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Randomized Clinical Trial of a Combination of an Inhaled Corticosteroid and Beta Agonist in Patients at Risk of Developing the Acute Respiratory Distress Syndrome

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Abstract

Objective—Effective pharmacologic treatments directly targeting lung injury in patients with the acute respiratory distress syndrome (ARDS) are lacking. Early treatment with inhaled corticosteroids and beta agonists may reduce progression to ARDS by reducing lung inflammation and enhancing alveolar fluid clearance.

Design—Double-blind, randomized clinical trial (ClinicalTrials.gov: NCT01783821). The primary outcome was longitudinal change in oxygen saturation divided by the fraction of inspired oxygen (S/F) through day 5. We also analyzed categorical change in S/F by > 20%. Other outcomes included need for mechanical ventilation and development of ARDS.

Setting—Five academic centers in the United States.

Patients—Adult patients admitted through the emergency department at risk for ARDS.

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Disclosures

None of the author has competing interests, MAM reports DSMB service for RocheGenentec and GlaxoSmithKline, Amgen grant to study lung injury in mice, GlaxoSmithKline grant to study biomarkers of sepsis, and consulting fees for Cerus Therapeutics, Biogen, and Quark Pharmaceuticals.

Interventions—Aerosolized budesonide/formoterol vs. placebo twice daily for up to 5 days.

Measurements and Main Results—Sixty-one patients were enrolled from September 3, 2013 to June 9, 2015. Median time from presentation to first study drug was < 9 hours. More patients in the control group had shock at enrollment (14 vs 3 patients). The longitudinal increase in S/F was greater in the treatment group (p=0.02) and independent of shock (p=0.04). Categorical change in S/F improved (p=0.01) but not after adjustment for shock (p=0.15). More patients in the placebo group developed ARDS (7 versus 0) and required mechanical ventilation (53% versus 21%).

Conclusions—Early treatment with inhaled budesonide/formoterol in patients at-risk for ARDS is feasible and improved oxygenation as assessed by S/F. These results support further study to test the efficacy of inhaled corticosteroids and beta agonists for prevention of ARDS.

Keywords

Prevention; oxygenation; ARDS; acute lung injury; budesonide; formoterol

Introduction

Despite being a focus of intense investigation for nearly 50 years (1), the acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality (2). Recent clinical trials have established the benefit of lung protective ventilation and other supportive measures (3–5), but pharmacologic treatments targeting the underlying lung injury have not improved survival (6–8). This has led to a paradigm shift toward the prevention and early treatment of ARDS (9). Recently, the Lung Injury Prediction Study (LIPS) established the LIPS score to identify patients at high–risk for developing ARDS at time of admission to the emergency department (ED) (10). A LIPS ≥ 4 had the best discriminatory value with a positive predictive value of 18%. In a secondary analysis of the LIPS cohort, the degree of impaired oxygenation measured by the oxygen saturation divided by the fraction of inspired oxygen (S/F) was the single best predictor of developing ARDS (11). Combined, these risk factors define an enriched population to target for early intervention to prevent the development of ARDS.

Dysregulated inflammation and increased pulmonary vascular permeability are important mediators of the ARDS pathogenesis (12,13). Studies of systemic corticosteroids in established ARDS have found mixed results (6,12–14), and, while, a phase II trial in patients with established ARDS found that intravenous salbutamol reduced extravascular lung water, two subsequent phase III trials were stopped early for futility (7,15). However, corticosteroids and beta agonists may be more effective as preventative therapies. A trial of inhaled beta agonists in patients undergoing esophagectomy did not reduce ARDS, but did show a reduction in post–operative complications, primarily pneumonia (16). Inhaled budesonide administered prior to single lung ventilation improved lung compliance and cytokine profiles post-lobectomy (17). Inhaled delivery directly to the lung may maximize therapeutic benefits with fewer systemic side effects. Moreover, early treatment prior to the onset of ARDS may enhance drug delivery and provide more clinically relevant benefit by preventing progression to respiratory failure. Preclinical (18–22) and observational (23,24) studies have also suggest possible preventative and ameliorating effects of inhaled

corticosteroids and beta agonists when delivered prior to hospitalization or in experimentally induced acute lung injury.

