

Lavage with diluted surfactant as a treatment option for atelectasis in pediatric intensive care patients

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The aim of this study was to assess the effect of fiberoptic aspiration and diluted surfactant administration on affected lungs in children with atelectasis. A convenience sample of 18 mechanically ventilated children were analyzed in this single center prospective study. The children had first been treated unsuccessfully by respiratory physical therapy, after which they underwent fiberoptic aspiration. After aspiration, nine children were randomly selected to receive therapeutic lavage with diluted porcine surfactant; the remaining nine received the same quantity of saline solution. Several parameters of lung function, including positive end-expiratory pressure (PEEP) and oxygenation index (OI), as well as lung x-ray images were determined before aspiration and lavage, then at 6 and 12 h after lavage. In both groups, most of the measured parameters showed improvement from baseline at 6 h after treatment. Improvement was even more significant 12 h after treatment. The surfactant group showed significant improvement in comparison to the saline group. The impact of surfactant administration was most visible on the following parameters 12 h after treatment ($p < 0.001$ in all cases): PEEP 5.22 (SD 0.44) in the saline group vs. 3.44 (SD 0.73) in the surfactant group; OI 3.84 (SD 1.13) vs. 2.1 (SD 0.38); and mean airway pressure (MAP) 8.56 (SD 0.88) vs. 6.33 (SD 0.5). In conclusion, fiberoptic aspiration is an efficient treatment in pediatric intensive care patients. The observed beneficial effects of therapeutic lavage with diluted surfactant should be confirmed prospectively in a larger number of patients.

Keywords: bronchoalveolar lavage; pulmonary surfactants; pulmonary atelectasis; intensive care units, pediatric

INTRODUCTION

Atelectasis refers to the lack of gas exchange in collapsed, airless regions of the lung (1). The condition itself is not a disease, but is associated with several pulmonary and chest disorders and is a symptom of the underlying disease (2). Clinical manifestations of atelectasis depend on the underlying cause, as well as on the degree of volume loss within the lung. When atelectasis is relatively small and associated with little physiological impairment, there may be no signs or symptoms. In massive unilateral atelectasis, however, tracheal deviation and a shift in heart sounds towards the atelectatic side may occur (3).

The standard treatment for atelectasis is respiratory physical therapy, including percussion, vibration, aspiration, aerosolized bronchodilators and positional drainage. Fiberoptic aspiration, alone or with therapeutic saline lavage, is used

when these procedures are ineffective. Bronchoscopic aspiration is a safe bedside procedure, even in pediatric population (4, 5).

Lobar atelectasis is frequently seen in pediatric patients undergoing mechanical ventilation (6). At least 8% of children on mechanical ventilation develop pulmonary atelectasis, with a concomitant increase in the morbidity and length of

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hospitalization (7). The most common types of atelectasis in children are resorption atelectasis following airway obstruction or adhesive atelectasis due to surfactant deficiency or dysfunction (8). In cases of the latter, surfactant administration as supplementary therapy may help minimize changes in surface tension and improve mucus transport within the narrow pediatric airways (4, 9). According to Strohmaier (10), lavage with diluted surfactant may not only replenish the missing endogenous surfactant, but it may also remove pathologic material more effectively than saline lavage because the washing agent is more uniformly distributed.

The effect of therapeutic lavage with diluted surfactant is still questionable. Several studies have shown lavage with diluted surfactant to be more therapeutically effective than conventional bolus or aerosol therapy (11-13). However, studies on pediatric and adult patients with different indications for exogenous surfactant application have given contradictory results (14-22). For example, the use of surfactant shows promise for treating severe bronchiolitis and acute respiratory distress syndrome (ARDS) (23), but its use in patients with bronchopneumonia remains controversial.

The present study was designed to investigate whether aspiration followed by therapeutic lavage with diluted exogenous surfactant can effectively treat atelectasis in pediatric patients on long-term ventilation.

MATERIALS AND METHODS

Patient recruitment

This prospective study was carried out in the intensive care unit (ICU) of the Zagreb Children's Hospital. The Hospital Ethics Committee approved the study, and a written informed consent was obtained from the parents. Patient characteristics (demographic data and diagnoses) are shown in Table 1.

Out of 42 children mechanically ventilated in the ICU during the study period, 18 of 25 patients that developed lobar atelectasis were enrolled in the study. Inclusion criteria were

pediatric status, presence of atelectasis, and mechanical ventilation longer than two weeks.

