Improved Oxygenation by Steroid Pulse Therapy in Early-Phase Acute Respiratory Distress Syndrome

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ABSTRACT Objective and Background: Although short-duration, high-dose glucocorticoid therapy is reportedly ineffective for early-phase acute respiratory distress syndrome (ARDS), steroid pulse therapy is often used in Japan for life-threatening cases because of its beneficial effects on oxygenation. Thus, we evaluated the effect of steroid pulse therapy on oxygenation for early-phase ARDS. Method: Cases of early-phase ARDS treated with steroid pulse therapy in intensive care units of four critical care medical centers in Japan from 2000 to 2003 were investigated. Clinical course and serial changes in $\text{PaO}_2/\text{FiO}_2$ ratio were evaluated. Results: Twenty-nine patients received methylprednisolone 1 g/day for 3 days; 20 patients subsequently received prolonged methylprednisolone treatment. Causes of ARDS were pneumonia ($n = 23$), extrapulmonary sepsis ($n = 4$) and other factors ($n = 2$). The overall mortality rate was 24.1%. $\text{PaO}_2/\text{FiO}_2$ ratios improved significantly after initiation of steroid pulse therapy, in comparison to pretreatment values (day 0: 119.8 ± 30.6 , day 1: $172.1 \pm 63.7^*$, day 2: $196.4 \pm 90.0^*$, day 3: $218.4 \pm 92.0^*$, mean $\pm$ SD, $*p < 0.05$ vs. day 0). Significant improvement in oxygenation was observed in both survivors and non-survivors, but the $\text{PaO}_2/\text{FiO}_2$ ratio in non-survivors subsequently deteriorated. In seven patients with life-threatening hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 100 at day 0), oxygenation improved significantly after pulse treatment; five of these patients survived. Conclusions: Three day steroid pulse therapy can improve oxygenation in patients with progressive ARDS even in the early phase. Steroid therapy for early-phase ARDS should be reconsidered.

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Introduction

Acute respiratory distress syndrome (ARDS), characterized by diffuse inflammation of the alveolar-capillary

membrane in response to various pulmonary and extrapulmonary insults, is a major cause of morbidity in intensive care units. Although mortality from ARDS has decreased in the last decade¹⁾, it remains high (30-40%), with most non-survivors dying within 2 weeks of disease development. The common pathologic feature of ARDS is an inflammatory process involving complex interaction between platelets, leukocytes, mononuclear cells, macrophages, and endothelial cells²⁾. Dysregulation of cellular responses often occurs, and diffuse lung injury causes spillover of cytokines and other inflammatory and thrombotic mediators into the blood stream, which can lead to multiorgan system dysfunction. Pharmacologic treatment of ARDS patients focuses on attenuating these inflammatory responses³⁾.

Although most pharmacologic ARDS therapies have been shown to be ineffective, glucocorticoids, which inhibit the inflammatory process at virtually all levels⁴⁾, have been used in the treatment of ARDS since the syndrome

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was first described over 35 years ago⁵⁾. Previous studies have concluded that glucocorticoids are not particularly effective against early ARDS but may have a role in the late phase⁶⁾. High-dose glucocorticoid treatment is indicated only for the subgroups of acute lung injury /ARDS patients who have *Pneumocystis carinii* pneumonia⁷⁾ or are at risk of ARDS due to fat embolization⁸⁾. But, practically, we often experience deteriorated ARDS patients who could not survive without steroid administration in early phase.

In many facilities in Japan, 3-day steroid pulse therapy have been often used for life-threatening ARDS on the basis of observation of its beneficial effects on oxygenation in the declining clinical course. There have been a few reported cases showing the efficacy of steroid pulse therapy for ARDS patients⁹⁻¹⁵⁾, but the precise effect or mechanism of this treatment has not been thoroughly investigated.

We conducted retrospective investigation of ARDS patients, received steroid pulse therapy in four critical care medical centers in Osaka, Japan during the past 3 years. The objective of the present study was to evaluate the effect of steroid pulse therapy on oxygenation for early-phase progressive ARDS patients.