Therefore, we performed a phase IIa multicenter randomized clinical trial testing the feasibility and efficacy of inhaled budesonide and formoterol for improving S/F as a surrogate marker of oxygenation in patients admitted through the ED at high risk for ARDS (LIPS score ≥ 4 and acute hypoxemia).

Materials and Methods

Study design

This was a double–blind, multicenter randomized clinical trial registered in clinicaltrials.gov (NCT01783821) and approved by site–specific Institutional Review Boards.

Patients

We enrolled patients at 5 academic centers from different regions of the United States. Inclusion criteria were adults (18 years or older) admitted through the ED with at least one known risk factor for ARDS, a LIPS ≥ 4, and acute hypoxemia (defined as at least 2 liters per minute of supplemental oxygen requirement to maintain an oxygen saturation between 92% and 98%). Major exclusion criteria were indications or contraindications for either inhaled corticosteroids or beta agonists (history of asthma or chronic obstructive lung disease; new cardiac arrhythmia including atrial fibrillation; uncontrolled atrial fibrillation or sinus tachycardia despite initial resuscitation); receipt of inhaled beta agonists or corticosteroids in prior seven days; receipt of systemic steroids; or onset of ARDS (by Berlin criteria including noninvasive ventilation) (25) prior to enrollment. Complete inclusion and exclusion criteria are listed in the supplementary material.

Randomization and masking

Patients were randomized within 12 hours of presentation to ED using Balance by RAVE, a cloud-based data analytics platform (Medidata Solutions, New York, NY) in one–to–one ratio stratified by center and baseline S/F (< or ≥ 300), to either placebo (4 ml normal saline) or combined standard aerosolized doses of budesonide (0.5 mg/2 ml) and formoterol (20 mcg/2 ml) twice daily for up to ten doses. Local pharmacies prepared identical appearing solutions and drug was delivered by blinded respiratory therapists within 4 hours post-randomization.

Procedures

Baseline S/F was measured immediately after obtaining consent and daily for up to 5 days. All S/F measurements were performed by respiratory therapist immediately prior to each morning dose of study drug per protocol using an air entrapment (“Venturi”) mask titrated to an oxygen saturation of 94 ± 2% unless the patient met this goal on room air or clinical status dictated invasive or noninvasive ventilation (supplementary material). Study drug was delivered using standard jet nebulizers that produce aerosol particle size within the respirable range (<5.5 microns). The first dose was administered within four hours after randomization (up to maximum 16 hours from ED presentation). The study data were

collected in the password protected Research Electronic Data Capture (REDCap) file, hosted at Mayo Clinic by study staff blinded to randomization. Clinical management other than study drug was not protocolized but adherence to standard care was recommended using the "Checklist for Lung Injury Prevention" (supplementary material).

Outcomes

The primary outcome was longitudinal change in the S/F for up to five days. Change in S/F was also assessed as a trichotomous categorical variable (> 20% decrease, no change, or > 20% increase). Because positive pressure ventilation may lead to improvement in the S/F, we performed a sensitivity analysis categorizing any step up or down in oxygen delivery mode (standard oxygen therapy to noninvasive or invasive ventilation, or vice versa) as a change in S/F. Other secondary outcomes were progression to ARDS, ICU and hospital length of stay, and need for non–invasive and invasive mechanical ventilation. The site–investigator provided a first adjudication of chest radiographs with a second adjudication performed by an alternate principal investigator (EF or JEL). Discrepancies were resolved by consensus between EF and JEL, who were blinded to subject identification and clinical data. Final diagnosis of ARDS was determined centrally after chest radiograph adjudication was considered together with other relevant data. Given our prior observational experience (23,24) suggesting more pronounced benefits of inhaled corticosteroids and inhaled beta agonists in patients with direct lung injury, we performed a preplanned subgroup analysis of patients with pneumonia as their primary risk factor for ARDS.

