Case Report

Wien Klin Wochenschr (2003) 115/21–22: 793–796

wiener klinische wochenschrift
the middle european journal of medicine
Printed in Austria

Acute hemorrhagic respiratory failure caused by Wegener's granulomatosis successfully treated by bronchoalveolar lavage with diluted surfactant

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Bronchiallavage mit verdünntem Surfactant als Therapieoption der akuten Lungenblutung bei Wegener Granulomatose

Zusammenfassung. Wegener Granulomatose (WG) ist eine idiopathische entzündliche Systemerkrankung, die mitunter zum Lungenversagen führen kann. Wir berichten über die erfolgreiche Behandlung einer jugendlichen Patientin mit Wegener Granulomatose mit diffuser Lungenblutung mittels Bronchiallavage mit verdünntem Surfactant. Die Lavage mit verdünntem porcinem Surfactant (Curosurf®, Chiesi, Parma, Italien; 4,8 mg/mL) und die anschließend durchgeführte Bolusgabe erfolgte mittels einem flexiblem Bronchoskop selektiv in beide Lungen. Die verabreichte Gesamtdosis betrug 40 mg/kg KG. Die Patientin war während der gesamten Bronchiallavage beatmet und hämodynamisch stabil, es wurde nur ein kurzer Abfall der pulsoxymetrischen Sättigung beobachtet. Das PaO_2/FiO_2 Verhältnis stieg von 54,8 auf 62,4 nach einer Stunde, auf 106 nach 17 Stunden und erreichte schließlich 280 am 4. Tag nach Therapie. Am Tag 5 nach Therapie konnte die Patientin extubiert werden. Bei Entlassung nach 8 Wochen wurde eine normale Lungenfunktion ermittelt. Die bronchoskopische Lavage mit verdünntem Surfactant ermöglicht eine selektive und direkte Form der Medikamtenapplikation und zusätzlich die Reinigung der Atemwege von Blut und Zelldebris. Diese Reinigung führt zu einer wesentlichen Verminderung der inhibitorischen Kapazität und dadurch zu einem wesentlich geringeren Bedarf an Surfactant. Wir schließen aus dem vorliegenden Fall, dass die frühe Surfactanttherapie mittels BAL zur Vermeidung invasiver Behandlungsmethoden wie ECMO, und damit zu einer schnelleren Wiederherstellung der Lungenfunktion, wesentlich beitragen könnte.

Schlüsselwörter: Surfactant, bronchoalveoläre Lavage, akute Lungenblutung, Lungenversagen, Wegener Granulomatose.

Summary. Wegener's granulomatosis (WG) is an idiopathic inflammatory systemic disease that can occasionally cause an acute respiratory distress syndrome. We report on a 17-year-old girl with Wegener's granulomatosis and acute hemorrhagic respiratory failure successfully treated using bronchoalveolar lavage with diluted porcine surfactant (Curosurf®; 4.8 mg/mL) followed by a low-dose bolus of surfactant. The cumulative dose of surfactant was 40 mg/kg BW. The lavage with diluted surfactant and the administration of the bolus were performed with a flexible bronchoscope. The patient was ventilated during the whole procedure, stayed hemodynamically stable and showed only a very short phase of desaturation. The PaO_2/FiO_2 ratio increased from 54.8 to 62.4 after one hour, to 106 after 17 hours and finally to 280 after four days. The patient was extubated five days after lavage treatment, and almost normal lung function was restored after eight weeks.

Bronchoalveolar lavage with diluted surfactant by flexible bronchoscopy allows selective and direct drug administration and removes airway and alveolar debris. The technique reduces the amount of surfactant needed to overcome inhibition and thereby reduces therapy costs. We conclude that this early therapeutic intervention with surfactant might help to avoid an invasive rescue therapy such as extra corporeal membrane oxygenation, thus improving outcome in terms of faster recovery of lung function.

