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Short-term perioperative treatment with ambroxol reduces pulmonary complications and hospital costs after pulmonary lobectomy: a randomized trial☆

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Abstract

Objective: To assess in a randomized clinical trial the influence of perioperative short-term ambroxol administration on postoperative complications, hospital stay and costs after pulmonary lobectomy for lung cancer. **Methods:** One hundred and forty consecutive patients undergoing lobectomy for lung cancer (April 2006—November 2007) were randomized in two groups. Group A (70 patients): ambroxol was administered by intravenous infusion in the context of the usual therapy on the day of operation and on the first 3 postoperative days (1000 mg/day). Group B (70 patients): fluid therapy only without ambroxol. Groups were compared in terms of occurrence of postoperative complications, length of stay and costs. **Results:** There were no dropouts from either group and no complications related to treatment. The two groups were well matched for perioperative and operative variables. Compared to group B, group A (ambroxol) had a reduction of postoperative pulmonary complications (4 vs 13, 6% vs 19%, $p = 0.02$), and unplanned ICU admission/readmission (1 vs 6, 1.4% vs 8.6%, $p = 0.1$) rates. Moreover, the postoperative stay and costs were reduced by 2.5 days (5.6 vs 8.1, $p = 0.02$) and 2765 Euro (2499 Euro vs 5264 Euro, $p = 0.04$), respectively. **Conclusions:** Short-term perioperative treatment with ambroxol improved early outcome after lobectomy and may be used to implement fast-tracking policies and cut postoperative costs. Nevertheless, other independent trials are needed to verify the effect of this treatment in different settings.

Keywords: Pulmonary lobectomy; Non-small cell lung cancer; Postoperative complications; Ambroxol

1. Introduction

Despite new techniques and recent advances in hospital care that are implemented to improve the quality and reduce costs, morbidity and hospital costs after major lung resection for lung cancer are still high.

Thoracic surgeons are faced with an increasing population of elderly patients with a significant prevalence of chronic obstructive disease. Surgery in these patients can be associated with increased risk of morbidity and mortality caused by the underlying lung disease.

This patient population is likely to have an increased incidence of significant postoperative pulmonary complications such as atelectasis, pneumonia, and acute respiratory failure requiring intubation and mechanical ventilation [1]. Therefore every effort must be implemented to rule out or reduce these complications.

Ambroxol is a trans-4 [2-amino-3, 5-dibromo-benzyl, amino] cyclohexanol-hydrochloride which has been shown to increase the number and activity of type 2 pneumocytes [2], and thus to increase surfactant levels and lecithin/sphyngomyelin ratio [3] and mucociliary clearance [4].

We conducted a randomized clinical trial to assess the influence of perioperative short-term ambroxol administration on postoperative complications, hospital stay and costs after lobectomy for lung cancer.

2. Patients and methods

The trial was designed and analyzed according to Consolidated Standards of Reporting Trials (CONSORT) recommendations and checklist (see Fig. 1 for CONSORT flowchart) [5]. Simple unrestricted randomization was used to allocate patients into the two groups before operation. Both patients and data manager analyzing the outcome were