Statistical analysis

Per the LIPS cohort data (10), the sample size was based on an expected mean S/F of 250 in the placebo group and an absolute delta of 50 units (20%), proposed as the minimum clinically relevant difference. At an alpha=0.05, 25 participants per group (50 total) would allow 82% power to detect a 50 unit difference between groups. Target enrollment was increased to 60 patients to account for early death and discharge. Actual power was expected to be higher given the preplanned primary efficacy analysis of the longitudinal change in S/F as a continuous variable in a mixed effects model. Due to our small sample size, preplanned adjusted p–values were reported for significant imbalances in baseline characteristics using logistic regression for categorical outcomes and mixed effects models for S/F as a continuous variable. Shock, LIPS, age, and their respective interactions with treatment and S/F were included in separate models (due to overfitting of a comprehensive model). Hospital length of stay was assessed using Cox proportional hazard models using the Fine and Gray adjustment for death as a competing risk (26). In a *post hoc* analysis, the longitudinal change in S/F ratio was also modeled using the last value carried forward to day five to account for bias of earlier discharge of patients with higher S/F ratios in the treatment group (supplementary material). All analyses including adjustments for imbalances in baseline characteristics were formulated *a priori* and performed using SAS version 9.4 with a p–value < 0.05 considered significant.

Results

We enrolled 61 patients between September 3, 2013 and June 9, 2015 but 59 patients were included in the analysis of the primary endpoint, as detailed in the CONSORT diagram (Figure 1). Although we used the intention to treat principle, one patient in the treatment group (ARDS on noninvasive ventilation prior to enrollment and transitioned to comfort care after first dose of study drug prior to obtaining a second S/F) and one patient in the placebo group (ventricular fibrillation prior to receiving study drug) were excluded due to unrecognized exclusion criteria and lack of primary endpoint, leaving 59 patients for the primary analysis. However, all 60 patients receiving at least one dose of study drug were included in mortality and length of stay analysis. The median time from ED presentation to study drug delivery was < 9 hours (8.8, IQR 6.9–12.8). Baseline characteristics are shown in Table 1. Patients in the treatment group were older (71 versus 57 years, $p = 0.002$), were less likely to have shock at enrollment (13% versus 47%, $p = 0.002$), and had lower LIPS scores (6.5 versus 7.5, $p = 0.04$).

Complete safety data is presented in the supplementary material (Tables S1 and S2). No new arrhythmias or hypokalemia occurred in the treatment group. No study drug-related adverse events were observed during treatment. The heart rates between the groups did not differ at baseline or at any treatment day. Therapy was permanently held in three patients in each group (Figure 1).

For the primary outcome, the increase in the S/F was greater in the treatment group ($p = 0.02$) with significant separation occurring at day two (Figure 2). There were no significant interactions between treatment effect and shock, age, or LIPS. The longitudinal change in S/F was independent of baseline differences in shock ($p = 0.04$), LIPS ($p = 0.01$), or age ($p = 0.01$) when adjusted individually (Figure 3). The secondary outcome of > 20% change in S/F as a categorical variable favored significantly the treatment compared to the placebo group ($p=0.01$, Table 2). No patient in the treatment group had a decrease in S/F compared to 8 (27%) patients in the placebo group. Sensitivity analysis considering a step up or down in oxygen delivery mode as a change in S/F yielded similar results (Table S3, supplementary material). Differences in categorical change in S/F were not significant after individual adjustments for shock or LIPS. However, change in S/F was significantly better with treatment among patients without shock, and the distribution of change in S/F was nearly identical among control patients with and without shock ($p = 0.96$) while all 3 treated patients with shock had improvement in S/F (Table 2). In the preplanned subgroup analysis of the 37 patients with pneumonia, those in the treatment group had significantly greater improvements in the S/F (Table 2); however, differences were not statistically significant after adjustment for shock.

Although the study was not powered for conclusive assessment of more established clinical endpoints, we explored these in order to assist with planning of future phase IIb trial. Seven patients in the placebo group (23%) and no patients in the treatment group developed ARDS. Patients in the placebo group were more likely to need invasive mechanical ventilation and to stay longer in the ICU during their hospitalization (Table 2). However, these differences were not statistically significant after adjustment for baseline shock.