Key words: Surfactant, bronchoalveolar lavage, acute hemorrhagic respiratory failure, Wegener's granulomatosis.

Introduction

Wegener's granulomatosis (WG) is an idiopathic inflammatory systemic disease first described in 1936 [1]. The disease is characterized by the clinico-pathologic complex of necrotizing granulomatous vasculitis of the upper and lower respiratory tract, glomerulonephritis, and a variable degree of small-vessel vasculitis [2]. The reported prevalence is 1 in 100,000 persons [3] and patients are usually 40–50 years old, although 15% are reported to be under 19 [4]. In addition to problems in the upper airways, most of these patients present either with involvement of the lower respiratory tract and nodular infiltrates or with confluent infiltrating lesions very similar to those seen by

chest x-ray in patients with acute respiratory distress syndrome (ARDS) [5]. Wegener's granulomatosis is considered an uncommon and unique form of acute respiratory failure characterized by pulmonary haemorrhage [6].

Despite extensive research, the treatment of ARDS is far from satisfactory. Among a variety of clinical trials, some have demonstrated beneficial effects of exogenous surfactant on gas exchange and lung mechanics, but no effect on mortality [7–10]; perhaps because there is no evidence-based proven method for the procedure of surfactant administration. Until recently our institutional policy was to use the bolus method [7, 8]. However, in this particular case of acute hemorrhagic respiratory failure we decided to use bronchoscopic lavage to combine removal of debris, blood and protein with better distribution of surfactant as a result of the higher volumes administered.

We report on a 17-year-old patient who has been successfully treated with diluted surfactant by bronchoscopic lavage followed by a low-dose bolus of surfactant given at an early stage of respiratory failure.

Case report

A 17-year-old girl (90 kg BW) was admitted to our children's hospital with fever, arthralgia and hemorrhagic maculopapular skin lesions. After three days the patient developed haemoptysis, microhematuria, proteinuria and severe dyspnoea. Inflammatory parameters were elevated: C-reactive protein was 220 mg/L (normal range up to 12 mg/L), erythrocyte-sedimentation rate (ESR) after 1 and 2 hours was 92/121 mm (normal 10/20 mm), leucocytosis was 18.6/nL, and fibrinogen exceeded 50 mg/L. Extensive diagnostic efforts were initiated. Skin biopsy revealed leukocytoclastic vasculitis. An ulcer on the tongue and infiltration of the lip, nasal inflammation, abnormal chest radiograph, abnormal urine sediment (dysmorphic erythrocytes), mild proteinuria and a high serum titer of c-anti neutrophil cytoplasmic antibodies (c-ANCA) fulfilled the criteria for diagnosis of WG in this patient [11]. Anti-glomerular-basement antibodies and p-ANCA were not detected. The chest CT-scan showed alveolar opacification of both lungs very similar to acute pulmonary haemorrhage caused by systemic vasculitis or WG.

To confirm the suspected diagnosis of Wegener's granulomatosis, the patient underwent an open lung biopsy and was intubated for this procedure. Lung histopathology showed an alveolar haemorrhage, rich in neutrophils, around the partly necrotic small vessels. These findings are very similar to the microscopic picture of polyangitis or WG. During the open lung biopsy the patient's gas exchange deteriorated (pulse oximetry values decreased below 85% and remained there although the FiO_2 was increased to 1.0). Consequently weaning became impossible and the patient was transferred to our PICU.

On admission to the PICU (day 6 in hospital), positive pressure ventilation (IPPV) was continued with an EVITA II (Draeger, Luebeck, Germany) ventilator. The patient still required an FiO_2 of 1.0. Tidal volume (V_T) was set at 9 mL/kg, positive end-expiratory pressure (PEEP) 3 cmH_2O, peak inspiratory pressure (PIP) 31 cmH_2O, I:E ratio 1:2 and ventilator rate 13 breaths per minute. Arterial gas analysis revealed a pH of 7.48, $paCO_2$ of 39 mmHg, paO_2 of 64 mmHg and base excess (BE) of 4 mmol/L.

