Does External Pleural Suction Reduce Prolonged Air Leak After Lung Resection? Results From the AirINTrial After 500 Randomized Cases

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Background. External pleural suction is used after lung resection to promote lung expansion and minimize air leak duration. Published randomized trials failed to prove this advantage but they are limited in number and underpowered in many cases. The aim of the AirINTrial study was to test the hypothesis that external pleural suction may reduce the rate of prolonged air leak in a large, randomized cohort.

Methods. All candidates for lung resection (with the exception of pneumonectomy) were considered eligible for this single-center study. At the end of operation, patients were stratified by the type of resection (anatomic versus nonanatomic) and randomly allocated into the external suction arm (−15 cmH2O, group A) or into the no external suction arm (control arm, group B) in a 1:1 ratio. Chest drains were maintained for 3 days and then they were either removed or connected to an Heimlich valve, when an air leak was present. The main endpoint was to compare groups in terms of prolonged air leak (defined as the rate of patients having a chest drain still in place by postoperative day 7).

Results. Starting on February 2011, 500 patients were randomized over a 21-month period, 250 in group A and 250 in group B. Twenty-one patients in group B (8.4%) required pleural suction owing to large pneumothorax or diffuse subcutaneous emphysema. On postoperative day 7, the chest drain was still in place in 25 patients in group A and in 34 patients in group B (10% and 14%, respectively; p = 0.2). Subgroup analysis showed that external pleural suction reduced the prolonged air leak rate in the subgroup of patients who underwent anatomic resection (n = 296, 9.6% in group A and 16.8% in group B; p = 0.05).

Conclusions. Results from the AirINTrial showed that the routine use of external suction reduces the rate of prolonged air leak after anatomic lung resection. More accurate strategies of pleural suction based on the amount of air flow and the degree of lung expansion should be probably established to improve its effectiveness.


No space, no problem [1]. According to this old dictum, many thoracic surgeons prefer maintaining chest drains on suction after lung resection, to improve lung reexpansion, minimize residual pleural space, and reduce the risk of system malfunction due to clots. In their opinion, the advantage of having visceral air-leaking surfaces reaching the parietal pleura largely overcomes the risk of maintaining open the source of the leak.

Other surgeons believe that air leak stops earlier when no external suction is applied, preferring the “water seal” mode. This term is misleading, as a certain amount of uncontrolled suction is applied to the chest even in the water seal mode. The entity of this suction is minimal, unpredictable, and influenced by several factors such as siphonage and the presence of fluid column within the system. For this reason, recently a panel of experts from The Society of Thoracic Surgeons, American Association for Thoracic Surgery, European Society of Thoracic Surgeons, and General Thoracic Surgical Club proposed that “no external suction applied” should replace the definition of the water seal mode [2].

Whether external suction may reduce the risk of prolonged air leak (PAL) remains matter of debate. In fact, a recently published metaanalysis from seven randomized studies [3–9] showed a tendency toward decreased duration of chest drainage when the water seal mode is adopted, combined with an increased risk of pneumothorax. Despite of that, researchers concluded that they were “unable to make any recommendations for the management of chest tubes following pulmonary resection” [10], mainly due to the small sample size of the considered studies.
In recent years, portable suction devices became available and renewed the interest in suction strategies. Additionally, these equipments record a large amount of data on airflow and intrapleural pressure, which has been suggested as being predictors of PAL [11].

The AirIntTrial is a single-center randomized study designed to verify in a large cohort of patients the hypothesis that postoperative external suction obtained by portable devices may reduce the incidence of PAL after lung resection. This report presents results of the first interim analysis after randomization of 500 cases.

Material and Methods

Study Design

The AirIntTrial is a prospective, single-center, phase III randomized trial designed to define the best strategy (external suction versus no external suction applied) of chest drain management after lung resection. This study reports results of the first planned interim analysis.