Hospital length of stay was also shorter in the treatment group (3.5 days, IQR 2–7 vs. 6.5, IQR 3–14). Accounting for the competing risk of death (4 deaths in the treatment and 5 in the placebo group), time to discharge was shorter for treated patients (HR 1.8, 95% CI 1.03–2.97, p=0.04) but differences were not significant after adjustment for baseline shock (HR 1.4, CI 0.82–2.49, p=0.21).

Discussion

In this phase IIa multicenter randomized clinical trial, we demonstrated safety and feasibility of early administration of inhaled budesonide and formoterol in patients at high–risk for ARDS admitted through the ED. There was significantly greater longitudinal improvement in S/F among treated patients, starting at day 2. While it has not been previously validated as an outcome in clinical trials, the S/F has been shown to correlate well with PaO_2/FiO_2 ratio and to predict mortality in patients with ARDS (25, 27). In a secondary analysis of the LIPS derivation cohort, S/F was the single best predictor of progression to ARDS and mortality, suggesting that S/F may be a reliable surrogate outcome for patients at risk of ARDS (11). To improve precision of the S/F, we standardized measurements using a Venturi mask titrated to achieve an oxygen saturation of 94 ± 2%, unless otherwise required by clinical status. The accuracy of FiO2 delivered by a Venturi mask is ± 1.9% at FiO2 ≤ 40% (93% of our S/F measurements) (28). The chosen target saturation is the most accurate range for pulse oximeters and is in the valid range of the oxygen-hemoglobin dissociation curve (27). While beta agonists could improve oxygenation through bronchodilation without impacting lung injury, we excluded all patients with known obstructive lung disease or patients whose treating physicians prescribed beta agonists prior to enrollment, so the results cannot be generalized to these patients. We did not prospectively obtain detailed smoking history and cannot comment on the potential impact of clinically unapparent airway responsiveness on our results. Treated patients also had lower rates of ARDS and need for mechanical ventilation, and earlier hospital discharge. However, the study was not powered to assess differences in these more established outcomes and we suspect the large observed differences in secondary outcomes are at least partially confounded by baseline imbalances in covariates, particularly shock.

Animal models of lung injury have consistently showed amelioration of histologic injury, and improvement in oxygenation and respiratory mechanics in animals treated with inhaled corticosteroids despite heterogeneity in timing of treatment and mechanism of inciting injury (18–22), while systemic steroids reduced treatment failure, including ARDS, in patients hospitalized with pneumonia (29,31,32). In both human and animal studies, inhaled beta agonists have demonstrated ability to preserve pulmonary vascular stability and upregulate alveolar fluid clearance (22, 30) and the combination of inhaled corticosteroids and beta agonists has established synergy in obstructive lung disease. Two observational studies showed patients using inhaled corticosteroids (23) and beta agonists (24) prior to hospitalization had decreased rates of progression to ARDS, especially in patients presenting with pneumonia. While beta agonists, failed to improve outcomes in patients with established ARDS (7,16), we hypothesize that both the combination of inhaled beta agonists and corticosteroids, and early delivery prior to onset of ARDS are necessary for the potential efficacy of these treatments.

Inhaled corticosteroids and beta agonists are safe, inexpensive, and widely available therapies making them ideal potential treatments for prevention of ARDS. The enriched signal in the subgroup of patients with pneumonia, in whom the potential confounding by shock was attenuated, is consistent with preliminary observational data (23,24). Patients with pneumonia and acute hypoxemia may represent a higher–yield population enriched for both disease-related outcomes and likelihood of response to therapy as recently recommended for future clinical trials in ARDS (33).

This study was designed as a phase IIa trial to demonstrate the safety, feasibility, and potential for efficacy of early treatment with inhaled corticosteroids and beta agonist in patients at high-risk for progressing to ARDS. Although we achieved timely enrollment from 5 EDs, less than 4% of screened patients were actually enrolled. This is similar to the 5% enrollment rate in the recently published Lung Injury Prevention Study with Aspirin (34) and only 22% of patients were excluded as they could not be enrolled within 12 hours, while another 62% were excluded due to prior use of steroids or beta agonists (including a dose of off-label albuterol in the ED). The main limitation of the study is the small sample size, which predisposed to the baseline imbalances in risk factors for ARDS and restricted power to assess impact on better-established outcomes such as ARDS or acute respiratory failure. The imbalance in shock at baseline is a main confounder and limits definitive interpretation of our results. We did not stratify randomization by shock, nor did we systematically record fluid balance, which should be performed in future trials of this therapeutic strategy. We believe our trial design will be of interest to ARDS investigators and may help inform future trial design in the nascent domain of ARDS prevention.