Atelectasis was diagnosed based on clinical and radiological criteria. The clinical criteria were fever, crepitation, partial pressure of carbon dioxide (PaCO_2) ≥ 45 mm Hg (6 kPa), peak inspiratory pressure (PIP) ≥ 25 , and partial pressure of arterial oxygen/fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 . Radiological criteria included opacification, a shift of the mediastinum, displacement of the interlobar fissure and elevated diaphragm. Laboratory investigations included complete blood count, blood cultures, and culture of airway secretions.

Procedures

Patients were randomly assigned to either of the two groups using closed envelopes. Both groups were ventilated with a Dräger Medical EVITA 4 (Lübeck, Germany). Peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) were adjusted to achieve a tidal volume of 7-8 mL/kg body weight.

No food was given to children through their nasogastric tube for at least 4 h prior to bronchoscopy. During the aspiration and lavage, inspiratory oxygen fraction (FiO_2) was 1.0. Procedures were performed through tracheostomy or endotracheal tube with an Olympus BF-3C30 bronchoscope. Lidocaine (2%, maximum dose of 1 mg/kg) was used for local anesthesia of the carina and to prevent straining. Oxygen saturation (SpO_2), end-tidal carbon dioxide in expired air (etCO_2) and invasive arterial pressure (ABP) were monitored throughout the procedure. Multiple intravenous (IV) accesses were secured. If SpO_2 fell below 85%, the procedures were stopped until the level recovered. All procedures were performed in the ICU or the operating room.

After fiberoptic aspiration, therapeutic lavage of the affected area was carried out using solutions pre-warmed to body temperature. Children in the control group received isotonic saline, while those in the surfactant group received an equal volume of porcine surfactant diluted in saline solution (5 mg Curosurf/mL; Curosurf[®], Chiesi, Italy). The whole amount of fluid surfactant was given instantly in the main bronchus of the affected lung. The mean volume (SD) given to each group was 34.3 (SD 13.76) mL, corresponding to a mean (SD) of 3.199 (0.411) mL/kg body weight. The mean amount (SD) of surfactant delivered to the experimental group was 15.66 (SD 2.33) mg Curosurf/kg body weight.

Measurements

Several gas exchange and pulmonary mechanic parameters were measured before and after aspiration and lavage: PIP

TABLE 1. Patient characteristics: demographic data and diagnoses

| | Control group | Experimental group |
|-------------------------------------|---------------|--------------------|
| Age (yrs) | 4.7±3.0 | 4.4±3.4 |
| Gender (F/M) | 2/7 | 4/5 |
| Diagnosis: | | |
| Spinal muscular atrophy | 3 | 2 |
| Trauma (head trauma/polytrauma) | 2/1 (67%/33%) | 1/1 (50%/50%) |
| Neuroblastoma | 2 | 1 |
| Posterior fossa tumor | | 1 |
| Combustion | 1 | 2 |
| Adult respiratory distress syndrome | | 1 |

in cm H₂O, PEEP in cm H₂O, PaO₂/FiO₂, oxygenation index (OI), PaCO₂ in mm Hg, and mean airway pressure (MAP) in cm H₂O. These measurements were made before treatment (baseline) and at 6 and 12 h after treatment. During the observation period, we minimized aspiration of the airways in order to keep the lavage solution at the site of action.

Descriptive lung x-ray evaluations were carried out at baseline and 12 h after treatment. Radiograms were independently assessed by two radiologists blinded to patient assignments.

Statistics

ANOVA tests were performed to determine significant differences in mean values between the study groups. Dependent-sample t-tests were used to test differences in mean values between baseline and 6 h post-treatment, as well as between baseline and 12 h post-treatment. Independent-sample t-tests were used to test differences in mean values between the control and experimental group for each of the three sets of measurements separately (baseline, 6 h post-treatment and 12 h post-treatment).

RESULTS

Lung x-ray evaluations were carried out at baseline and 12 h after treatment. Since the evaluations were qualitative, they were difficult to analyze statistically. Chest x-ray analysis indicated improvements in both groups, ranging from 20% to 90%. Several lung function parameters were measured, including PIP (cm H₂O), PEEP (cm H₂O), PaO₂ (mm Hg)/FiO₂, OI, SpO₂, PaCO₂ (mm Hg), and MAP (cm H₂O). The two groups did not differ significantly in any of the parameters at baseline (Table 2).

