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The Window of Improved Neonatal Respiratory Compliance after Rescue Antenatal Steroids

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Abstract

Objective—To evaluate if premature infants delivered ≤7 days after rescue antenatal steroid treatment (ideal treatment) have increased passive respiratory compliance compared to those delivered ˃7 days after treatment (remote treatment).

Methods—Secondary analysis of a randomized trial of rescue antenatal steroids on respiratory compliance. Infants in the treatment group were stratified by the interval between rescue antenatal steroids and delivery. We then compared the respiratory compliance in the ideal versus remote groups.

Results—44 women (56 infants) received rescue antenatal steroids. 49 infants had evaluable respiratory compliance measurements, with 27 (GA 30.0 weeks, BW 1362g) “ideally” treated, and 22 (GA 33.8 weeks, BW 2248g) “remotely” treated. Respiratory compliance was significantly higher for the ideal compared to the remote group (1.32 vs 1.06 mL/cm H_20/kg; p = 0.037).

Conclusion—Infants treated with rescue antenatal steroids have a significantly higher respiratory compliance if delivery occurs within 7 days after treatment.

Introduction

Since Liggins and Howie’s seminal work on the benefits of antenatal steroids (AS) among preterm infants[1], a substantial body of evidence has definitively demonstrated that AS improve neonatal respiratory function[2,3] and clinical outcomes[4] in infants born prematurely. The benefits of AS issue from both structural[5] and physiological changes[6,7] in the lung. While the AS-induced architectural changes are likely stable over time, the physiologic changes, particularly those mediated by induction of surfactant pools to improve lung function, are proposed to be time-limited, with waning effects seven days after treatment[1,8–10]. As a result, repeated (or rescue) doses of AS have been used in some undelivered women who remain at risk of preterm delivery in an attempt to maintain the benefits of AS on neonatal lung function and outcomes – though the practice of giving more

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than one additional course of AS is controversial due to concerns about the cumulative effect of AS on fetal growth.[11–14]

Subsequent studies of the effects of repeat AS have shown that, like the initial course of AS, repeat doses of AS improve lung function. In a prior randomized controlled trial (RCT), our group showed that a single rescue course of AS in pregnancies undelivered more than 14 days after the initial course of AS significantly increased passive respiratory compliance (Crs) measured within 72 hours of delivery when compared to those randomized to placebo[15]. Similarly, a meta-analysis of 10 RCTs showed a reduction in RDS and in a composite outcome among infants treated with repeated doses of AS[16]. As clinicians struggle with balancing this harm/benefit assessment, the question of duration of effect following a rescue course of AS remains an important and unanswered one.

The objective of this study is to determine if the increase in Crs following administration of rescue AS diminishes over time. Though previous work has shown that the duration of increased Crs after initial AS is approximately 1-7 days[10], no study to date has evaluated the duration of increased Crs after rescue AS. We hypothesized that, similar to the effects demonstrated after an initial treatment with AS, Crs will be higher for infants delivered within the “ideal window” (≤ 7 days after treatment with rescue AS) compared to those delivered remotely (> 7 days after treatment with rescue AS).

Methods

Subjects and Study Design

This study is a subgroup analysis of data initially collected in a randomized, placebo-controlled, blinded trial of the effect of rescue AS on passive lung compliance[15]. The original study was conducted in two neonatal intensive care units in the USA: Oregon Health & Science University in Portland, OR and Sacred Heart Hospital in Pensacola, FL. The study protocol was approved by IRBs at both institutions and informed consent was obtained from all subjects prior to enrollment. Details of the original study are described elsewhere (clinicaltrials.gov NCT00669383)[15]. In brief, women with a singleton or twin gestation between 26 to 34 weeks, who had received an initial course of AS ≥14 days prior to enrollment, were randomized to receive either a two-dose rescue course of AS (Celestone Soluspan; Schering-Plough Corporation, Kenilworth NJ) or placebo if signs of possible preterm delivery occurred. Pulmonary function studies were performed on the infants born to these women within 72 hours of birth and prior to surfactant if needed.