The first chest x-ray after admission to the PICU showed homogenous alveolar consolidation in both lungs. Only the most apical lung areas were almost regularly ventilated. The lung injury score (LIS) [12] was 2.6, the calculated PaO_2/FiO_2 ratio was 64 and decreased to 54.8 about four hours later. The oxygenation index ($OI = MAP \times FiO_2 \times 100 / p_aO_2$) was 24. At this time the patient did not fulfil our institutional criteria ($OI > 40$) for extra corporeal membrane oxygenation (ECMO) but did fulfil the criteria for administration of exogenous surfactant (e.g. increasing OI despite adjustment of ventilator therapy, $LIS > 1.5$) [7]. About four hours after admission most of the upper parts of both lungs were opacified (Fig. 1). At this time we decided against more aggressive ventilator therapy to avoid an aggravation of lung injury from using higher peak inspiratory pressure, PEEP levels, or changing the I : E ratio to 1 : 1 with higher ventilator rate.

Surfactant treatment was initiated and both lungs were lavaged with diluted surfactant.

2400 mg Curosurf (Nycomed/Chiesi, Parma, Italy) were diluted with 500 mL Ringer solution (final phospholipid concentration 4.8 mg/mL). The first 250 mL were applied bronchoscopically (OLYMPUS BF 3C40; Olympus Optical Co. Hamburg, Germany; 3.6 mm bronchoscope) to the right lung (main bronchus) in portions of 50 mL and suction was started after administration of the first portion. This procedure was repeated five times and took about 10 minutes while the patient was supine. The left lung was then treated similarly. 207 mL were recovered from both lungs (= 41.4%). After the lavage procedure a further 600 mg of Curosurf were applied to each lung as a bolus via bronchoscope. No endotracheal suctioning was performed for about eight hours after the bolus application. The total administered dose of surfactant was 40 mg/kg BW.

The patient was ventilated during the whole procedure, stayed hemodynamically stable and showed only a very short phase of decreased saturation (75%) measured by pulse oximetry.

One hour after treatment, the PaO_2/FiO_2 ratio increased from 54.8 to 62.4 despite a volume overload of approximately 320 mL. Chest x-ray four hours after lavage showed a visible reduction of consolidated areas (Fig. 2); in particular the uppermost parts of the lungs became better ventilated. Ten hours after lavage the chest x-ray showed a further reduction of consolidated areas. Perihilar areas of the middle and lower parts of both lungs showed better ventilation (Fig. 3). About 17 hours after treatment, the PaO_2/FiO_2 ratio continuously increased to 106.

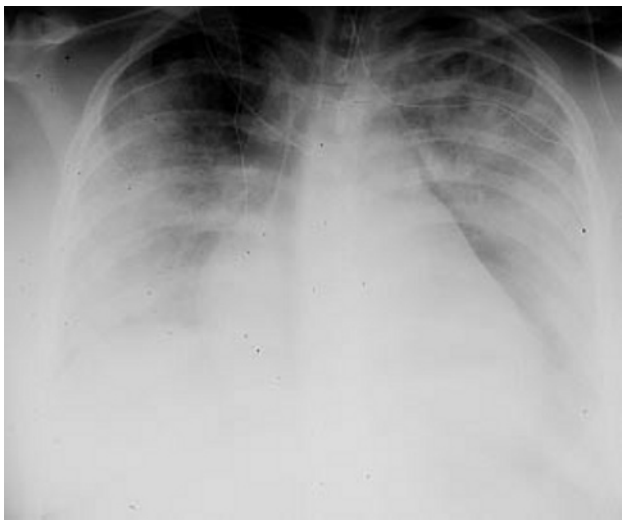

Fig. 1. Four hours after the patient's admission to the PICU, the chest x-ray showed an almost homogenous opacification of both lungs

