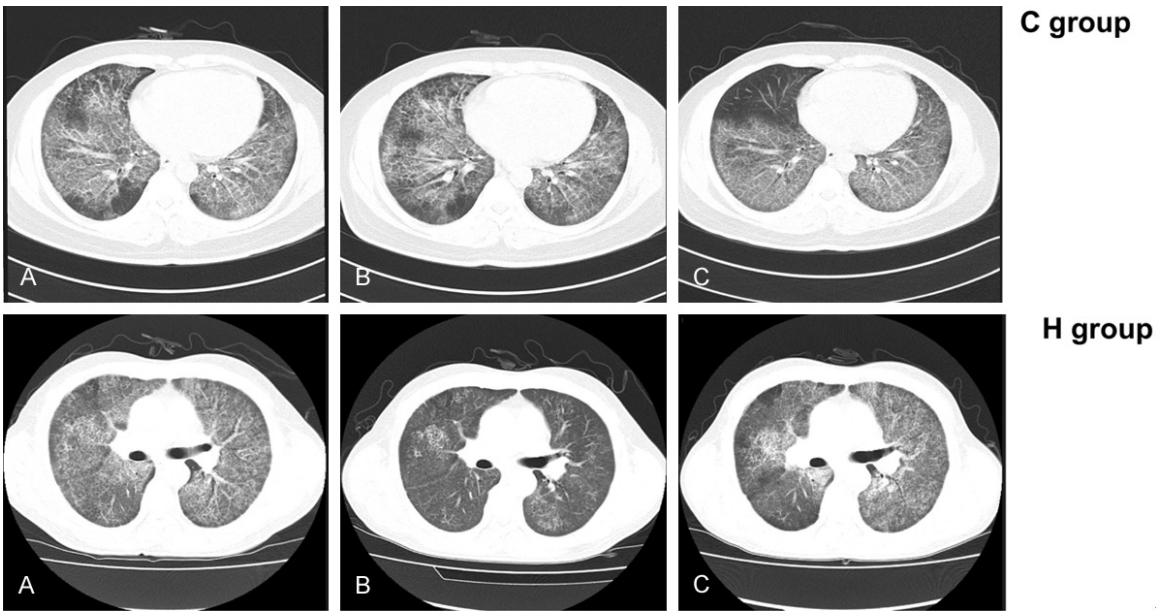

Figure 5. Comparison of radiographic features between C group and H group. A. Radiographic features before whole-lung lavage. B. Radiographic features in one week after lavage. C. Radiographic features in six months after lavage.

increased and the recovery rate remained unaffected. All these contributed to the respiratory mechanics and hemodynamic stability. Consequently, complications of lavage, including spilling of fluid, hydropneumothorax, and dosage of dopamine and atropine did not increase in higher lavage height.

Large-volume WLL (ie, 40 to 70 L per lung) and assisting therapy result in more lung area cleared, improvement in the clearance of lipoproteinaceous material and longer remission of the disease process [13]. Higher lavage height maybe increased lavage pressure, allowing more alveolar area to be lavaged and lipopro-

teinaceous material to be cleared more effectively. But in our observation, there was no significant improvement in gas exchange at the end of lavage, three days and one week after lavage in higher lavage height. Both Pulmonary function test and chest radiograph results had no significant difference between groups in one week after lavage. These supposed that higher lavage height couldn't improve lavage effect than normal lavage height within a short time after lavage. In six months after lavage, although the ratio of chest radiograph improvement was similar in both two groups, the FEV_1, FVC were higher in C group than in H group. This was not consistent with our assumption. We speculated that a much more total lavage volume and a shorter lavage duration in higher lavage height may not lavage more lung area. Higher lavage height increased lavage speed, but did not increase lavage effect.

Our study protocol still remained to be modified. First, supplement of extra groups of relatively lower height may be more cogent. A main reason for the current grouping is that previously reported cases with lavage height of 30 or 60-100 centimeters. Conventionally, we lavaged PAP patients at 100 cm height, so we observed only the changes at height between 100 cm and 150 cm. Second, follow-up lasting for a long time, such as one or two years, may incur more influence factors, such as treatment compliance, infection and other uncertainty factors. These may bring about the bias in results. Third, although the sample size is only twenty patients, our observation was performed from different variables to reflect the influence of increasing lavage height. In future, we should need a further observation to investigate whether other lavage methods really improve lavage effects in a long-term.

Conclusion

According to the observation, whole lung lavage at higher lavage height can be tolerated by pulmonary alveolar proteinosis patients without causing unstable respiratory mechanics and hemodynamics changes, but it is not better than traditional method to improve the gas exchange, pulmonary function and chest radiograph in one week and six months after lavage. Increasing lavage height is not an effective method to improve long-term lavage effect.

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Disclosure of conflict of interest

None.

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