Conclusions

This phase IIa trial demonstrated the safety and feasibility of early treatment with inhaled budesonide and formoterol in patients at high–risk for developing ARDS. Although there were imbalances between groups, treated patients had improvement in the S/F as a surrogate marker for oxygenation. The results in this pilot trial warrant validation in a larger clinical trial targeting improvement in more patient-centered outcomes such as preventing ARDS and need for mechanical ventilation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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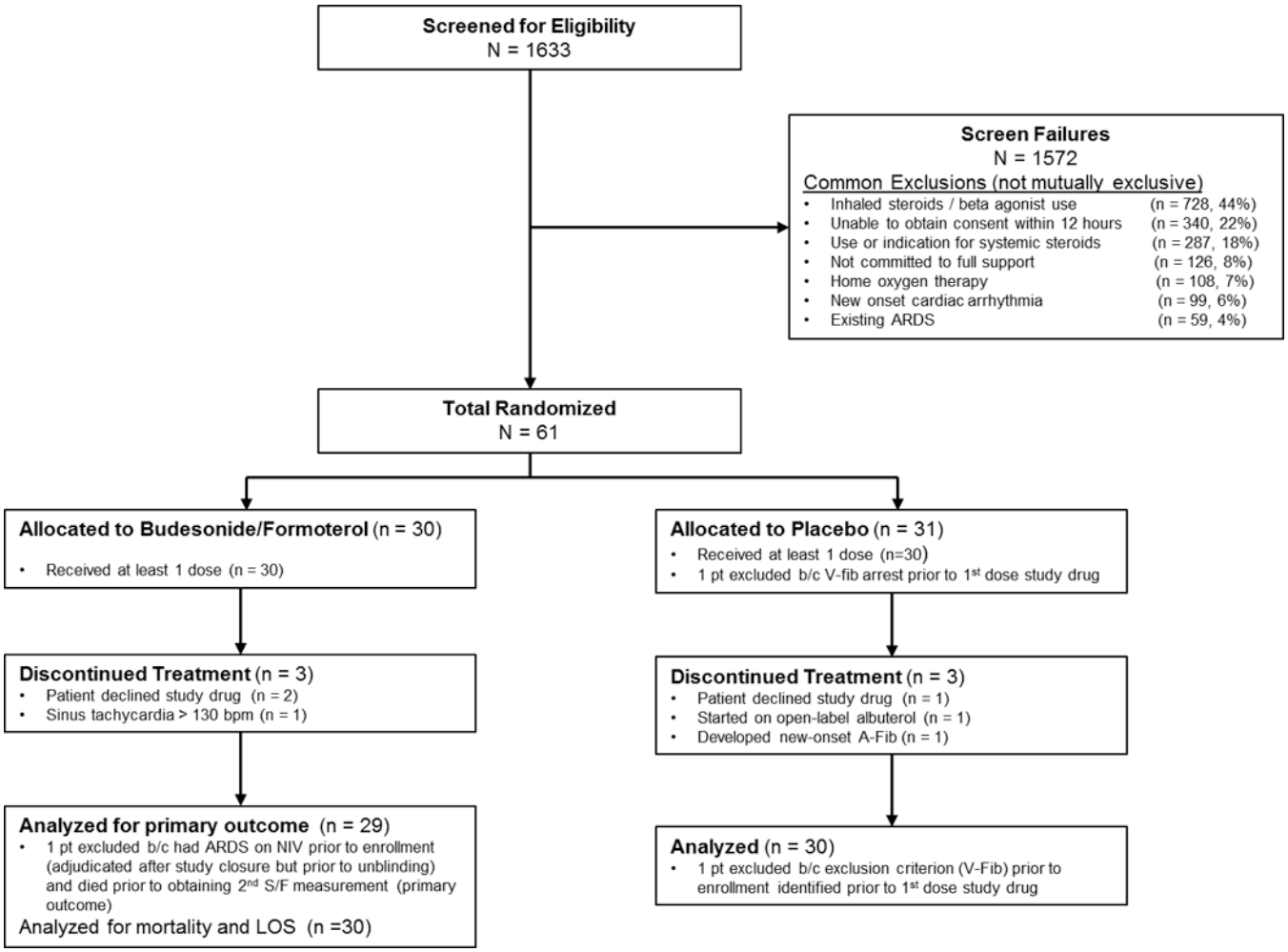