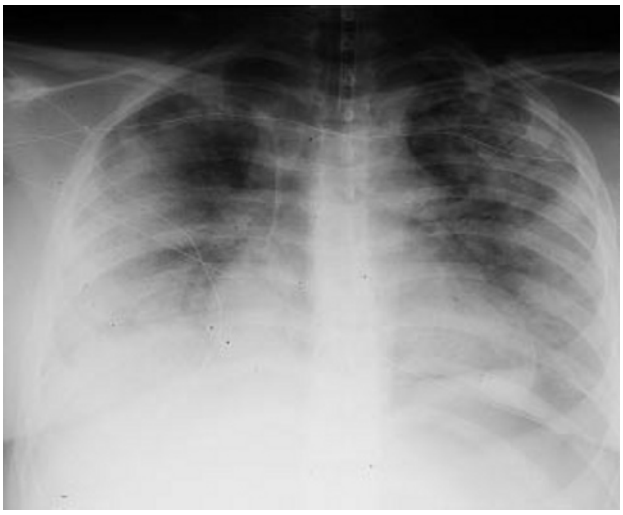

Fig. 2. Four hours after surfactant lavage, the upper parts of both lungs showed a significant improvement of the ventilated areas. Perihilar areas of the middle and lower parts of the lungs showed a slight reduction of consolidation

It is important to note that specific therapy for Wegener's granulomatosis was started about 24 hours after the surfactant treatment. This therapy included 400 mg prednisolone and 800 mg cyclophosphamide given as a bolus infusion four times at intervals of one week [13] and daily sulfomethoxazole-trimethoprim. High dose immunglobulins (1 g/kg) were also given four times at weekly intervals [14].

About four days after surfactant treatment the PaO_2/FiO_2 ratio had increased to 280. The chest x-ray showed only residual mild opacifications in the middle and lower parts of the lungs, and the LIS dropped to 1.0. Five days after the surfactant treatment the patient was extubated, after a further six days transferred to a normal ward, and discharged from hospital in good condition after 41 days. The ESR decreased from 92/121 mm to 16/40 mm within the first three weeks.

Four weeks after discharge from hospital a routine check-up in the children's rheumatology outpatients department revealed a normal chest x-ray with no signs of lung injury (LIS = 0). The lung function test was normal.

Discussion

In the present case of acute hemorrhagic respiratory failure caused by WG we successfully treated our patient with diluted surfactant by bronchoscopic lavage followed by a low-dose bolus of surfactant. The patient was extubated after five days of mechanical ventilation, and almost normal lung function was restored eight weeks after admission to our PICU.

At present there are no recommended models for clinical application and no treatment schedules for the use of surfactant in cases of respiratory failure or ARDS. In clinical studies, surfactant is normally instilled as a bolus [7], sometimes bronchoscopically on a segmental or lobar level [15]. The bolus method appears to be more efficacious than slow tracheal instillation or aerosol delivery [16, 17], but there are disadvantages. Firstly, the distribution of the delivered surfactant in the lung is non-uniform, although there is evidence that higher volumes favour uniformity of distribution [18]. The administration of surfactant via an endotracheal tube does not permit control of the distribution of the surfactant, which may not reach the regions of the lungs that are most severely affected. Secondly, the patient must be rotated to multiple positions during the application procedure, and this may alter the hemodynamic situation. Thirdly, the method is very expensive because of the large amounts of surfactant needed to overcome the inhibitory effects of serum proteins or blood within the air spaces [7, 15]. If we had treated our patient with the bolus method alone (using a minimum of 200 mg/kg BW), instead of combining bolus treatment and lavage with diluted surfactant, the cost of therapy would have been five times higher.