Methods

The subjects of this retrospective study were ARDS patients who underwent steroid pulse therapy during the period 2000 to 2003 in intensive care units of four critical care medical centers in Osaka, Japan: Department of Traumatology at Osaka University Medical School, Senri Critical Care Medical Center, Nakakawachi Medical Center of Acute Medicine, and Senshu Critical Care Medical Center. The collected data consisted of patient demographics, serial changes in clinical and laboratory factors, therapy, complications, and mortality.

ARDS was defined as acute-onset bilateral infiltrates depicted on the chest radiograph; hypoxia, defined as a ratio of PaO₂ to the fraction of inspired oxygen (FiO₂) (PF ratio) less than 200; and the absence of left atrial hypertension according to the revised definition proposed by American-European Consensus Conference on ARDS¹⁶⁾.

There were 54 ARDS patients who were treated with steroid pulse therapy; 52 of these patients (96.3%) were treated with methylprednisolone in the early phase of ARDS (duration of ARDS ≤ 7 days). Of these 52 patients, 23 with significant comorbid disease (severe chronic liver disease, severe chronic respiratory disease, burns requir-

Table 1. Patient characteristics (n=29).

Age (yr)	57.3 ± 21.0 (range, 14-80)
Sex (M/F)	20/9
Duration of ARDS (days)*	2.5 ± 2.1 (mean ± SD)
Origin of ARDS	
Direct injury (n=25)	pneumonia (n = 23) pulmonary contusion (n = 1) chemical aspiration (n = 1)
Indirect injury (n=4)	extrapulmonary sepsis (n = 4) pelvic abscess (n = 1) peritonitis (n = 1) pancreatitis (n = 1) VAHS† (n = 1)

* At the time steroid pulse therapy was initiated.

† VAHS: virus- associated hemophagocytic syndrome

ing skin grafting), clinical evidence of active untreated infection, and extracorporeal support of gas exchange were excluded to permit evaluation of the precise effect of steroid pulse therapy on the clinical course. The exclusion criteria were selected from the criteria used in the Late Steroid Rescue Study by ARDS network (<http://www.ardsnet.org/>). The remaining 29 patients (twenty men, nine women; mean age 57.3 ± 21.0 years, range 14-80 years) comprised the study subjects. Mechanical ventilation was based on lung protective strategy (Tidal Volume < 10ml / kg of body weight, Peak airway pressure < 35cmH₂O). The major clinical disorders associated with the development of ARDS were pneumonia (n = 23), extrapulmonary sepsis (n = 4), and others (n = 2) (Table 1). The pathogens to cause pneumonia were *K.pneumoniae* (n = 2), *P.aeruginosa* (n = 3), *Chlamydia* (n = 1), *E.coli* (n = 1), *Legionella* (n = 1), methicillin- resistant *Staphylococcus aureus* (n = 1), while those in 14 cases were undetermined. APACHE II score on day 0 was 16.4 ± 6.2.

All 29 patients received MP pulse treatment (1 g/day for 3 days) in the early phase of ARDS, and 20 patients subsequently received prolonged MP depending on their clinical response to MP (mean duration of 11.0 ± 4.8 days, mean ± SD). The mean interval between meeting the criteria for ARDS and the initiation of MP treatment was 2.5 ± 2.1 days.

§ Statistical analysis

Data are expressed as mean ± SD. Categorical variables were analyzed by chi-square test (Fisher's exact test). Continuous variables were analyzed by unpaired t test. For each arm, mean values on days of treatment were contrasted with values on day 0 (day of initiation of steroid

Table 2. Patient characteristics (Survivors vs. Non-survivors).

Clinical Data	Survivors (n = 22)	Non-survivors (n = 7)	p value [†]
Mean age (yr)	54.1 ± 23.0	62.9 ± 22.7	0.38
Sex (M/F)	18/4	2/5	0.008
Primary diagnosis			
Pneumonia	18	5	NS
Extrapulmonary sepsis	2	2	NS
Other	2	0	NS
PaO ₂ /FiO ₂ at day 0*	125.3 ± 31.9	104.1 ± 20.8	0.61
PEEP [‡] (cmH ₂ O) at day 0*	11.0 ± 5.2	11.0 ± 3.5	0.98

Numbers of patients are shown unless otherwise indicated.