Both groups showed significant improvement in multiple lung function parameters between baseline and 6 h after

TABLE 2. Comparison of baseline lung function parameters between control and surfactant groups

| | Control group | Experimental group |
|--|---------------|--------------------|
| PIP (cm H ₂ O) | 29.11 | 29.56 |
| PEEP (cm H ₂ O) | 6.44 | 6.56 |
| PaO ₂ /FiO ₂ (mm Hg) | 210.18 | 205.97 |
| OI | 7.13 | 7.20 |
| SpO ₂ | 93.22 | 93.56 |
| PaCO ₂ (mm Hg) | 63.00 | 56.44 |
| MAP (cm H ₂ O) | 14.44 | 14.67 |

PIP = peak inspiratory pressure; PEEP = positive end expiratory pressure; PaO₂/FiO₂ = partial pressure of arterial oxygen/fraction of inspired oxygen ratio; OI = oxygenation index; SpO₂ = oxygen saturation; PaCO₂ = partial pressure of carbon dioxide; MAP = mean airway pressure

TABLE 3. Comparison of lung function parameters in control group before and after treatment

| | Baseline measurement | 6 h after treatment | 12 h after treatment |
|--|----------------------|---------------------|-----------------------|
| PIP (cm H ₂ O) | 29.11 | 26.67 ^a | 26.33 ^b |
| PEEP (cm H ₂ O) | 6.44 | 5.22 ^a | 5.22 ^a |
| PaO ₂ /FiO ₂ (mm Hg) | 210.18 | 226.62 ^a | 238.65 ^{a 1} |
| OI | 7.13 | 4.74 ^b | 3.84 ^{b 1} |
| SpO ₂ | 93.22 | 96.67 ^a | 97.00 ^a |
| PaCO ₂ (mm Hg) | 63.00 | 57.56 ^a | 55.56 ^a |
| MAP (cm H ₂ O) | 14.44 | 10.67 ^b | 8.56 ^{b 2} |

PIP = peak inspiratory pressure; PEEP = positive end expiratory pressure; PaO₂/FiO₂ = partial pressure of arterial oxygen/fraction of inspired oxygen ratio; OI = oxygenation index; SpO₂ = oxygen saturation; PaCO₂ = partial pressure of carbon dioxide; MAP = mean airway pressure

^astatistical difference when compared to the baseline measurement p<0.01; ^bstatistical difference when compared to the baseline measurement p<0.001; ¹statistical difference between second and third measurement p<0.05; ²statistical difference between second and third measurement p<0.001

TABLE 4. Comparison of lung function parameters in surfactant group before and after treatment

| | Baseline measurement | 6 h after treatment | 12 h after treatment |
|--|----------------------|---------------------|-----------------------|
| PIP (cm H ₂ O) | 29.56 | 24.67 ^b | 24.00 ^{b 1} |
| PEEP (cm H ₂ O) | 6.56 | 4.67 ^b | 3.44 ^{b 2} |
| PaO ₂ /FiO ₂ (mm Hg) | 205.97 | 251.94 ^a | 297.67 ^{b 3} |
| OI | 7.20 | 3.76 ^b | 2.10 ^{b 3} |
| SpO ₂ | 93.56 | 98.00 ^a | 98.67 ^a |
| PaCO ₂ (mm Hg) | 56.44 | 43.44 ^b | 41.33 ^b |
| MAP (cm H ₂ O) | 14.67 | 9.22 ^b | 6.33 ^{b 3} |

PIP-peak inspiratory pressure, PEEP- positive end expiratory pressure, PaO₂/FiO₂- partial pressure of arterial oxygen/fraction of inspired oxygen ratio, OI- oxygenation index, SpO₂- oxygen saturation, PaCO₂- partial pressure of carbon dioxide, MAP- mean airway pressure

^astatistical difference when compared to the baseline measurement p<0.01; ^bstatistical difference when compared to the baseline measurement p<0.001; ¹statistical difference between second and third measurement p<0.05; ²statistical difference between second and third measurement p<0.01; ³statistical difference between second and third measurement p<0.001

treatment, which increased further by 12 h post-treatment. In the control group, PaO₂/FiO₂, OI, and MAP significantly improved from 6 h to 12 h after treatment (Table 3). By 12 h post-treatment, all measured parameters improved significantly compared to baseline. In the experimental group, most of the parameters were significantly better at 6 h as compared to baseline: PIP, PEEP, PaO₂/FiO₂, PaCO₂, OI, and MAP (Table 4). Most of the measured parameters in this group further improved significantly between 6 h and 12 h post-treatment: PIP, PEEP, PaO₂/FiO₂, OI and MAP. By 12 h post-treatment, all the measured parameters showed significant improvement compared to baseline.