For this secondary analysis, we focused only on the infants in the treatment arm (who had received both an initial and rescue AS course) and separated them into two groups based on the number of days between treatment with rescue AS and delivery. We then compared mean initial Crs for the infants in the “ideally treated” group (delivered ≤7 days after rescue AS) with that of infants in the “remotely treated” group (> 7 days) using linear mixed modeling to account for the correlation between twins and to adjust for additional covariates and confounders.

Pulmonary Function Testing

All pulmonary function testing was performed on infants sleeping quietly in the supine position with quality control in accordance with American Thoracic Society and European Respiratory Society guidelines[17–19]. Measurements were taken with a computerized infant pulmonary function cart (Sensor-Medics 2600; Sensor-Medics Corp, Yorba Linda, CA) using either a mask interface or endotracheal tube for intubated patients. Within 72 hours of birth and prior to administration of surfactant if required, we measured Crs by eliciting the Hering-Breuer reflex with the single-breath occlusion technique[3,10,20,21]. Crs measurements were considered acceptable if they were obtained at a stable end-expiratory baseline, with a plateau pressure >100 ms, variance of <0.125 cm H2O, with appropriate flow volume loops by visual inspection, and at least 10 breaths with a measured coefficient of variation <20% [17–19].

Statistical analysis

We used SPSS for Windows, Version 22 (IBM, Armonk, NY) for all statistical analyses. Means, standard deviations, and standard errors of the mean were calculated for Crs in the ideal and remote groups. Categorical variables were analyzed with χ^2 testing. A linear mixed model, developed in the analysis of the data from the primary RCT[15], was used to test for statistical significance. This model was chosen to account for the non-independence of covariates among the twins in the dataset, and was used to control for confounding effects of gestational age, gestational diabetes, maternal smoking, rupture of membranes, and multiple gestation.

Results

Description of population

A total of 44 women and their 56 infants (12 sets of twins) were included in this analysis. All 44 women had been treated with both an initial course of AS and at least the first dose of a rescue course. Of the 30 infants in the Ideal group delivered at ≤ 7 days from receipt of rescue AS, 27 infants (90%) had technically acceptable measurements of passive respiratory compliance as per the above standard acceptance criteria. Of the 26 infants in the Remote group delivered >7 days from receipt of rescue AS, 22 infants (84.6%) had acceptable measurements of passive respiratory compliance (Figure 1). The average gestational age at delivery was 30.1 weeks in the Ideal group compared to 33.8 weeks in the Remote group. Similarly, average birthweight was 1361 g in the Ideal group compared to 2248 g in the Remote group. Additional maternal and infant demographic details are presented in the Table. Figure 2 depicts the distribution of the latency periods (between the initial maternal dose of rescue AS and delivery) among these 49 infants with technically acceptable passive respiratory compliance measurements. In the Ideal group, 8/27 (29.6%) were delivered ≤ 1 day after the first maternal rescue AS dose.

Description of Crs findings

Average compliance for infants in the Ideal group (delivering ≤ 7 days after AS treatment) was 1.32 mL/cm H_2O/kg (SEM 0.11), and average compliance for infants in the Remote

group (>7 days) was 1.06 mL/cm H_2O/kg (SEM 0.10) (Figure 3a). The raw compliance data is shown for infants delivered 0 – 21 days following rescue AS (Figure 3b). When the groups were redefined using a 14-day instead of a 7-day interval, average compliance for the 32 infants in the ≤ 14 days group was 1.31 mL/cm H_2O/kg (SEM 0.09), and average compliance for the 17 infants in the > 14 days group was 1.02 mL/cm H_2O/kg (SEM 0.13) (data not shown).

Discussion

Main Findings

This study is a secondary analysis of data collected in a randomized, blinded, placebo-controlled trial evaluating the impact of rescue AS on pulmonary function. Here, we report that among infants of mothers treated with an initial course of AS followed by a subsequent rescue course of AS, those delivered within the ideal window (≤ 7 days) after maternal treatment with rescue AS had an increased passive respiratory compliance compared to infants delivered more remotely (> 7 days). This early post-natal measurement of compliance (measured within 72 hours of birth) was significantly increased in the ideally-treated group even though the infants in the remotely-treated group were almost 4 weeks older (30.1 vs 33.8 weeks' gestation) and ~900g heavier (1361 vs 2248 grams) on average.