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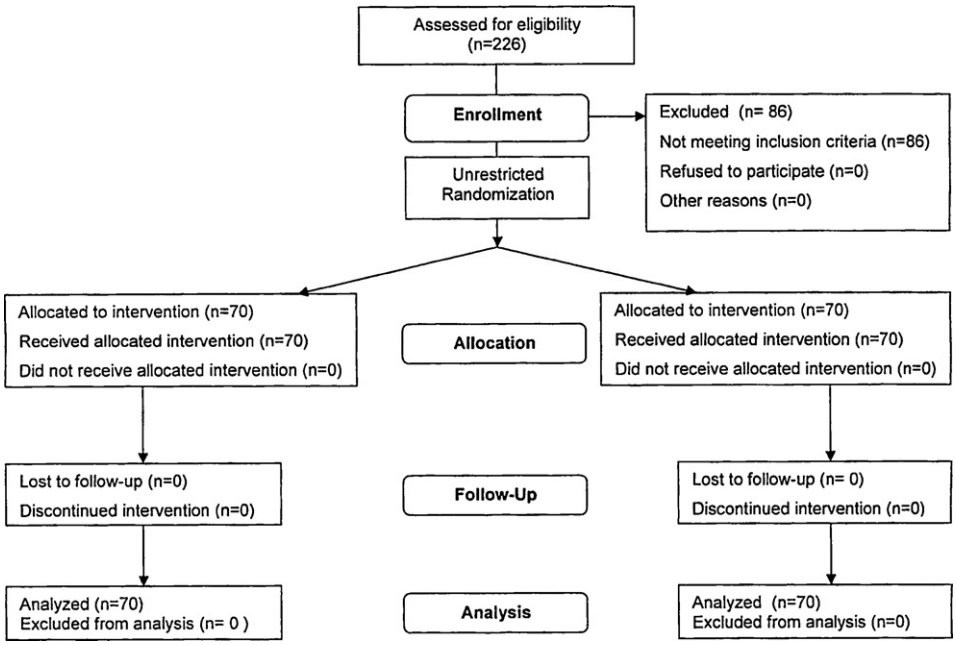

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart.

blinded to group allocation. Randomization was performed by computerized numerical sequence.

Sample size was set to reach a statistical power of 90% to detect an expected difference in postoperative stay of at least 2 days. Exclusion criteria were wedge resection/segmentectomy (62 patients) or pneumonectomy (20 patients), and lung resection associated with chest wall resection (4 patients). All patients gave their informed consent to participate in the study and to use their data in a prospective database. This study protocol was approved by the local institutional review board (IRB).

One hundred and forty consecutive patients (females: 28, males: 112) undergoing lobectomy for lung cancer from April 2006 through November 2007 were randomized by simple unrestricted randomization into two groups before operation. Group A (70 patients): ambroxol was administered by intravenous infusion (1000 mg/day) in the context of the usual fluid therapy on the day of operation and on the first three postoperative days. Group B (70 patients): fluid therapy only was administered without ambroxol. On the second and third postoperative days patients in both groups received only the amount of fluid necessary to administer ambroxol or placebo (500 ml).

There were no dropouts from either group and no complications related to treatment.

All patients were subjected to a strict preoperative evaluation and contraindications to major lung resections were according to the American College of Chest Physician criteria (ppoFEV1 $<$30%, ppoDLCO $<$30%, VO2peak $<$10 ml/kg/min) [6].

All patients were operated on in a single dedicated thoracic surgery center by qualified thoracic surgeons.

All lobectomies were performed by muscle-sparing lateral thoracotomy. Short-term antibiotic prophylaxis with cefazolin was administered. Postoperative treatment was standardized for all patients and focused on early mobilization and physical rehabilitation. Physical rehabilitation was supervised twice a day by a specialist physiotherapist with standard exercises aimed at chest physiotherapy and physical rehabilitation. Thoracotomy chest pain was controlled by intravenous continuous infusion of non-opiates and was titrated to achieve a visual analogic pain score (VAS) below four (range 0—10) during the first 48—72 h after the operation. Patients were mobilized as soon as possible and bronchodilators were administered only in case of an objective evidence of reversible obstruction after bronchodilator administration at the preoperative pulmonary function tests (PFTs).

All patients were managed in a dedicated thoracic ward with specialized personnel and resorted to intensive care unit (ICU) only in case of cardiorespiratory complications requiring active life-supporting treatments.

The following outcomes were analyzed:

Total cardiopulmonary morbidity, cardiac complications, pulmonary complications, mortality, postoperative stay and costs.
Postoperative morbidity and mortality were considered as those occurring within 30 days postoperatively or for a longer period if the patient was still in the hospital.

For the purpose of this study and for the sake of comparison with previous studies [7—9] the following complications were included:

Pulmonary, respiratory failure requiring mechanical ventilation for more than 48 h; pneumonia (chest X-rays infiltrates, increased white blood cell count, fever); atelectasis requiring bronchoscopy; adult respiratory distress syndrome (ARDS); pulmonary edema; pulmonary embolism;

Table 1
Results of the comparison of baseline and operative characteristics between the two groups.