Gommers et al. reported that in lung injury bronchoalveolar lavage (BAL) with diluted surfactant suspension before later surfactant instillation resulted in a stable improvement of lung function. However, three of six animals that underwent BAL with saline died during the observation period as a result of insufficient gas exchanges. Gommers therefore speculated that, in contrast to BAL with saline, lavage with diluted surfactant is less harmful to the lungs, removes more of the potent surfactant inhibitors and contributes to a more uniform surfactant distribution over the lungs [19].

We agree with Nakamura et al. [15] who described a case of bronchoscopic instillation of surfactant in a 9-year-old girl with ARDS and found that this technique allowed surfactant to be given exactly to the desired regions of the lungs. Further, we would suggest combining the application modes and using diluted surfactant to make a bronchoalveolar lavage, the idea being to combine the advantageous effects of large volumes, protein removal and lower amounts of surfactant necessary to improve gas exchange [7]. Nakamura et al. used a much higher dose of surfactant (140 mg/kg BW) than we did (40 mg/kg BW). However, their patient had a sepsis-induced ARDS

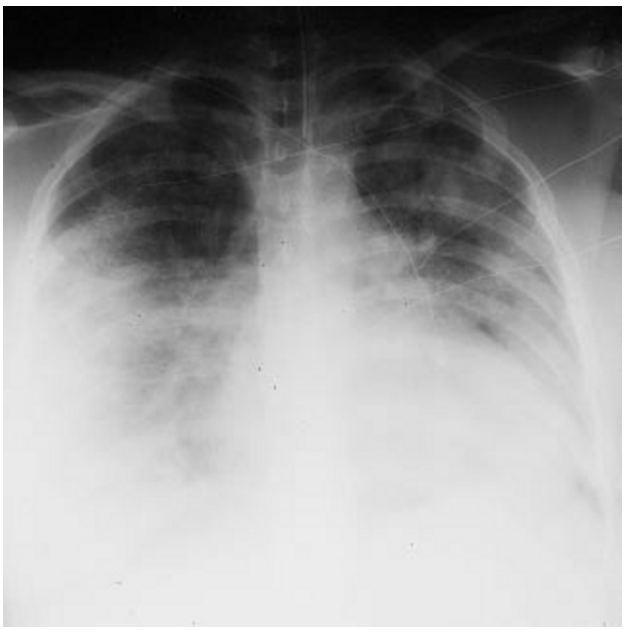

Fig. 3. Ten hours after surfactant lavage, again a significant reduction of the consolidation was visible

and probably had present more inflammatory mediators and inhibitors of surfactant than our patient, thus requiring more surfactant for therapy regardless of the technique. These workers were able to improve gas exchange and lower the ventilator settings but, unlike our patient, there was no improvement of chest X-ray (Fig. 1 before surfactant treatment, Figs. 2 and 3 after treatment). We think that our patient's improvement in the first 12 hours after surfactant treatment was due to this intervention. The further clinical course was probably influenced by the immunosuppressive therapy with prednisolone and cyclophosphamide given 24 hours after surfactant treatment. Loscar et al. [6] described a 19-year-old patient with WG and ARDS where ECMO was initiated because of rapid hemodynamic and respiratory deterioration; after 10 days of ECMO they ventilated the patient for another 50 days.

In conclusion, therapeutic BAL with diluted surfactant followed by a low-dose bolus seems to be an effective, feasible and safe method of treating patients with various types of acute respiratory failure and/or ARDS. It should be emphasized that the lavage technique with diluted surfactant provides a method of selective and direct drug administration together with substantial removal of airway and alveolar debris. Furthermore, the method appears to be very cost-effective. We think that it is the removal of foreign protein, cellular breakdown products, blood, bacteria and mucus that enhances the therapeutic efficacy of the surfactant and thereby enhances ventilation and gas exchange. We therefore suggest that this case report could be used to generate hypotheses for future prospective controlled studies, which may prove that diluted surfactant lavage is effective and improves outcome.

