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Reasons for Nonenrollment in a Clinical Trial of Acute Lung Injury*

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Abstract

Background—Enrolling critically ill patients in clinical trials is challenging. We observed that eligible patients at San Francisco General Hospital (SFGH), a public hospital that cares largely for indigent patients, were less likely to be enrolled in a clinical trial of acute lung injury (ALI) than eligible patients at the University of California, San Francisco (UCSF), a university referral center. We examined the reasons for nonenrollment and the impact of the availability of a surrogate decision maker on critical care clinical trials enrollment.

Methods—Data collected from the ARDS Network trial of lower vs traditional tidal volume ventilation for patients with ALI was analyzed. Patient demographics and reasons for nonenrollment were analyzed among 531 consecutively screened patients at the two hospitals: UCSF and SFGH.

Results—At UCSF, 1% of screened patients were not enrolled because they lacked surrogates, whereas 18% of screened patients were not enrolled at SFGH because they lacked surrogates. Lack of surrogate was the most common reason for nonenrollment among eligible patients at SFGH.

Conclusions—Critically ill patients with ALI at a public hospital were less likely to be enrolled in a clinical trial than patients at a university hospital primarily because they lacked surrogates. Lack of a surrogate also was a major factor in nonenrollment in other ARDS Network hospitals. In order to provide all affected patients an opportunity to participate in research, innovative strategies for increasing enrollment in critical care research without compromising protection from research risks are needed.

Keywords

acute lung injury; ARDS; clinical trials; critical care; informed consent; surrogate consent

Acute lung injury (ALI) affects approximately 200,000 persons per year in the United States and has a mortality rate approaching 40%.[1] Clinical trials are vital tools for enhancing knowledge about ALI and advancing the care of patients with this disorder. The largest clinical trial to demonstrate a positive effect on mortality from ALI was conducted by the National

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Heart, Lung, and Blood Institute ARDS Network between 1996 and 1999.[2] This trial reported that a lung protective ventilation strategy with a lower tidal volume and a reduced plateau airway pressure significantly reduced mortality in patients with ALI. The trial enrolled 902 patients from 24 hospitals in 10 cities. The trial was designed to include all categories of patients with ALI who did not have risk of excessive mortality from comorbid conditions.

In this study, we examined the reasons for nonenrollment in the above trial and tested the hypothesis that the lack of a surrogate decision maker to provide consent for study participation could substantially decrease enrollment at a public hospital compared to a university hospital. We analyzed the ARDS Network data from two hospitals in San Francisco: University of California, San Francisco (UCSF) Moffitt-Long University Hospital, an academic referral center, and San Francisco General Hospital (SFGH), the public hospital for the city of San Francisco serving a large proportion of indigent and uninsured patients. The screening practices at these two hospitals were similar.

MATERIALS AND METHODS

Study Subjects

This study was approved by the Natural History Committee of the ARDS Network and by the Institutional Review Board at UCSF. We focused on patients from the 1996 to 1999 ARDS Network trial that tested the effects of ventilations with different tidal volumes and airway pressures on outcomes from ALI. A total of 531 patients with ALI were screened for eligibility to enroll in the ARDS Network study: 172 at UCSF and 359 at SFGH.

Study Design

The design was a cohort study. For the 531 patients screened at UCSF and SFGH, the data included enrollment status, reason for nonenrollment, patient age, gender, ethnicity, study site, type of ICUs (*ie*, medical, surgical, cardiac, burn, trauma), and the underlying reason for ALI. Because of institutional review board restrictions and variations in screening practices, we were unable to obtain individual subject data for all ARDS Network hospitals. However, aggregate data on the reasons for nonenrollment among the entire ARDS Network cohort of 7,434 screened patients were available. We focused on UCSF and SFGH because the screening practices were similar, the entire screening data set was available, and the patient populations are not the same.

Patients in the ICUs at both hospitals were screened 7 days per week either by the primary study coordinator or the assistant study coordinator with help from the principal investigators and coprincipal investigators when they attended in the ICU. Screening occurred twice daily, and every patient receiving mechanical ventilation was screened for eligibility. Ventilator status was determined primarily by bed-to-bed screening in the morning and again in the mid-to-late afternoon to catch any new admissions.

We investigated the reasons for nonenrollment of patients in the entire ARDS Network cohort and at each of the two hospitals in San Francisco (UCSF and SFGH) that participated. In the cohort of 531 screened patients in San Francisco, we compared the characteristics of those patients who were enrolled to those who were not enrolled.