The study was designed for 90% power at p less than 0.05, assuming 15% of PAL in the control arm (based on the review of the institutional surgical database) and a 30% PAL reduction in the treatment arm (external suction). Sample size was defined in 1,600 patients, and two interim analyses were planned after the enrollment of 500 and 1,000 patients. To avoid imbalances between groups at the time of interim analysis, patients were stratified according to the type of resection (anatomic versus nonanatomic) before randomization [12]. Restricted urn randomization was adopted to limit undesirable sample size imbalances. The study was approved by the Ethics Committee on November 25, 2010, and started enrollment on February 1, 2011.

Population

All patients admitted for elective surgery to the thoracic surgery department of the Istituto Nazionale dei Tumori in Milan were considered for the trial. Patients fulfilling all these criteria were enrolled: (1) age of 18 years or more; (2) candidate for any type of lung resection; and (3) presence of written informed consent before any study-related procedures were started. Patients were excluded from the study in case of study refusal, planned pneumonectomy, prohibitive respiratory risk (defined as a postoperative predicted forced expiratory volume of air in 1 second or diffusion capacity of lung for carbon monoxide less than 30% of the expected value) or inclusion in other studies requiring a predefined chest drainage setting.

Intraoperative and Postoperative Management

Intraoperative techniques (fissure development, aero-stasis management, bronchial closure) were chosen according to surgeon’s preference. At chest closure, the number of drains was decided according to the type of lung resection and the adopted surgical access: two 28 Charriere drains (apical and basal) in case of anatomic lung resection or any lung resection performed through hemiclamshell or combined approaches; one 28 Charriere drain (with additional fenestrations) in case of limited nonanatomic resection or video-assisted thoracoscopic anatomic resection with minimal fissure dissection. Stratification and randomization were performed in the operating room. Chest drains were then connected to a portable suction device (Thopaz, Medela, Switzerland, for the external suction arm; and Drentech; Redax, Mirandola, Italy, for the control arm) and ~15 cmH2O suction was applied, regardless of the allocated treatment, until 8 AM of the first postoperative day. By that time, suction was discontinued in the control group and maintained in the external suction group. The allocated treatment was maintained until postoperative day 3, when the basal drain was removed (if fluid <300 mL in 24 hours) and the apical connected to an Heimlich valve. On postoperative day 4, the apical drain was then removed if air was absent in the bag connected to the valve and the amount of fluid was less than 300 mL in the last 24 hours. In case of persisting air leak, the patient was discharged with the chest drain in place and checked every week in the clinic. Every patient had a chest roentgenogram taken daily until postoperative day 5, then it was decided on a case-by-case basis by the attending surgeon.

External suction was applied in control group patients in case of the following conditions: (1) enlarging subcutaneous emphysema; (2) pneumothorax involving the entire lung surface; and (3) postoperative bleeding not requiring surgery, with intrathoracic fluid collection. External suction was reduced or discontinued in case of (1) clinical suspect of bronchopleural fistula; (2) air flow higher than 5,000 mL/min; and (3) postoperative bleeding not requiring surgery, without intrathoracic collection.

Study Endpoints

The main endpoint of the study was to compare between groups the rate of patients having a chest drain in place on postoperative day 7 due to the presence of persisting air leak, either in the entire population and within the stratified subgroups (anatomic versus nonanatomic lung resection).

Two additional endpoints were defined. (1) The comparison of postoperative complication rate, which has been reported as being higher in patients receiving no external suction [7]; in this regard, postoperative complications were classed as pleural complications (pneumothorax, subcutaneous emphysema, empyema without fistula), pulmonary (pneumonia, atelectasis requiring bronchoscopy, respiratory failure), cardiac (atrial arrhythmia, pulmonary edema, cardiac ischemia), surgical (bronchial fistula, bleeding, reoperation for other reasons, laryngeal nerve palsy), and others. (2) The analysis of digital data on airflow and pressure from the first 100 patients of the study, searching for a model of PAL risk stratification. Portable suction systems record data on air leak flow (expressed in mL/min for Thopaz and in L/hour for Drentech) and on the maximal and minimal pressure of the system (Thopaz), which are indirect expression of the intrapleural pressure variations, were analyzed. With regard to the amount of air flow, the tested hypothesis was that the amount of air leak

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on postoperative day 2 was a predictor of persistent air leak on postoperative day 7. With regard to system pressure, the tested hypothesis was that resolution of the air leak by postoperative day 7 is unlikely when maximal pressure is close to zero on postoperative day 2; meanwhile, it is facilitated in case of more negative pressure. Data on intrapleural pressure are not commercially available and were unlocked by the manufacturer for scientific purposes only on request of researchers.