Interpretation

The use of an initial course of AS is widely accepted as the standard of care for pregnancies at risk for preterm delivery[22], due to their ability to increase early lung compliance[3] and to improve neonatal outcomes[4]. However, these beneficial effects have been shown to diminish if the delivery occurs more than 7-14 days after treatment[9,10].

In a previous publication, we showed a significant increase in Crs (measured within 72 hours of birth and prior to surfactant administration) following a single rescue course of AS[15]. In this follow up study, we show that among infants who received repeat doses of AS, those who are born within 7 days of receipt of these rescue doses have significantly increased Crs compared to those who delivered more than 7 days after treatment. To our knowledge, this is the first study to evaluate the duration of effect of rescue AS on lung compliance in neonates. These data support the conclusion that compliance is increased in a time-limited manner following rescue AS, lasting 7-14 days, and waning thereafter. These physiologic data may also explain the improvement in a variety of respiratory-related clinical outcomes found in infants born within 7 days of treatment with rescue AS. Two retrospective studies of repeat doses of AS showed reductions in RDS and in the need for CPAP lasting > 24 hours for infants delivered within 7 days of treatment[23,24]. Similarly, in an RCT Garite et al showed that the largest effect on composite morbidity (including RDS) occurred in infants who delivered 2-7 days following treatment with rescue AS[25].

The approximately 7 day duration of this effect is also similar to that seen in previous studies of Crs following the initial course of AS[10]. Our data also demonstrate a similar effect for infants delivered up to 14 days after rescue AS. However, as Figure 2 illustrates, this effect appears to be largely driven by infants born ≤ 7 days. Taken together with prior

studies[3,4,9,10,15,25,26], these data support a model that neonatal respiratory compliance can be reversibly increased in a time-limited manner for 7-14 days following both the initial and rescue AS courses before ultimately increasing naturally due to increasing gestational age near term (Figure 4). We speculate that this reversible increase in compliance is secondary to glucocorticoid-regulated upregulation of surfactant proteins, a mechanism that been shown in fetal lambs and in human fetal explants[8,27].

In light of evidence showing both benefits on lung function and neonatal outcomes and harm to growth[11,13,16,26], the use of repeat doses of AS in pregnancies with ongoing risk of preterm delivery – especially beyond a single rescue course – remains controversial[12,28]. In this context, the data presented in this study make two important contributions to the existing literature on repeat doses of antenatal steroids. First, they support the mounting evidence that rescue doses of AS confer tangible, objective benefits to preterm infants, particularly in the lung function among infants delivered within 7 days of treatment.

Second, although preterm delivery is very difficult to predict, these data can help inform the obstetrician when deciding on the timing of a rescue course of AS. Further, these results emphasize the fact that important clinical information regarding anticipated neonatal lung compliance can be learned by noting the latency period between administration of rescue AS and delivery in premature infants. This understanding can help neonatologists anticipate the clinical trajectories of their patients and may help inform clinical decisions regarding the need for surfactant administration in infants with RDS.

Strengths and Weaknesses

This study's strengths include the fact that the data were collected in a randomized, placebo-controlled, blinded trial. Similarly, appropriate confounders were measured to account for potential unmeasured bias. Measurements of Crs were subject to strict international testing standards to ensure the data were accurate and reproducible. And finally, the findings are consistent with the duration of effect seen in prior studies of compliance after treatment with a primary course of AS[10] and with our *a priori* hypothesis. However, this study has some limitations. Though the data come from a RCT, the infants were not randomized to the two groups analyzed in this study. There might be confounding differences in indication for delivery that could then lead to different outcomes with respect to the respiratory compliance. However, we measured potential confounders including pre-eclampsia, maternal diabetes, chorioamnionitis, maternal smoking, rupture of membranes, duration of rupture of membranes, preterm labor, and mode of delivery and found no differences between the two groups.

Conclusions

This study demonstrates that among infants of mothers treated with both an initial and a rescue course of AS, those who delivered within the ideal window (≤ 7 days) after maternal treatment with rescue AS have an increased compliance compared to infants delivered more remotely (> 7 days). This early post-natal measurement of compliance (measured within 72 hours of birth) was significantly increased in the ideally-treated group even though the infants in the remotely-treated group were almost 4 weeks older and ~900g heavier at birth

on average. These data mirror the time-limited increase in respiratory compliance observed in premature infants delivered within 7 days of an initial course of AS[10]. These data also support the conclusion that respiratory compliance is increased in a time-limited manner following rescue AS, lasting 7-14 days, and waning thereafter.