Statistical Analysis

The primary goal of this analysis was to examine the impact of lacking a surrogate on enrollment in an ARDS Network clinical trial at UCSF and SFGH. In this context, we described the reasons for nonenrollment and identified predictors of nonenrollment among the variables available. χ^2 tests and logistic regression were used to compare nominal data. Continuous

variables were compared using a Student two-sample *t* test. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Cohort Description

Inclusion criteria for the ARDS Network study of low tidal volume ventilation were based on the American-European Consensus conference.[3,4] Overall, 7,434 patients who met these criteria were screened, and 902 patients (12%) were enrolled. Table 1 describes the characteristics of the study population broken down by study site and participation status. At UCSF, 64 of 172 screened patients were enrolled. At SFGH, 47 of 359 screened patients were enrolled. Screened patients did not differ significantly from enrolled subjects by age, gender, or race/ethnicity at either hospital.

Subject Accrual and Reasons for Nonenrollment

Eligible patients were those with ALI who were screened and did not have medical reasons for exclusion. Of the 531 patients screened in San Francisco, 111 patients (21%) ultimately enrolled in the clinical trial. There was a significant difference between hospitals in the percentage of screened patients who were enrolled (13% at SFGH and 37% at UCSF, $p < 0.001$). The difference between hospitals in the percentage of eligible patients who were enrolled was also statistically significant (29% at SFGH and 89% at UCSF, $p < 0.001$).

Reasons for nonenrollment are detailed in Table 2. The most common nonmedical reason for nonenrollment at SFGH was lack of an available surrogate decision maker. Among screened patients, 18% at SFGH were not enrolled because they lacked a surrogate, whereas 1% at UCSF were not enrolled for the same reason ($p < 0.001$). Among the cohort of eligible patients, 40% at SFGH were not enrolled because they lacked a surrogate, whereas 3% at UCSF were not enrolled for the same reason ($p < 0.001$). Logistic regression was used to compare patients with surrogates to those lacking surrogates. Hospital was the only measured variable that predicted lack of surrogate. Patients lacking surrogates did not differ significantly from those with surrogates by age, race/ethnicity, or category of lung disease.

Other reasons for nonenrollment among eligible patients were physician refusal and patient or family refusal. There were statistically significant differences between UCSF and SFGH for the rates of both of these reasons. These differences were statistically significant when examining the entire screened cohort and among the smaller cohort of eligible patients. Physician refusal accounted for 8% of screened patients not being enrolled at SFGH, but only 2% at UCSF ($p < 0.02$). In the multivariate logistic regression analysis, trauma as a reason for lung injury was the only statistically significant predictor of physician refusal. Hospital, patient gender, and patient ethnicity did not predict physician refusal.

Patient or family refusal accounted for 6% of screened patients at SFGH but only 1% at UCSF ($p < 0.02$). These differences were also statistically significant among the smaller cohort of eligible patients. In the multivariate logistic regression analysis of eligible patients, both hospital and minority status were significant predictors of patient or family refusal.

DISCUSSION

We found that eligible critically ill patients with ALI at a public hospital were much less likely to be enrolled in a clinical trial than patients at a university hospital for three reasons: lack of a surrogate decision maker, physician refusal, and patient or family refusal. The primary reason for nonenrollment at the public hospital was lack of a surrogate decision maker authorized to provide consent. Surrogate decision makers are essential elements of recruitment in critical

care clinical trials.[5–8] Apart from exceptional emergency situations when there is no time to obtain consent,[9,10] informed consent is considered to be an inviolable requirement for ethically conducted research. In critical care research, this requirement is tested by the fact that most subjects are incapable of providing consent themselves because the severity of their illness renders them decisionally incapacitated. In this circumstance, the burden of consent falls on surrogate decision makers. The unavailability of a surrogate decision maker serves as a barrier to study enrollment.[11] It is important that strategies for overcoming such barriers are developed, especially if certain populations are disproportionately affected, which can then lead to nonrepresentative enrollment in clinical research trials.

At SFGH, more resources were expended in screening patients for the ARDS Network trial than at UCSF because the percentage of eligible patients who enrolled was low. For every patient enrolled at SFGH, 1.4 eligible patients were excluded because they lacked a surrogate to give consent. At UCSF, 0.03 patients were excluded for lacking a surrogate for every patient enrolled. This is of concern for several reasons. First, the high proportion of patients without surrogate decision makers increases the amount of resources needed to screen and enroll subjects. This takes away from the resources that can be devoted to conducting the trial itself and increases the time it takes to conduct the trial by increasing the time it takes to enroll an adequate sample. Second, lacking a surrogate raises concerns about generalizability and justice. Do those patients without surrogates differ from those with surrogates? The data collected in the ARDS network study is insufficient to address this question. We know that there are no statistically significant differences between those with and without surrogates in terms of race/ethnicity, age, and underlying category of lung injury. Are there other differences? Homeless and socioeconomically disadvantaged patients are more likely to be hospitalized at SFGH than at UCSF. Hospital admissions data from SFGH and UCSF indicate that during the 4 years that the ARDS Network trial operated, the percentage of homeless patients at SFGH was 18% compared to < 1% at UCSF. We hypothesize that homeless and socioeconomically disadvantaged patients are more likely to lack surrogate decision makers. Even if excluding disadvantaged patients from clinical trials of ALI does not affect the generalizability of the results, it does raise questions about fairness. Patients who are already disadvantaged may be further marginalized by excluding them from the potential benefits of participating in a trial.