**Statistical Analysis**

Considered clinical variables were (1) factors previously reported as being predictors of air leak (reduced forced expiratory volume of air in 1 second, upper anatomic resection, concomitant pneumothorax, reduced diffusion capacity, preoperative use of steroids, presence of pleural adhesions, diabetes mellitus) [13]; (2) the stratification variable (anatomic versus nonanatomic lung resection); (3) age, sex, use of suction, active smoking, need of aerostatic procedure at the end of the resection; and (4) digital data recordings (median air flow on postoperative day 2 comparing the lowest quartile versus others, and the median of the maximal intrapleural pressure on postoperative day 2 comparing the highest quartile versus others). The suction and the water seal group were compared in terms of clinical variables, presence of air leak on postoperative day 7 and of postoperative complications by the χ² test, considered as being significant a p value less than 0.05. No multivariate analysis was planned at the first interim analysis.

**Results**

From February 2011 to September 2012, 553 patients were considered for the AirINTrial and 500 were actually enrolled, 250 in each arm (Fig 1). The reason for exclusion was unplanned pneumonectomy in 14 patients, inclusion into a trial requiring specific chest drain management in 24 patients, poor respiratory function in 11 patients, and consent refusal in the remaining 4 cases. Clinical characteristics of the population are listed in Table 1.

At the time of randomization, 296 patients (59.2%) had undergone anatomic resection and 204 patients (60.8%), nonanatomic resection. During the first week, in the control arm a switch to external suction was recorded in 27 cases (13.6%) due to subcutaneous emphysema in 9 patients, to large pneumothorax in 12 cases, and to intrathoracic hematoma in 6 cases. In the treatment arm, external suction was reduced or discontinued in 16 patients (6.4%), due to suspect of bronchopleural fistula in 3 cases, air flow exceeding 5,000 mL/min in 12 cases (4.8%), and conservative management of moderate bleeding in 1 case.

In 18 cases (3.6%), the main endpoint was not evaluable owing to adverse events occurring before postoperative day 7: 2 postoperative deaths occurred on postoperative day 3 and postoperative day 5, respectively; 8 patients required early reoperation (1.6%); and 8 patients were intubated and ventilated by that time.

**Main Endpoint**

By postoperative day 7, 65 patients had the apical chest drain still in place, in 59 of them because of persistent air leak (11.8%). According to the allocated treatment, overall rate of persistent air leak was slightly more frequent in the control group (n = 34, 13.6%) than in the external suction group (n = 25, 10%), but the difference was not statistically significant (p = 0.2). As expected, incidence of persistent air leak was higher after anatomic resection (39 of 296, 13.1%) than after nonanatomic resection (20 of 204, 9.8%, p = 0.2; Table 2).

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**Figure 1. Flow diagram of the progress through the different phases of the study. (POD = postoperative day.)**
Table 1. Clinical Characteristics of the Population at Randomization

<table>
<thead>
<tr>
<th>Factor</th>
<th>External Suction</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median</td>
<td>63</td>
<td>64</td>
<td>0.7</td>
</tr>
<tr>
<td>Male</td>
<td>162 (64.8%)</td>
<td>160 (64%)</td>
<td></td>
</tr>
<tr>
<td>Active smoking</td>
<td>40 (16%)</td>
<td>46 (18.4%)</td>
<td>0.8</td>
</tr>
<tr>
<td>FEV1 &lt;50%</td>
<td>52 (20.8%)</td>
<td>62 (24%)</td>
<td>0.3</td>
</tr>
<tr>
<td>DLCO &lt;50%</td>
<td>71 (28.4%)</td>
<td>66 (26.4%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Steroids, inhaled or systemic</td>
<td>26 (10.4%)</td>
<td>35 (14%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (16.4%)</td>
<td>36 (14.4%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Upper resection</td>
<td>88 (35.2%)</td>
<td>78 (31.2%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Aerostatic procedure</td>
<td>146 (58.4%)</td>
<td>149 (59.6%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pleural adhesions</td>
<td>26 (10.4%)</td>
<td>20 (8%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Air flow digital data available</td>
<td>236 (94.4%)</td>
<td>220 (88%)</td>
<td>...</td>
</tr>
</tbody>
</table>