Acknowledgments

We acknowledge the scientific support of Assoc. Prof. Wolfgang Strohmaier PhD from the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria.

References

1. Wegener F (1936) Über generalisierte septische Gefäßerkrankungen. Verh Dtsch Ges Pathol 29: 202–210
2. Fauci AS, Haynes BF, Katz P, Wolff SM (1983) Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 98: 76–83
3. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targenski P, Kaslow RA (1996) The epidemiology of Wegener's granulomatosis. Estimation of the five-year period prevalence, annual mortality, and geographic disease distribution from population based data sources. Arthritis Rheum 39: 87–92
4. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS (1992) Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 116: 488–498
5. Farrelly CA (1982) Wegener's granulomatosis: a radiological review of pulmonary manifestations at initial presentation and during relapse. Clin Radiol 33: 545–551
6. Loscar M, Hummel T, Haller M, Briegel J, Wiebecke B, Samtleben W, Berger H, Eichhorn P, Schelling G (1997) ARDS und Wegener-Granulomatose. Aneasthesist 46: 969–973
7. Hermon MM, Golej J, Burda G, Boigner H, Stoll E, Vergesslich K, Strohmaier W, Pollak A, Trittenwein G (2002) Surfactant therapy in infants and children: three years experience in a pediatric intensive care unit. Shock 17: 247–251
8. Marx M, Golej J, Furst G, Hermon M, Trittenwein G (1995) Acute respiratory failure (ARDS) in a young child after near drowning accident: therapy with exogenous surfactant and high frequency oscillatory ventilation. Wien Klin Wochenschr 107: 146–148
9. Anzueto A, Baughman RP, Guntupalli KK, Weg JG, Wiedemann HP, Raventos AA, et al (1996) Aerosolized surfactant in adults with sepsis induced acute respiratory distress syndrome. N Engl J Med 334: 1417–1421
10. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, et al (1997) Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 155: 1309–1315
11. Leavitt RY, Fauci AS, Bloch D, Michel BA, Hunder GG, Arend WP, et al (1990) The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis and Rheumatism 33: 1101–1107
12. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Resp Dis 138: 720–723
13. Haubitz M, Schellong S, Göbel U, Schurek HJ, Schaumann D, Koch KM, et al (1998) Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement. Arthritis and Rheumatism 41: 1835–1844
14. Stegeman CA, Tervaert JWC, De Jong PE, Kallenberg CGM (1996) Trimethoprim-sulfamethoxazol (co-trimoxazol) for the prevention of relapses of Wegener's granulomatosis. N Engl J Med 335: 16–20
15. Nakamura CT, Ripka JF, McVeigh K, Kapoor N, Keens TG (2001) Bronchoscopic instillation of surfactant in acute respiratory distress syndrome. Ped Pulm 31: 317–320
16. Segerer H, Van Gelder W, Angenent FW, van Woerkens LJ, Curstedt T, Obladen M, et al (1993) Pulmonary distribution and efficacy of exogenous surfactant in lung-lavaged rabbits are influenced by instillation technique. Ped Res 34: 490–494
17. Lewis JF, McCraig L, Veldhuizen R, Goffin J, You P (1994) Surfactant delivery technique influences the efficacy of exogenous surfactant preparations in acute lung injury. Am J Respir Crit Care Med [Suppl] 149: 125
18. Gilliard N, Richman PM, Merritt TA, Spragg RG (1990) Effect of volume and dose on the pulmonary distribution of exogenous surfactant administered to normal rabbits or to rabbits with oleic acid lung injury. Am Rev Resp Dis 141: 743–747
19. Gommers D, Eijking EP, So KL, van't Veen A, Lachmann B (1998) Bronchoalveolar lavage with diluted surfactant suspension prior to surfactant instillation improves the effectiveness of surfactant therapy in experimental acute respiratory distress syndrome. Int Care Med 24: 494–500

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(Received May 27, 2003, accepted after revision September 17, 2003)