* day 0: the day of methylprednisolone was started.

Values are mean ± SD.

[†] With chi-square test; NS: not significant.

[‡] PEEP: positive end-expiratory pressure.

Fig. 1. Changes in PaO₂/FiO₂ (PF) ratio and PEEP in all patients (n = 29). (Data are expressed as mean ± SD.). At the initiation of steroid therapy (day 0, before administration of methylprednisolone), the mean PF ratio was 119.8 ± 30.6, significantly decreased in comparison to that on previous days (p < 0.05). The PF ratio improved significantly on the first, second, and third days after the start of steroid pulse therapy, in comparison to the pretreatment value, though PEEP was almost unchanged. * p < 0.05 vs. day 0 (pre).

therapy before administration of MP). We used ANOVA of repeated test to evaluate serial change of PF ratio in survivors and non-survivors. In addition, partial correlation coefficients were estimated to quantify the relation between the PF ratio, clinical variables, and clinical course. A p value of < 0.05 was considered significant.

Results

Of the 29 patients with progressive early-phase ARDS received steroid pulse therapy, 22 survived (75.9%) and

seven died (24.1%). Non-survivors were significantly more likely to be female (M: F = 2:5) in comparison to survivors (p < 0.05) (Table 2). The causes of death were respiratory failure (57.1%, n = 4) and septic shock (42.9%, n = 3). The non-survivors died on day 25.3 ± 14.2 (range, day 6–45) after starting MP pulse treatment. Among the seven non-survivors, the primary diagnosis was pneumonia (n = 5), peritonitis (n = 1), and virus-associated hemophagocytic syndrome (n = 1).

Changes in the mean PF ratio in all patients are shown in Fig. 1. At the initiation of steroid therapy (day 0), the

Fig. 2. Changes in $\text{PaO}_2/\text{FiO}_2$ (PF) ratio (survivors vs. non-survivors). (Data are expressed as mean $\pm$ SD. Closed circle express survivors, open square with a dotted line express non-survivors.). A significant improvement in oxygenation after the start of steroid pulse therapy was observed in both survivors ($n = 22$) and non-survivors ($n = 7$) ($p < 0.05$), but the PF ratio in non-survivors subsequently decreased. From day 6 after the start of treatment, the PF ratio was significantly lower in the non-survivors than in the survivors ($p < 0.05$). * $p < 0.05$ vs. day 0, # $p < 0.05$ vs. survivors.

Fig. 3. Changes in $\text{PaO}_2/\text{FiO}_2$ (PF) ratio in seven life-threatening acute respiratory distress syndrome patients (PF ratio < 100 at day 0). (Data are expressed as mean $\pm$ SD.) The mean PF ratio improved significantly after the start of steroid pulse therapy. * $p < 0.05$ vs. day 0.

mean PF ratio was 119.8 ± 30.6 and positive end-expiratory pressure was 11.0 ± 4.8 cmH₂O. The PF ratio on day 0 was significantly decreased in comparison to that on previous days ($p < 0.05$). The PF ratio improved significantly on the first day, the second day, and the third day after initiation of steroid pulse therapy in comparison to the pretreatment (day 0) value (day 0: 119.8 ± 30.6 , day 1: $172.1 \pm 63.7^*$, day 2: $196.4 \pm 90.0^*$, day 3: $218.4 \pm 92.0^*$,

* $p < 0.05$ vs. day 0), though PEEP was almost unchanged.

The serial changes in the mean PF ratio in survivors and non-survivors are shown in **Fig. 2**. Significant improvement in oxygenation after the start of steroid pulse therapy was observed in both survivors and non-survivors ($p < 0.05$), but the PF ratio in the non-survivors subsequently deteriorated. From day 6 after the initiation of treatment, the PF ratio in non-survivors was significantly lower than

Table 3. Complications.

	Survivors (n = 22)	Non-survivors (n = 7)
Bacteremia	6 (27%)	5 (71%)*
Hyperglycemia	12 (55%)	4 (57%)
Gastrointestinal bleeding	1 (5%)	1 (14%)

Number (and percentage) of patients are shown.