TABLE 5. Significance of differences in lung function parameters between control and surfactant groups at 6 h and 12 h after treatment

| | Measurements at 6 h P value | Measurements at 12 h P value |
|--|--------------------------------|---------------------------------|
| PIP (cm H ₂ O) | 0.041 | 0.014 |
| PEEP (cm H ₂ O) | 0.106 | 0.000 |
| PaO ₂ /FiO ₂ (mm Hg) | 0.038 | 0.000 |
| OI | 0.115 | 0.036 |
| SpO ₂ | 0.012 | 0.010 |
| PaCO ₂ (mm Hg) | 0.310 | 0.034 |
| MAP (cm H ₂ O) | 0.007 | 0.000 |

PIP = peak inspiratory pressure; PEEP = positive end expiratory pressure; PaO₂/FiO₂ = partial pressure of arterial oxygen/fraction of inspired oxygen ratio; OI = oxygenation index; SpO₂ = oxygen saturation; PaCO₂ = partial pressure of carbon dioxide; MAP = mean airway pressure; the level of statistical significance was set at $P < 0.05$

Comparisons were then carried out between the control and surfactant groups to determine whether the surfactant gave significantly different outcomes. For most of the lung function parameters, values were significantly better in the surfactant group than in the control group at both 6 h and 12 h post-treatment (Table 5). At 6 h after treatment, the surfactant group showed significantly better values of PIP, OI, PaCO₂ and MAP. By 12 h after treatment, the surfactant group showed better values of these parameters, as well as of PEEP and PaO₂/FiO₂.

DISCUSSION

This study was designed to investigate whether therapeutic lung lavage with diluted surfactant can improve treatment of atelectasis in pediatric patients. The results showed that, although both surfactant and control groups showed improvement in lung function parameters at 6 h post-treatment and even more by 12 h, the improvement was greater in the surfactant group. In particular, PIP, PEEP, OI, PaCO₂ and MAP appeared to improve with surfactant treatment. These values were significantly lower than in the control group at both 6 h and 12 h post-treatment.

The fact that mechanical cleaning of the airways by itself was sufficient to improve lung function in the control group, together with the fact that the surfactant group showed greater recovery of lung function, suggests that atelectasis in our patients was partly resorptive due to airway obstruction and partly adhesive due to the lack or dysfunction of surfactant.

The driving force for alveolar opening during inspiration is PIP (24, 25). PEEP, in contrast, appears to measure the force to maintain alveolar patency (24, 26-28). Maintaining high PIP and PEEP in order to open and stabilize collapsed alveo-

li can produce over-distention of healthy alveoli due to the variability in alveolar response (29, 30). This can result in barotrauma, which should be avoided. Therefore, in the present study, we sought to achieve sufficient PEEP and moderate PIP to ensure adequate oxygenation. At the same time, we sought to avoid high PEEP levels that would interfere with hemodynamic stability or affect the central nervous system function. Achieving a reduction in PEEP is particularly important in hemodynamically unstable patients and in children with elevated intracranial pressure, regardless of its cause. A total of 6 (67%) and 7 (78%) patients in our control and surfactant groups, respectively, fell into these two categories.

In the present study, atelectasis treatment was considered successful on the basis of improved oxygenation, as measured by increased SpO₂; a decrease in OI, PIP, PEEP, MAP and PaCO₂; and an increase in the PaO₂/FiO₂ (P/F) ratio. In atelectasis, blood flow is shunted through non-ventilated areas. When ventilation is restored, PaO₂ and SpO₂ increase, and the inspired FiO₂ may fall. OI, which is the ratio between the amount of oxygen delivered to the lungs and the amount diffusing into the blood, may be the best indicator of clinical improvement because it integrates airway pressure and oxygenation into a single variable. A reduction in OI indicates the "opening" of atelectatic parts of lungs, improved gas exchange across alveolar membranes, and shunt reduction. Lungs become more pliant, lowering PIP, PEEP, and the risk of lung collapse. MAP may also decrease. These changes improve the elimination of carbon dioxide, leading to a decrease in PaCO₂. Improvement in all measured parameters in both groups 12 h after treatment indicated that the opened atelectasis remained open and that recurrent atelectasis did not occur.