Figure 1. CONSORT diagram of enrollment

One patient in treatment arm was excluded for having ARDS on noninvasive ventilation prior to enrollment. This patient received a single dose of study drug but shortly afterwards was changed to comfort care and died without being intubated or having a post-treatment S/F measured to allow assessment of primary outcome. One patient randomized to placebo arm had ventricular fibrillation prior to enrollment and was excluded prior to receiving study drug.

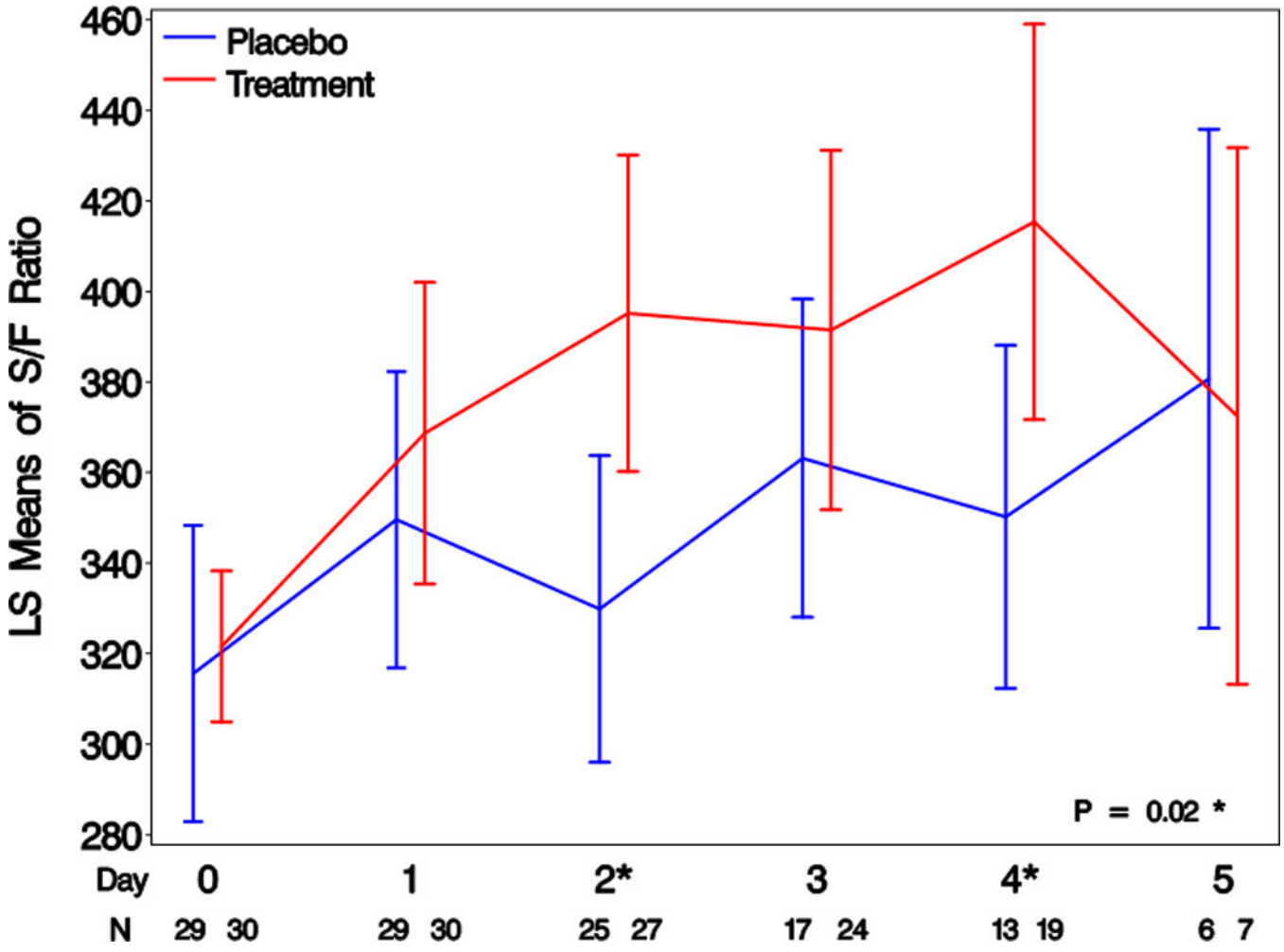

Figure 2. S/F ratio by treatment day

Plot of least square (LS) means of saturation divided by FiO2 (S/F) ratio to day 5 from mixed effects modeling of S/F by study day, treatment, and interaction between treatment and study day. *Denotes individual days as well as entire model with significant (< 0.05) unadjusted P values for day*treatment interaction. N=number of hospitalized patients remaining in the study without adjustment for last S/F for early discharges.