With chi-square test, * $p < 0.05$ vs. survivors

that in survivors ($p < 0.05$).

Even in the seven patients with life-threatening hypoxemia (PF ratio < 100 at day 0), the mean PF ratio was significantly improved after initiation of steroid pulse therapy (**Fig. 3**). Five of these patients survived (mortality rate of 28.6%), and two patients died due to septic shock, one on day 6 and one on day 29. There are no statistically significant difference about SOFA score on day 0 (7.4 ± 3.8 v.s. 8.1 ± 3.7), day3 (5.5 ± 3.6 v.s. 7.4 ± 3.7), day7 (3.5 ± 2.8 v.s. 5.5 ± 3.8) and day10 (3.1 ± 2.7 v.s. 5.2 ± 3.6) between survivors and non-survivors (mean $\pm$ SD). But, serial changes in SOFA score was significantly different between survivors and non-survivors ($p = 0.02$).

With respect to complications, the hyperglycemia and gastrointestinal bleeding occurred with similar frequency in survivors and non-survivors, but the frequency of bacteremia was significantly higher in the non-survivors ($p < 0.05$, **Table 3**). Bacteremia in the non-survivors was caused by *Enterococcus* ($n = 3$), methicillin-resistant *Staphylococcus aureus* ($n = 1$), and *Candida* ($n = 1$).

Discussion

In the present study, we found that steroid pulse therapy for 3 days can improve oxygenation in patients with early-phase progressive ARDS. Our data shows that although steroid pulse therapy was initiated at the point when the clinical course was declining, pulmonary oxygenation improved rapidly after the start of treatment, with an overall survival rate of 75.9%. These remarkable results of steroid pulse therapy were observed both in survivors and non-survivors. Even in the life-threatening ARDS cases (PF ratio < 100 at day 0), in which we had no other therapeutic alternatives, oxygenation recovered dramatically after the initiation of steroid pulse therapy, and all patients were salvaged during the 3-day treatment, with a 71.4% intensive care unit survival rate. These results suggest that steroid pulse therapy can exert a beneficial effect on poor oxygenation and reverse the life-threatening course of pro-

gressive ARDS in the early phase.

Glucocorticoids inhibit the inflammatory pathways at all levels and exert most of their influence via specific, ubiquitously distributed intracellular glucocorticoid receptors. The dosage for steroid pulse therapy (MP 1 g/day for 3 days) was first chosen after experience in treating graft rejection in renal transplant recipients in 1976¹⁷⁾. This MP pulse treatment has been used for patients with severe manifestations of autoimmune diseases such as systemic lupus erythematosus¹⁸⁾, dermatomyositis¹⁹⁾, and Still's disease⁹⁾, and rapid beneficial effects on the clinical course were reported repeatedly. In these reports, steroid pulse therapy was described as having a strong anti-inflammatory effect on exaggerated inflammatory response in organ and/or life-threatening conditions.

The duration of efficacy of administered MP is 24 to 72 hours after the pulse dose and does not change significantly even with higher doses. After 24 hours, approximately 99% of the MP pulse dose is eliminated. These characteristics of MP pulse therapy result in decreased steroid-related side effects, such as suppression of the hypothalamic-pituitary-adrenal axis, in comparison to oral prednisolone (20 mg daily) treatment for as few as 5 days²⁰⁾. In previous studies in humans and rabbits, greater concentrations of MP than of prednisolone appeared in the lung, in part because of the greater tendency of MP to be retained in the epithelial lining fluid²¹⁾. Recent in-vitro studies showed that MP pulse therapy produces strong anti-inflammatory action through immediate effects on lymphocyte activation by interacting directly with the cell membrane and decreasing intracellular Ca^{2+} concentrations. These results indicate additional therapeutic benefits of MP pulse therapy in comparison to low-dose prednisolone therapy because of nongenomic effects mediated by membrane-bound receptors and initiated by physiochemical interactions with cellular membranes.