Variables	Group A (70 patients, ambroxol)	Group B (70 patients, no ambroxol)	*p* value
Age	67.3 (9.6)	65.1 (12.1)	0.2
FEV1%	86.6 (17.8)	84.1(19.5)	0.4
ppoFEV1%	68.7 (12.8)	67.6 (15.0)	0.6
FVC%	97.6 (17.7)	93.8 (16.4)	0.2
FEV1/FVC ratio	0.7 (0.1)	0.7(0.1)	0.7
DLCO%	80.7 (20.9)	84.0 (17.5)	0.3
ppoDLCO%	64.3 (16.9)	67.8 (13.6)	0.2
Hb preoperative	13.8 (1.5)	14.1 (1.5)	0.3
Preoperative albumin (g/dl)	4.2 (0.3)	4.2 (0.9)	0.7
Pack-years	49.4 (38.7)	50.3 (44.6)	0.9
CAD	10 (14%)	11 (16%)	1
Neoadjuvant chemotherapy (*n*, %)	10 (14%)	5 (7%)	0.3
ASA	2.2 (0.6)	2.3 (0.5)	0.3
ECOG	0.6 (0.7)	0.5 (0.8)	0.7
CCI	1.7 (1.5)	2.1 (2.1)	0.2
Operation time (min)	177.2 (47.2)	176.4 (50.6)	0.9
Right side (*n*, %)	44 (62%)	39 (56%)	0.4
Upper resection (*n*, %)	43 (61%)	51 (73%)	0.2

Results are reported as mean ± SD unless otherwise specified. CAD: coronary artery disease; ASA: American Society of Anesthesiology score; ECOG: Eastern Co-operative Oncology Group score; CCI: Charlson comorbidity index.

Cardiovascular myocardial infarction (suggestive electrocardiogram findings and increased myocardial enzymes); hemodynamically unstable arrhythmia requiring medical treatment; cardiac failure (suggestive chest X-rays, physical examination and symptoms); acute renal failure (change in serum creatinine greater than 2 mg/dl compared to preoperative values); stroke.

Fixed and variable costs were retrieved from the hospital's accounting and pharmacy departments' data systems. Fixed costs included capital, employee salaries, building maintenance, and utilities. Variable costs included patient care supplies, food, radiographic film, laboratory reagents, and medications, with their delivery systems (such as intravenous catheters or bottles), and the cost of other postoperative therapeutic procedures such as cardioversion, bronchoscopy, blood transfusions, etc.

3. Statistical analysis

Simple unrestricted randomization was used to allocate patients into the two groups. Both patients and data manager analyzing the outcome were blinded to group allocation. Along with the occurrence of complications, postoperative stay and postoperative costs, the groups were compared in terms of several other preoperative and operative variables: gender, age, predicted postoperative forced expiratory volume in 1 s (ppoFEV1%), predicted postoperative carbon monoxide lung diffusion capacity (ppoDLCO%), smoking history (pack-years), preoperative hemoglobin and serum albumin values, coronary artery disease, ASA score, Charlson — comorbidity index and ECOG score, neoadjuvant chemotherapy, side and site of resection and duration of operation.

Pulmonary function tests were performed according to the American Thoracic Society criteria. Results of spirometry were collected after bronchodilator administration. DLCO measurement was performed by the single breath method.

ppoFEV1 and ppoDLCO were expressed as percentages of predicted for age, gender and height and were calculated by taking into account the number of functioning segments removed during operation.

Differences between the two groups were ascertained by the unpaired Mann—Whitney test (non-parametric distribution) for numeric variables, and by chi-square or Fisher's exact test for the categorical variables. All tests were two tailed with a significance level of 0.05.

4. Results

The two groups were well matched for preoperative and operative variables (Table 1). Compared to the untreated patients, those treated with ambroxol (group A) showed a lower rate of postoperative cardiopulmonary complications (17 vs 9, 27% vs 13%, $p = 0.03$) and a statistical significant reduction of postoperative pulmonary complications (4 vs 13,

Table 2
Results of the comparison of early outcomes between the two groups.