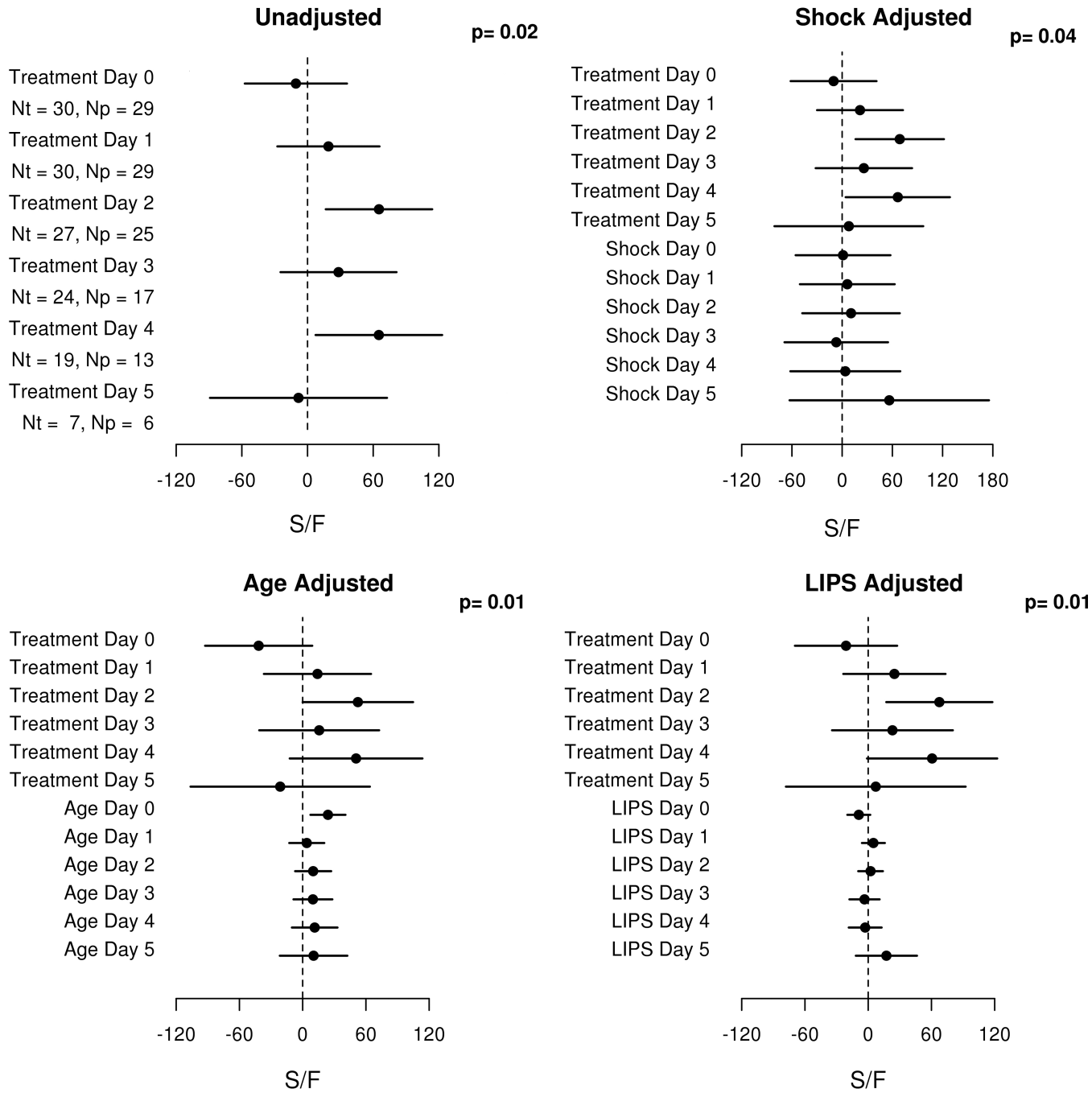

Figure 3. Unadjusted and adjusted treatment by study day effects on S/F (interactions) with the 95% CI of LS means

Forest plots of confidence intervals of treatment effect in unadjusted and adjusted models by treatment interactions with shock, age and LIPS (Lung Injury Prediction Score). Full model with simultaneous adjustment for all covariates appeared over-fitted and not presented.

Table 1

Baseline characteristics

Characteristic	Placebo N=30	Treatment N=30
Sex		
Male (%)	20 (67)	19 (63)
Race		
White (%)	23 (77)	24 (80)
Risk factor for ARDS *		
Shock#	14 (47)	4 (13)
Sepsis	23 (77)	23 (77)
Pneumonia	16 (53)	21 (70)
Aspiration	5 (17)	5 (17)
Acute abdomen	1 (3)	2 (7)
Trauma		
Multiple long bone fractures	2 (7)	1 (3)
Lung contusion	2 (7)	0
Near drowning	0	1 (3)
Age (years)#		
Median (IQR)	57 (49–67)	71 (59–80)
LIPS#		
Median (IQR)	7.5 (5.5–8.5)	6.5 (5.5–7.0)
APACHE II		
Median (IQR)	15.5 (11–22)	14 (11–19)
S/F		
Median (IQR)	334 (269–380)	316.5 (256–343)
Acute renal failure		
Yes (%)	10 (33)	5 (17)

*Not mutually exclusive;

#Significant at $p < 0.05$

Table 2

Secondary Outcomes