Our study is the first *in vivo* study to evaluate the efficacy of steroid pulse therapy on oxygenation for early-phase ARDS of various origins. A few reports in the English literature describe the efficacy of steroid pulse therapy for ARDS patients with specific disease. Ho et al¹¹⁾, recently reported that severe acute respiratory syndrome patients initially treated with steroid pulse therapy had a lesser oxygen requirement and better radiographic outcome than patients treated with non-pulse steroid therapy. They suggest that initial use of pulse methylprednisolone therapy is more efficacious and equally safe steroid regimen when compared with regimens with lower dosage. Trivedi et al¹²⁾, showed that early steroid pulse therapy after the onset of dyspnea

can reverse the lethal pulmonary involvement of leptospirosis. A beneficial effect of steroid pulse therapy was reported in ARDS patients with leukopenic pneumococcal pneumonia¹³⁾, petroleum naphtha ingestion¹⁴⁾, chronic granulomatous disease following pulmonary invasive aspergillosis¹⁰⁾, and rapid- progressive bronchiolitis obliterans organizing pneumonia¹⁵⁾. The regimen of methylprednisolone (500mg-1g/day for 3-5 days) in these studies is similar to our regimen. These reports are consistent with our findings that deteriorated oxygenation recovered significantly after the initiation of steroid pulse therapy even in cases in which the disease had progressed to a life-threatening stage.

A prospective randomized trial²²⁾ was reported in which high-dose MP did not affect the outcome of patients with established ARDS due to sepsis, aspiration, or mixed causes. The investigators started MP (30 mg/kg every 6 hours for 24 hours) in patients within 48 hours after diagnosing ARDS. Principally because of these results, high-dose MP treatment for early-phase ARDS has been considered ineffective. However, there were several factors in their study that inhibit precise evaluation of the effect of steroid treatment in early-phase ARDS. First, almost half of their patients (44%) suffered severe active infection including bacteremia upon entering the study, and mortality rates in both the treatment group and placebo group were significantly high (about 60%). Second, the corticosteroid regimen (30 mg/kg every 6 hours to four doses) lasted only 1 day, and there was no additional treatment until resolution. Thus, there were strong non-pulmonary determinants of outcome in their study, and the treatment period might have been too short to produce a constant effect.

In another prospective trial, Luce et al²³⁾, found that high-dose MP treatment given in the similar regimen reported by Bernard et al²²⁾, did not affect the incidence of ARDS or hospital mortality in sepsis patients at high risk for developing ARDS. In our study, patients with bacteremia were excluded, and steroid therapy lasted at least 3 days. Moreover, ARDS was caused by direct pulmonary injury in more than 80% of our patients. Considering these differences in the patient group and treatment regimen, our findings of beneficial effects of steroid pulse therapy in early-phase ARDS do not contradict the previous reports that ruled out high-dose MP for patients at risk or with early ARDS. Mervyn et al²⁴⁾, found that hydrocortisone (800 mg/day for 48 hours) was useful in the treatment of previously healthy patients with early-phase life-threatening varicella pneumonia. Confalonieri et al. re-

cently reported that hydrocortisone treatment (200mg bolus plus 240mg/day for 7days) improved the clinical course in severe acquired pneumonia²⁵⁾. Thus, further study is needed to determine the appropriate indications and treatment regimen for steroid therapy in patients with early-phase ARDS.

In our study, oxygenation in the survivors continued to improve after steroid pulse therapy, whereas oxygenation in the non-survivors subsequently deteriorated. Prolonged steroid therapy for a mean duration of 9.8 days after the pulse therapy was used in 68.2% of the survivors. The efficacy of prolonged steroid treatment in late-phase ARDS patients has been controversial. Meduri et al^{6,26)}, reported that prolonged administration of MP (initial dose of 2 mg/kg/day, tapered over 32 days) in patients with unresolving ARDS was associated with improvement in lung injury and reduced mortality; this was a controlled study with a small number of patients. Biffi et al²⁷⁾, also found that MP therapy (1-2 mg/kg every 6 hours for a mean duration of 21.3 days) significantly improved oxygenation and lung injury score in six patients with refractory late-phase ARDS, and saved five patients in life-threatening condition. On the other hand, Late Steroid Rescue Study of ARDS network found that prolonged methylprednisolone has not improved the outcome of persistent ARDS patients despite the improvement in cardiopulmonary physiology²⁸⁾.