Variables	Group A (70 patients, ambroxol)	Group B (70 patients, no ambroxol)	*p* value
Pulmonary complications (*n*, %)	4 (6%)	13 (19%)	0.02
Cardiac complications (*n*, %)	9 (13%)	7 (10%)	0.8
Total complications (*n*, %)	9 (13%)	17 (27%)	0.03
Unplanned ICU admissions (*n*, %)	1 (1.4%)	6 (8.6%)	0.1
Postoperative hospital stay (days)	5.6 (2.2)	8.1 (7.5)	0.02
Postoperative costs (Euro)	2499 (1635)	5264 (11949)	0.04

Table 3
Cost analysis in the two groups.

	Ambroxol (€)	No ambroxol (€)	*p* value
Hospital stay	2049 (808)	2956.5 (2741)	0.02
ICU stay	82 (491)	1205.4 (7189)	0.04
Variable costs	237 (338)	950 (2615)	0.02
Total cost	2499 (1635)	5264 (1949)	0.15

Results are reported as mean ± SD.

6% vs 19%, $p = 0.02$), In group A (ambroxol) we had 4 patients with pulmonary complications (2 atelectasis and 2 pneumonia), while in group B (no ambroxol) we had 13 patients with pulmonary complications (6 atelectasis, 5 pneumonia, 5 respiratory failure and 1 pulmonary edema; 4 patients had more than 1 complication).

No difference was observed in terms of cardiac complications (9 vs 7, 13% vs 10%, $p = 0.8$).

Moreover, the unplanned ICU admission/readmission was lower in the ambroxol group (1 vs 6, 1.4% vs 8.6%, $p = 0.1$).

As a consequence, in the ambroxol group the mean postoperative stay and costs were reduced by 2.5 days (5.6 vs 8.1, $p = 0.02$) and by 2765 Euro (2499 Euro vs 5264 Euro, $p = 0.04$), respectively (Table 2). The large difference in costs may be explained by the higher ICU costs in the non-treated group (Table 3).

Total morbidity and mortality rates in this series were 20% (28 cases) and 1.4% (2 cases), respectively. The two deaths occurred in group B: one patient died due to respiratory failure and the second patient died due to cardiac arrest.

5. Discussion

This study was designed to assess the role of ambroxol in preventing complications after lung resection. Ambroxol has been shown to have specific properties in increasing surfactant level. Surfactant is a heterogeneous mixture of phospholipids and proteins (80—85% of phospholipids, 5—10% of proteins and 10% of neutral lipids and dipalmitoylphosphatidylcholine is the main surface active agent) [10,11], Jablonka and colleagues showed that intravenous administration of 1000 mg/day of ambroxol for 8 days before resection produced elevation of disaturated phosphatidylcholine and the general level of phosphatidylcholine [12]. Nowak and colleagues found that ambroxol was a scavenger of HCLO and OH and also revealed its capacity to decompose H_2O_2 [13]. Gibbs and colleagues found that this molecule was able to inhibit acute mediator release from mast cells and leukocytes and also to reduce immunomodulatory cytoxine generation from basophiles and may have beneficial effects in the treatment of allergic respiratory diseases [14]. Olivieri and colleagues [4] showed its capacity to improve mucociliary clearance, and Wiemeyer showed an increase of antibiotic absorption in the bronchopulmonary tissue after treatment with ambroxol [15]. These pharmacologic properties of ambroxol may explain the beneficial effects found in previous clinical showing an improved postoperative course after lung resection [16,17]. However, these few studies applied ambroxol for several days before and after operation, and this schedule may be not applicable in modern times of fast-tracking and shorter hospital stay. A shorter schedule of administration should be needed and was tested in this study for this reason. The selection of the time schedule was empirically dictated by the admission policy of our unit that we wanted not to alter. In our unit, patients are admitted the day before or the same day of operation making it logistically impractical to organize lengthier administrations.

In the era of managed care systems that demand an increased effort in delivering high standards of quality of care in a context of cost containment, every effort must be implemented to optimize the perioperative treatment with the aim of reducing postoperative complications, hospital stay and costs.

In this context, we observed a statistical significant reduction of postoperative pulmonary complications in those patients treated with ambroxol and, as a result, a reduced unplanned ICU admission/readmission rate. Moreover, the postoperative stay and costs were reduced compared to the untreated patients. Considering the low cost of the entire ambroxol treatment this regimen appeared very cost-effective and its short-term use may be recommended in the context of fast-tracking policies.