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Abbreviations

AS	Antenatal steroids
Crs	passive respiratory compliance
RDS	respiratory distress syndrome
RCT	randomized controlled trial
PFTs	pulmonary function tests

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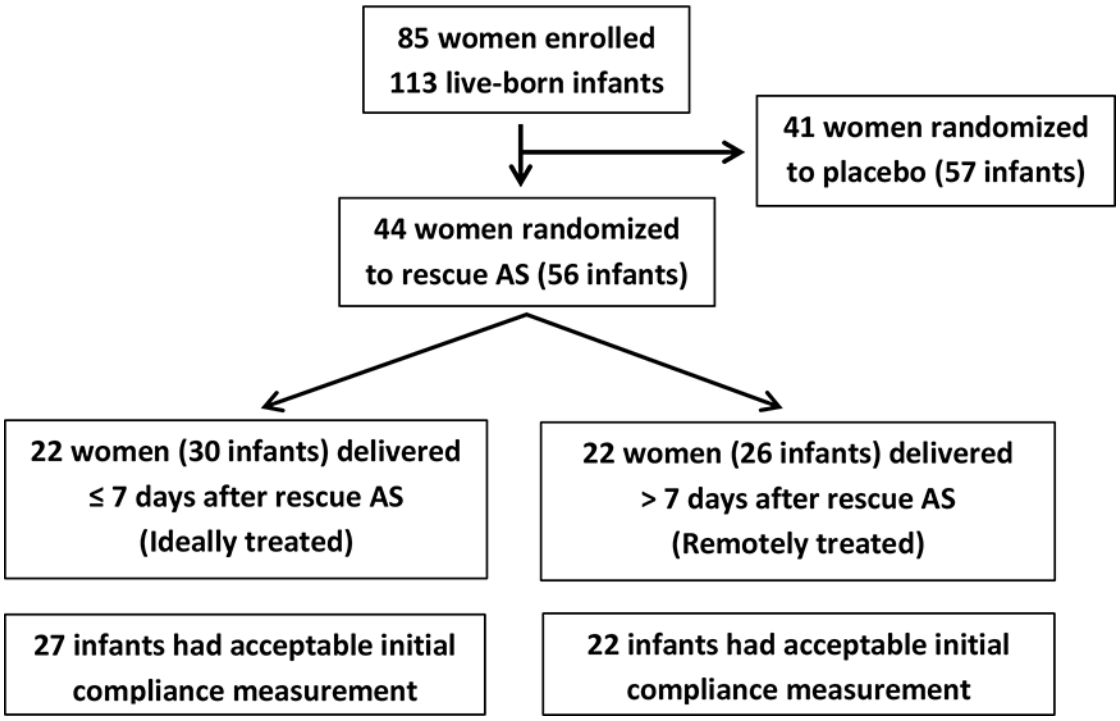

Fig. 1.
Flow diagram of study participants.