Outcome	Placebo N=30	Treatment N=29	P-value
Categorical Change in S/F ratio			0.01[1]
>20% Decrease	8 (27%)	0	
No Change (within 20%)	9 (30%)	11 (38%)	
>20% Increase	13 (43%)	18 (62%)	
Baseline Pneumonia[*]	N=16	N=21	0.03
>20% Decrease	5 (31%)	0	
No Change	4 (25%)	7 (33%)	
>20% Increase	7 (44%)	14 (67%)	
No Pneumonia	N=14	N=8	0.51
>20% Decrease	3 (21%)	0	
No Change	5 (35%)	4 (50%)	
>20% Increase	6 (43 %)	4 (50%)	
Baseline Shock[†]	N=14	N=3	0.37
>20% Decrease	4 (29%)	0	
No Change	4 (29%)	0	
>20% Increase	7 (44%)	3 (100%)	
No Shock	N=16	N=26	0.04
>20% Decrease	4 (25%)	0	
No Change	5 (31%)	11 (42%)	
>20% Increase	7 (44%)	15 (57%)	
ARDS	7 (23%)	0	0.01[2]
Mechanical ventilation	16 (53%)	6 (20%)	0.01[1]
Hospital days through day 28	N=30	N=30	0.02[3]
Median (IQR)	6.5 (3–14)	3.5 (2–7)	
ICU days through day 28	N=21	N=13	0.01[4]
Median (IQR)	6 (4–14)	3 (2–4)	

[1] Chi-square;

[2] Fisher exact;

[3] Cox Proportional Hazard with Fine/Gray adjustment;

[4] Kruskal-Wallis;

[*] Preplanned subgroup analysis by pneumonia;

[†] Post-hoc subgroup analysis by shock to address major imbalance in baseline shock with randomization.