This study has potential limitations.

First, our results were obtained in a dedicated thoracic surgery unit with qualified surgeons and with standardized perioperative pathways of care. Generalization to different settings may not yield the same results and should be verified particularly with different analgesia modalities and different rehabilitation programs. Moreover, the short-term schedule was empirically set to fit (without changing) the daily practice of our unit. Reproducibility of results with other treatment regimens needs to be verified. Finally, no serologic or pathologic investigations were performed to assess the pharmacodynamic upon which the observed positive results were based. As mentioned above, previous experimental studies have proven several effects of ambroxol that can explain the efficacy of the drug in our analysis.

In conclusion, a short-term perioperative administration of ambroxol may reduce the incidence of pulmonary complications after lobectomy and cut the average postoperative costs. Based on the results generated in this study, we started to systematically use this perioperative administration schedule of ambroxol to all patient candidates for major lung resection at our institution. Nevertheless, other independent trials are needed to verify the effect of this treatment in other settings.

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Appendix A. Conference discussion

Dr T. Grodzki (*Szczecin, Poland*): I would like to congratulate you on an elegant and simple study, however, it looked like a little bit of kicking the open doors, because ambroxol is widely used, at least in my department, for four years, and we do not randomize it because we know that expectorants and all that stuff, including ambroxol, are beneficial for the patient. However, I appreciate that you did a simple randomized study and you finally proved it and I hope you will publish it to close the discussion.

Dr Refai: I know that some authors from Poland have already published articles about the use of ambroxol, but in these studies the period of administration was longer. So we tried to use it in a short-term treatment and verify its efficacy.

Dr S. Cassivi (*Rochester, MN*): I am not sure that Dr Grodzski wanted to close the discussion there. I am going to take the opportunity to give you an opinion from the other side of the ocean where this is a completely novel approach. We are aware of mucolytics and expectorants, such as *N*-acetylcysteine. But in terms of something that has such a remarkable effect — clearly they know it in Szczecin and now you know it in Ancona — I would be interested to poll the audience here to see who is using ambroxol routinely.

(Show of hands).

Dr Cassivi: I count six, maybe 10 out of 100 people here, and five of them are from Szczecin. This is a well-kept secret of yours, Tomasz, and now it looks like the Ancona group is letting everyone know about it.

Is Ambroxol available in oral form, too?

Dr Refai: Yes.

Dr Cassivi: Do you have any experience with that?

Dr Refai: No. We have only tried the intravenous form.

Dr Cassivi: It seems fairly inexpensive from an intravenous standpoint but I am wondering if the oral form would be even more inexpensive and as effective.

Dr Refai: We didn't test the oral form because we think that the intravenous would be more efficacious in terms of pharmacodynamic. The oral administration may take more time to be effective and obtain equal results.

Dr Cassivi: What kind of side effects can you expect from this treatment?

Dr Refai: In our patients, we didn't have any important side effects. It has been described that you may have occasional nausea and headache, and there are some contraindications, especially in patients who have severe liver disease or renal insufficiency.

Dr Cassivi: Are you using this routinely now or are you choosing patients specifically, such as patients with severe COPD, or are you using it for every pulmonary resection?

Dr Refai: Now we are using it routinely, especially for patients for lobectomy. This is because of its cost-effectiveness.

Dr Cassivi: It is a remarkable difference in your study. I would be surprised if it doesn't raise widespread interest with results such as yours.

Dr Refai: We hope so.

Dr H. Eid (*Dubai, UAE*): I don't have experience with that medicine, but I ask you if you can use it preoperatively? As you are using it as a prophylaxis for your patients, especially those high-risk patients, old age, wouldn't it be beneficial to use it before induction of anesthesia or before the operation, for example one night before the operation?

Dr Refai: As I said before, we usually administer the first dose on the day of the operation since most of our patients come to the hospital the same day.

Dr Eid: Would it make a difference if you use it before or after?

Dr Refai: Unfortunately, this cannot be ascertained from the present series.