DLCO = diffusion capacity of lung for carbon monoxide; FEV1 = forced expiratory volume of air in 1 second; POD = postoperative day.

External suction reduced persistent air leak after anatomic lung resection. In fact, PAL after lobectomy or segmentectomy was present in 14 cases in the suction arm (n = 146, 9.6%) and in 25 cases in the control arm (n = 150, 16.8%, p = 0.05). After nonanatomic lung resection, no difference was detected between groups.

Postoperative Outcome

Four postoperative deaths were recorded, 2 in each group (overall mortality 0.8%). The overall complication rate did not differ between groups, apart from air-related events, which were more frequent in the control group (52 versus 35 [20.8% versus 14%], p = 0.04; Table 3). A trend toward significance was recorded grouping pulmonary complications together (pneumonia, atelectasis, and respiratory failure) in favor of patients who underwent external suction (15 versus 26 [6% versus 10.4%], p = 0.07). No other difference was detected between groups.

Digital Data Analysis

The analysis was performed on the first 117 patients of the external suction arm, whose digital data were unlocked and inserted into a dedicated database. In terms of flow, the amount of air leak on postoperative day 2 was effective in quantifying the risk of having persistent air leak on postoperative day 7 (Table 4). In fact, patients in the lowest quartile on postoperative day 2 had a risk of PAL on postoperative day 7 of 3.5%; meanwhile, patients in intermediate classes (25% to 75%) had that risk increased (10.3%) and the highest quartile recorded the highest risk of PAL (43%). According to maximal recorded intrapleural pressure, the PAL rate was increased in patients who had a median pressure value on postoperative day 2 in the highest quartile (suggesting an intrapleural pressure closer to positive values [6 of 26, 23%]), as compared with PAL rate in patients who had more negative pressure values (14 of 91, 15%, p = 0.3). This effect became more evident focusing only on patients with an intermediate air leak on postoperative day 2 (quartile 25% to 75%). More positive intrapleural pressure on postoperative day 2 tripled the risk of persistent air leak on postoperative day 7 as compared with lower pressures (4 of 25, 16%, versus 2 of 33, 6%; p = 0.3).

Comment

The first interim analysis of the AirINTrial was planned after inclusion of 500 patients to verify correctness of study estimates and to exclude the need of amendments. Considering that the overall persistent air leak rate approached the expected rate (11.8% and 15%, respectively) and that suction reduced PAL by 30%, study design was not modified.

With regard to the main endpoint, a benefit of postoperative suction has been identified in the subgroup of patients who underwent anatomic resection, trending against several randomized trial published in the past. Several reasons may explain this finding. First of all, the large dimension of the study avoided the need of biasing endpoints, such as the time to drain removal or hospital stay. Second, the use of the Heimlich valve after postoperative day 3 avoided the risk of supporting small air leaks by suction until postoperative day 7. Finally, increased mobility due to portable suction may have played a role in promoting lung healing. All these elements can also contribute to explain the apparent paradox of the concomitant superiority of water seal compared with suction and of alternating suction compared with water seal previously reported [14].

Conversely, suction does not reduce the overall postoperative complication rate, as previously reported. In terms of pleural complications, a higher number of pneumothoraces was expected when no external suction was applied, and it has been confirmed by presented data. Whether it played a role in causing the higher number of recorded pulmonary complications remained unclear owing to the limited number of events and the composite nature of the endpoint.