In addition to its antiinflammatory properties, MP is known to inhibit proliferation of fibroblasts and synthesis of collagen by fibroblasts in tissue cultures²⁹⁾. The use of steroid in the late phase of ARDS is based on the assumption that the fibroproliferative phase begins 7-10 days after insult. However, some investigators report that the proliferative phase begins much sooner. Rocco et al. found that corticosteroid treatment in the early phase of acute lung injury improved *in vivo* and *in vitro* respiratory mechanics, acting on the remodeling process, mechanism by which oxygenation was significantly improved in both the early phase and late and significantly reducing collagen fiber deposition³⁰⁾. This may partly explain the phase with the use of MP therapy in our study.

In an analysis of notable complications after the start of steroid pulse therapy, we found that hyperglycemia and gastrointestinal bleeding occurred with similar frequency between survivors and non-survivors, whereas bacteremia was significantly more frequent among non-survivors (71%). Thus, bacteremia can be considered an important determinant of clinical outcome in ARDS patients treated with steroid pulse therapy. Because bacteremia occurs

around 15 days after the start of steroid treatment, appropriate and repeated use of antimicrobial drugs should be considered during steroid treatment on the basis of information obtained from bacterial cultures repeated every 3 to 4 days. Our study was an uncontrolled retrospective study; a prospective randomized study is needed to clarify both the efficacy and risk of steroid pulse therapy for early-phase ARDS.

In the present study, the non-survivors in comparison to survivors were significantly more likely to be female. Although ARDS comprises clinically heterogeneous syndromes of various causes and clinical courses, sex-specific and genetic susceptibilities have been investigated. Kollef et al³¹⁾ reported a greater risk of hospital mortality for women requiring mechanical ventilation than for men with equivalent requirements, which is consistent with our findings in ARDS patients. Gong et al³²⁾ showed that the variant polymorphism of the surfactant protein-B gene is associated with ARDS and with direct pulmonary injury in women, but not in men. These reports may support the hypothesis that individual difference in susceptibility to developing ARDS depends on sex and genotype. The utility of steroid treatment in patients with different genetic susceptibilities is yet to be elucidated.

Conclusions

Steroid pulse therapy for 3 days can improve oxygenation even in the early phase of progressive ARDS. Steroid therapy for early-phase ARDS should be reconsidered, and further prospective randomized studies need to be conducted to clarify the efficacy of steroid pulse therapy in patients with ARDS.

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原著論文

早期 ARDS 患者におけるステロイドパルス療法の酸素化改善効果

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要旨 背景：欧米では早期 acute respiratory distress syndrome（以下 ARDS と略す）に対する高容量ステロイドの使用は否定されているが、本邦では臨床経験をもとに重症ARDSに対してステロイドパルス療法が行われてきた。しかしながら、その有効性は十分評価されていない。本研究の目的は、早期ARDS症例に対するステロイドパルス療法の効果を多施設で検討することである。対象と方法：対象は、2000年から2003年までの3年間に4つの救命センターでARDSの診断基準を満たし、ARDS発症1週間以内にステロイドパルス療法を施行した29症例（肺炎23例、敗血症4例、その他2例）。全例の臨床経過および酸素化能の推移をretrospectiveに評価した。結果：29例全例メチルプレドニゾン 1g × 3日間のパルス療法を行い、うち20例はパルス療法後維持療法へと移行した。ICU死亡率は24.1%であった。悪化中のPF比（ $\text{PaO}_2/\text{FiO}_2$ ）は、ステロイドパルス開始を契機に翌日より有意に改善した（day 0: 119.8 ± 30.6 , day 1: $172.1 \pm 63.7^*$, day 2: $196.4 \pm 90.0^*$, day 3: $218.4 \pm 92.0^*$, mean $\pm$ SD, * $p < 0.05$ vs. day 0）。また、PF比100以下の致死的重症例もパルス療法によって有意な酸素化の改善がみられ、7例中5例の生存を得た。総括：ステロイドパルス療法は、早期 ARDS 患者の酸素化能を有意に改善する。早期ARDSにおけるステロイド療法の適応を再検討すべきと考える。

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