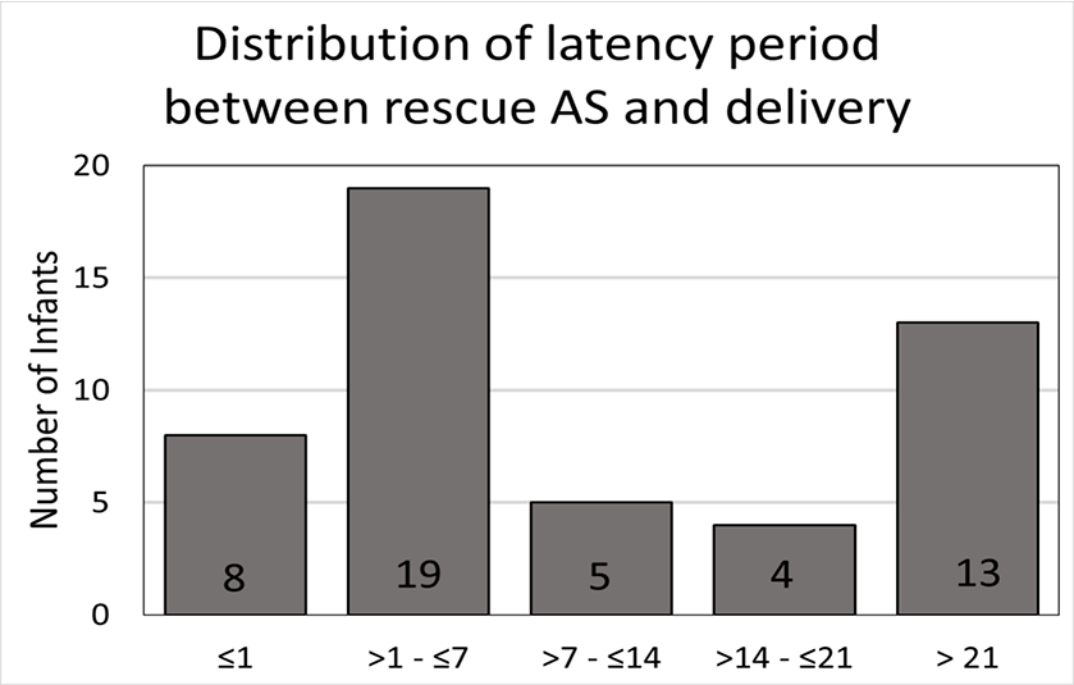

Fig. 2.

Distribution of latency period in days between receipt of rescue antenatal steroids and delivery for the 49 infants with evaluable measurements of Crs.

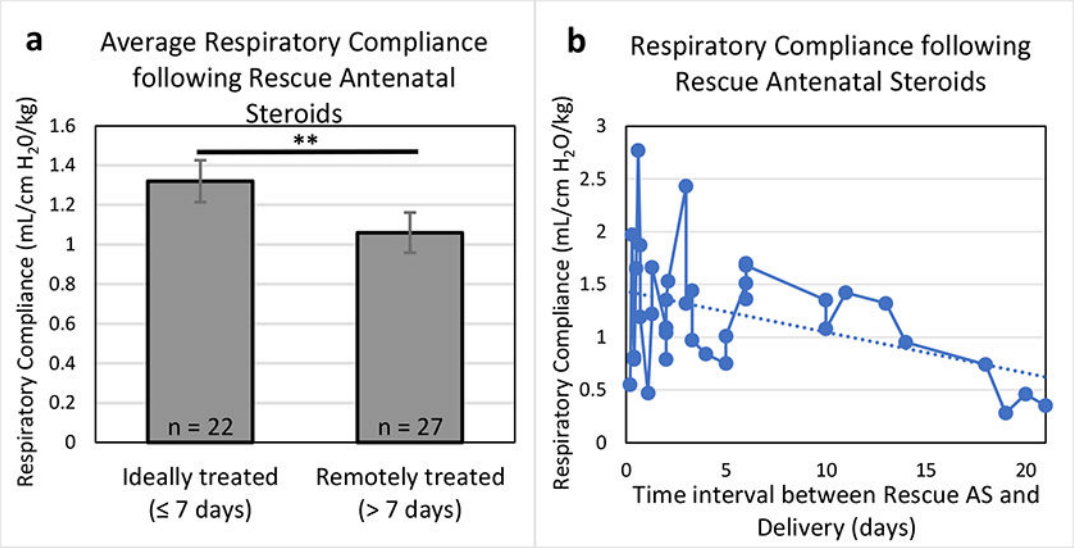

Fig. 3.

a. Mean ± SEM of respiratory compliance in 27 infants who delivered ideally after a rescue course of antenatal steroids and 22 infants who delivered remotely after a rescue course of antenatal steroids; ** $p<0.05$ comparing ideally versus remotely treated. P value is adjusted for gestational age, rupture of membranes, maternal smoking, maternal diabetes, and multiple gestation using a linear mixed model developed on a prior analysis of this dataset[15]

b. Graph of individual respiratory compliance data following maternal administration of rescue AS. Data from 0 – 21 days following rescue AS is shown. Dashed line represents the trendline.