Physician refusal was also an important reason for nonenrollment and accounted for 17% of eligible patients not being enrolled at SFGH, but only 6% at UCSF ($p < 0.02$). The only statistically significant predictor of physician refusal in the multivariate logistic regression analysis was trauma as a reason for lung injury. Because trauma may have different biological mechanisms that lead to ALI and differentiate it from other causes, it will be important to insure that trauma patients are adequately represented in ALI trials. Strategies to improve the acceptability of critical care research among trauma physicians are needed.

Patient or family refusal was the third reason for nonenrollment among eligible patients. Patients or their families were more likely to refuse if they were at a public hospital. Patients from an ethic minority at the public hospital were more likely to refuse than nonminority patients. These observations raise questions about trust in medical research among certain populations and highlight the importance of developing strategies to increase knowledge and awareness of research among these groups.

To our knowledge, reasons for nonenrollment have not been previously reported for studies of ALI. Our study adds to what is known about enrollment of critically ill patients in clinical trials by providing information about the reasons for nonenrollment and the factors that predict nonenrollment. It highlights the fact that the reasons for nonenrollment may differ significantly between study sites for the same trial even when screening practices are similar. In San Francisco, the study hospital had the greatest impact on whether or not a patient was enrolled

in the ARDS Network trial (odds ratio for enrollment, 17.8 for UCSF vs SFGH). This was primarily due to a higher percentage of patients at SFGH who lacked surrogates. In order to maximize efficiency of recruiting, it will be important to develop strategies that address barriers to enrollment such as lack of available surrogates, physician reluctance to enroll their patients, and patient/family unwillingness to participate.

Our study has some limitations. We included hospitals from only one city in the analysis because we were not sufficiently confident that the sites outside of our own institution utilized similar practices to screen potential subjects. We were unable to link data on homelessness and socioeconomic status to our data set; therefore, we were not able examine how these characteristics relate to having a surrogate decision maker. Finally, while we were able to identify reasons for nonenrollment and some of the characteristics that predicted those reasons, we did not have access to data on other factors that may affect enrollment, such as the relationship of the surrogate decision maker to the patient, the study coordinator who did the recruiting, and patient and family beliefs and attitudes about participation in research.

CONCLUSIONS

In conclusion, this study contributes to what is known about the reasons for nonenrollment in clinical trials of critically ill patients with a specific emphasis on how the lack of a surrogate decision maker markedly compromised enrollment in a clinical trial of ALI. Future investigations are needed to identify additional barriers to research participation and develop strategies for overcoming these barriers.

Abbreviations

ALI, acute lung injury; SFGH, San Francisco General Hospital; UCSF, University of California, San Francisco.

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APPENDIX

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Table 1

Baseline Characteristics, Enrolled vs Not Enrolled*

Characteristics	Entire Enrolled Cohort (n = 902)	UCSF (n = 172)		SFGH (n = 359)	
		Enrolled (n = 64)	Not Enrolled (n = 108)	Enrolled (n = 47)	Not Enrolled (n = 312)
Age, yr	52 ± 17	58 ± 19	53 ± 17	45 ± 13	49 ± 17
Female gender	41	41	47	28	24
Ethnicity					
White non-Hispanic	73	56	64	53	50
Black non-Hispanic	17	13	6	21	18
Other	10	33	29	26	32
Hispanic		8	14	19	17
Asian		23	15	4	14
Other		2	0	2	1
Lung injury					
Pneumonia	36	29	26	35	31
Sepsis	26	35	53	30	31
Aspiration	15	13	7	11	11
Trauma	11	0	0	4	18
Other	10	16	14	20	8
Multiple transfusion	3	8	0	0	1

* Data are presented as mean ± SD or %.

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Table 2

Enrollment Statistics

Variables	UCSF	SFGH	Entire Multicenter Cohort
Total screened, No.	172	359	7,434
Reason, No. (%)			
Medically ineligible	77 (45)	132 (37)	3,645 (49)
Patient < 18 yr old	0 (0)	3 (1)	114 (2)
Other trial 30 d	1 (1)	10 (3)	216 (3)
Inclusion criteria > 36 h	21 (12)	48 (13)	1272 (17)
Other	1 (1)	6 (2)	92 (1)
Doctor refused	4 (2)*	27 (8)*	492 (7)
Patient/family refused	2 (1)*	21 (6)*	312 (4)
No surrogate available	2 (1)†	65 (18)†	386 (5)
Enrolled	64 (37)†	47 (13)†	902 (12)

* $p < 0.02$ for the comparison between UCSF and SFGH.

† $p < 0.001$ for the comparison between UCSF and SFGH.