In cases of adhesive atelectasis, the pathological substrate is mostly resistant to the treatment consisting of percussion, vibration, aspiration, aerosolized bronchodilators, positional drainage and fiberoptic aspiration. After mechanical cleaning, which is sufficient in most cases, in the adhesive type of atelectasis recurrent atelectasis mostly appears because of the lack and/or dysfunction of surfactant and increased surface tendency. Mechanical ventilation further alters the monolayer of surfactant and causes direct alveolar damage, exacerbating surfactant deficiency (5). Being aware of the detrimental impact of mechanical ventilation on surfactant production, we thought that surfactant administration as supplementary therapy might be helpful to our mechanically ventilated patients who developed atelectasis. Our results are consistent with the idea that therapeutic lavage of affected lung areas with diluted surfactant minimizes surface tension and improves mucus transport within the narrow pediatric airways (9).

Natural porcine surfactant was used in the present study. Natural surfactants, including porcine surfactant, have been found to be effective in increasing arterial oxygenation and alveolar stability, while being less sensitive than artificial ones to inhibition by serum proteins and other inflammatory mediators (24, 25). Lavage with diluted surfactant seems to have advantages over the usual methods of surfactant application because it avoids preferential surfactant deposition in lung areas without atelectasis, which can further increase the ventilation imbalance (11-13). Various concentrations of diluted surfactant have been reported in the literature (2, 31-33). The concentration in the present study (5 mg/mL) was lower than the previously reported ones, translating to a mean dose (SD) of 15.66 (2.33) mg surfactant /kg body weight. The greatest limitation in studying the effects of higher concentrations is the high cost of the surfactant.

It is important to note that treatment by lavage without surfactant may wash out surfactant from noncompromised areas of the lung instead of replenishing the surfactant pool, thus further aggravating the patient's condition. In the present study, therapeutic lavage of affected areas in both control and surfactant groups was performed with small volumes, so our approach seems unlikely to generate such problems.

CONCLUSION

The results of this study demonstrate that fiberoptic airway cleaning is an efficient method for atelectasis treatment in children, and that simultaneous therapeutic lavage of atelectatic lung segments with diluted surfactant can improve gas exchange and pulmonary function. For definitive conclusions, larger prospective randomized studies are needed.

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Karaman Ilić M. – ideja i dizajn rada, provedba istraživanja, pisanje rada/*idea and design of the study, implementation of research, writing paper*
 Madžarac G. – obrada podataka, rasprava, pisanje rada/*data processing, discussion, writing paper*
 Babić I. – pomoć kod izvedbe i provedbe istraživanja/*assistance in the implementation of the survey*
 Milavić B. – statistička obrada podataka/*statistical data processing*

SUKOB INTERESA/CONFLICT OF INTEREST

Autori su popunili the *Unified Competing Interest form* na www.icmje.org/coi_disclosure.pdf (dostupno na zahtjev) obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u po-

sljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./*All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.*

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SAŽETAK

Ispiranje bronha surfaktantom kao metoda liječenja atelektaze u jedinici intenzivnog liječenja djece

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Cilj je bio ispitati učinak bronhoskopske primjene razrijeđenog surfaktanta u liječenju atelektaze u djece. U ovu prospektivnu studiju je bilo uključeno 18 djece na mehaničkoj ventilaciji koja su neuspješno liječena fizikalnom terapijom i bronhoskopskom aspiracijom. U devetoro bolesnika je nakon bronhoskopske aspiracije apliciran surfaktant u bronh zahvaćenog pluća, dok je u drugih devetoro aplicirana jednaka količina fiziološke otopine. Mjereni su parametri plućne funkcije, PEEP, OI, a radiološka analiza rtg snimki provodila se prije aspiracije te 6 i 12 sati nakon ispiranja. U obje skupine većina mjerenih parametara pokazala je poboljšanje u odnosu na osnovne vrijednosti. Skupina kojoj je apliciran surfaktant pokazala je značajno poboljšanje u usporedbi s drugom skupinom. Najznačajniji učinak surfaktanta pokazao se na mjerenjima provedenim 12 sati nakon aplikacije ($p < 0,001$ u obje skupine): PEEP 5,22 (SD 0,44) u skupini ispiranoj fiziološkom otopinom prema 3,44 (SD 0,73) u skupini ispiranoj surfaktantom; OI 3,84 (SD 1,13) naspram 2,1 (SD 0,38); srednji tlak u dišnom putu (MAP) 8,56 (SD 0,88) naspram 6,33 (SD 0,5). U zaključku, bronhoskopska aspiracija učinkovita je metoda u liječenju atelektaze u jedinici intenzivnog liječenja djece. Terapijski učinak ispiranja bronha razrijeđenim surfaktantom u takve djece mora se potvrditi u daljnjim istraživanjima na većem uzorku.

Ključne riječi: bronhoalveolarno ispiranje; plućni surfaktant; plućna atelektaza; jedinica intenzivnog liječenja djece