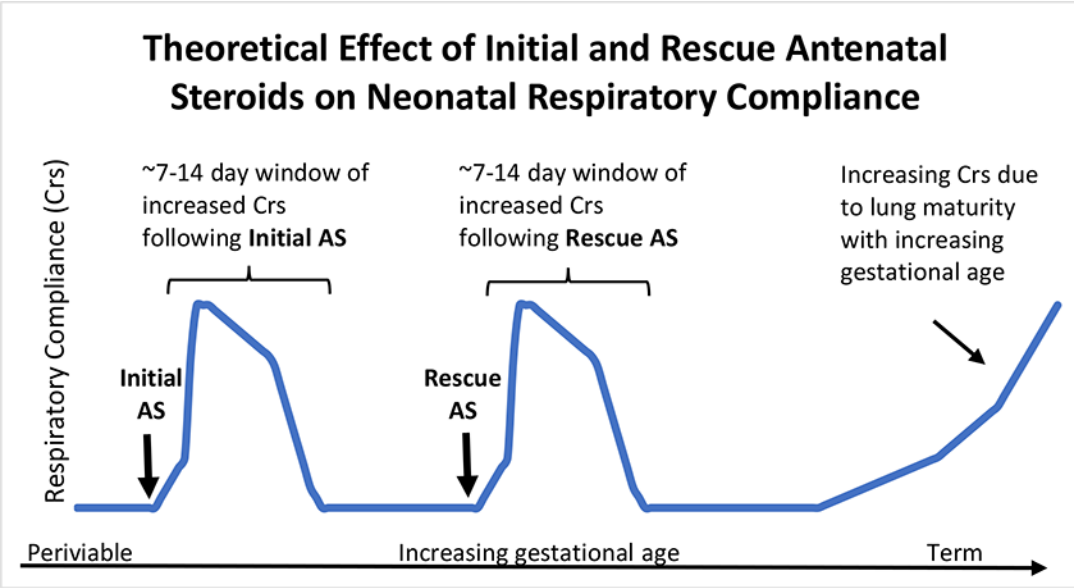

Fig. 4.

Theoretical model of the effect of the initial course and rescue course of antenatal steroids (AS) on neonatal respiratory compliance. This model demonstrates the anticipated improvement in lung compliance for infants delivered within the 7 to 14-day windows following maternal administration of the initial course and rescue course of AS, as well as the time-limited nature of these increases.

Table

Baseline demographic data characteristics of study participants. Values given are mean ± standard deviation unless otherwise indicated. Non-significant p values are denoted NS.

Maternal characteristics	**Ideal (n =22)**	**Remote (n = 22)**	**p value**
Maternal Age, yrs ± sd	27.6 ± 8.9	26.2 ± 6.0	NS
Gestational Age at initial AS, wks ± sd	26.5 ± 1.9	26.7 ± 2.0	NS
Gestational Age at rescue AS, wks ± sd	30.0 ± 2.0	30.0 ± 1.9	NS
Twin gestation, n (%)	8/22 (36.4)	4/22 (18.2)	NS
Smoker by history, n (%)	4/22 (18.2)	7/22 (31.8)	NS
Pre-eclampsia, n (%)	2/22 (9)	1/22 (4.5)	NS
Antepartum hemorrhage, n (%)	6/22 (27.3)	1/22 (4.5)	NS
Preterm labor, n (%)	19/22 (86.4)	16/22 (72.7)	NS
Gestational diabetes, n (%)	1/22 (4.5)	1/22 (4.5)	NS
C section delivery, n (%)	13/22 (59.1)	11/22 (50.0)	NS
Rupture of membranes > 24 hrs, n (%)	4/22 (18.2)	5/21 (23.8)	NS
Rupture of membranes, hrs ± sd	115.2 ± 293.0	313.2 ± 606.4	NS
Chorioamnionitis, n (%)	0/22 (0)	0/22 (0)	NS
Infant characteristics	**Ideal (n = 27)**	**Remote (n = 22)**	**p value**
Gestational age at birth, wks ± sd	30.1 ± 2.2	33.8 ± 2.8	<0.001
Birthweight, g ± sd	1361 ± 383	2248 ± 736	<0.001
Small for gestational age, n (%)	5/27 (18.5)	1/22 (4.5)	NS
Surfactant use, n (%)	10/27 (37.0)	4/22 (18.2)	NS