The use of portable suction devices represented the innovative part of the study. This choice was justified by two reasons: (1) to avoid detrimental effect of limited mobilization in patients treated by external suction; and (2) to collect data on air flow and pressure. Pilot analysis results showed that air flow and pressure data recorded...
in the second postoperative day may be useful to define different types of air leak and to stratify the risk of PAL, and in the future it opens the possibility of tailored pleural suction according to the airflow or to a target of predefined intrapleural pressure.

This report presents four limitations. The first is the lack of a multivariate analysis measuring the impact of suction and other predictors on the risk of PAL. The decision to place such analysis after the end of the accrual was justified by the need of preserving final interpretation by intercurrent false negative findings (type II errors). The second is that surgical techniques of intraoperative air leak management were not standardized at the beginning of the study. The reason of that was maximization of results applicability outside the context of the trial. The third is the paradox of using digital devices for suction and an analogic method to assess the presence of air before drain removal, renouncing to a method with a higher agreement rate [15], but this strategy was decided on to limit the number of minimal air leak self-renewed by suction. The fourth limitation is the use of two different devices in the study because of the different type of suction they generate. The device used in the external suction arm (Thopaz) adjusts suction according to the measured pressure within the system, to obtain the predefined level of suction (−15 cmH₂O in the study). It means that whenever pressure drops, suction is started. By this mechanism, it is impossible to obtain the equivalent of the water seal mode. To avoid active external suction and to collect digital data in the control arm, another digital device (Drentech) was chosen, as it was the only device in the market permitting a pure water seal mode.

In conclusion, results from the first AirINTrial interim analysis showed that external suction decreased the risk of PAL after anatomic lung resection and the overall rate of pleural complications. Additionally, preliminary results from a subgroup analysis showed interesting application of airflow and pressure data to categorized the risk of PAL and possibly to tailor suction according to it.

The authors thank Martin Walti (Medela) for his help in unlocking pressure data of patients in the external suction arm and for his technical assistance; Andrea Gibertoni (Redax) for his technical support and his open-minded approach to problem solving; Federica Pirovano and the nursing staff of the Thoracic Surgery Department for their active role in surveillance and data collection; and Elena Bertocchi for her precious assistance in the management of the study.

Table 3. Postoperative Outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>External Suction n (%)</th>
<th>Controls n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (0.8%)</td>
<td>2 (0.8%)</td>
<td>1</td>
</tr>
<tr>
<td>Pleural</td>
<td>35 (14%)</td>
<td>56 (22.4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Persistent air leak (POD7)</td>
<td>25</td>
<td>34</td>
<td>0.2</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>4</td>
<td>12</td>
<td>0.04</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>4</td>
<td>9</td>
<td>0.16</td>
</tr>
<tr>
<td>Empyema, without fistula</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>15 (6%)</td>
<td>26 (10.4%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>Atelectasis, requiring bronchoscopy</td>
<td>5</td>
<td>11</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac</td>
<td>27 (10.8%)</td>
<td>23 (9.2%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>23</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>2</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Surgical</td>
<td>16 (6.4%)</td>
<td>15 (6%)</td>
<td>1</td>
</tr>
<tr>
<td>Bronchial fistula</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding, reoperated</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Air leak, reoperated</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Laryngeal nerve palsy</td>
<td>6</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

POD = postoperative day.

Table 4. Relation Between Median Airflow Measured on Postoperative Day 2 and Risk of Having Air Leak on Postoperative Day 7

<table>
<thead>
<tr>
<th>Air Flow (mL/min) Median Value POD2</th>
<th>Persistent Air Leak on POD7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low flow (lower quartile, n = 29)</td>
<td>3.4% (1/29)</td>
</tr>
<tr>
<td>Intermediate flow (25%–75%, n = 58)</td>
<td>10.3% (6/58)</td>
</tr>
<tr>
<td>High flow (upper quartile, n = 30)</td>
<td>43% (13/30)</td>
</tr>
</tbody>
</table>

POD = postoperative day.

References


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