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LETTER TO THE EDITOR

Understanding how deferred consent affects patient characteristics and outcomes: an exploratory analysis of a clinical trial of prone positioning for COVID-19

1. Introduction

Deferred consent, the process of enrolling patients in a clinical trial before consent is obtained, is often employed in studies of minimal risk [1−4], or when patients are unable to consent at the time of study enrollment [5−8]. Deferred consent has several possible benefits including decreasing the time to study enrollment, allowing for enrollment when study personnel are unavailable [9,10], and allowing the inclusion of populations less represented in clinical trials [4,11,12]. Multiple studies have identified that deferred consent is considered an acceptable substitute for pre-enrollment consent by both participants and clinicians [13,14]. Our objective was to assess patient-level characteristics, adherence, and rate of withdrawal among participants enrolled with consent obtained before (nondeferred consent) vs. after (deferred consent) randomization in the COVID-PRONE randomized trial (NCT04383613).

2. Methods

We conducted a secondary analysis of the COVID-prone international, pragmatic randomized clinical trial, which assessed prone positioning in patients with COVID-19 [15].

Deferred consent was allowed as the benefit of prone positioning was thought to be greatest when immediately implemented, because patients may be in respiratory distress at the time of enrollment, and because we expected potential harms from prone positioning to be minimal. Deferred consent was allowed at all except two hospitals. The decision on timing of consent was made by the site lead at the time of recruitment.

The primary outcome of this analysis was the difference in patient characteristics, time spent prone, and rate of withdrawal among participants who were enrolled with consent obtained before vs. after randomization. We did not compare the primary outcome between the two groups because our study was stopped for futility and our primary outcome was similar between patients randomized to prone positioning compared to standard of care.

3. Results

Among 248 total patients, 125 (50.5%) were enrolled after consent, and 123 (49.5%) were enrolled with deferred consent. The median time between randomization and consent was 1 day (interquartile range [IQR] 0−2 days) in the deferred consent group. Patients in the deferred consent group were more likely to be enrolled on weekends (14.6% vs. 9.6%), male (67.5% vs. 60.8%), and older (median age 60 vs. 54 years) Table 1. The frequency of deferred consent varied significantly by hospital (median 41.5%; range: 0−100%). Patients in the deferred consent group were more likely to require oxygen via face mask (9.8% vs. 2.4%) and less likely to have received remdesivir (27.6% vs. 56%).

There was no difference in the rates of study withdrawal ([3%] in each group) or median number of hours spent in prone position within the group randomized to prone positioning (nondeferred = 7 [IQR 2.3−16.8], deferred = 4 [IQR 1.3−12.0]). The rate of serious adverse events was 4.9 % in the deferred consent group and 1.6 % in the nondeferred consent group Table 2.

4. Discussion

In this secondary analysis of an international randomized controlled trial of prone positioning for noncritically ill patients with COVID-19, patients who underwent deferred consent were more likely to be male, older, and be

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What is new?

Key findings

- Differences in characteristics were found between patients in the deferred consent and nondeferred consent groups.
- Primarily it was found that the patients in the deferred consent group were more likely to be enrolled on weekends and were more likely to be older.

What this adds to what was known

- This finding shows that deferred consent, the process of enrolling patients in clinical trials prior to obtaining consent, may allow for the enrollment of a greater number of individuals.

What is the implication and what should change now?

- These findings may have implications for obtaining consent when conducting clinical trials in the future.

enrolled on a weekend. We observed similar rates of both participant withdrawal and protocol adherence.

Our study has several limitations. First, data were unavailable for why deferred consent was chosen. Second, we did not ascertain patients' and providers' perspectives on deferred consent, though prior literature has shown that both groups find it to be an acceptable alternative [13,14]. Third, this was an exploratory and post-hoc analysis, and thus we did not test for statistical significance and our findings require replication.

Our results suggest that the use of deferred consent may allow for the inclusion of patients who would not otherwise have been enrolled (e.g., patients hospitalized on weekends), potentially improving the external generalizability of randomized trials.

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Table 1
Baseline characteristics

Characteristic	Deferred ($N = 123$)	Nondeferred ($N = 125$)
COVID status		
COVID-19 test result	120 (97.6%)	122 (97.6%)
Randomization timing		
Number of days between admission and randomization	1 [1, 1]	1 [1, 1]
Days between randomization and consent	1 [0, 2]	0 [0, 0]
Randomized on a saturday or sunday	18 (14.6%)	12 (9.6%)
Age		
Median [IQR]	60 [49.5, 68]	54 [39, 61]
<50	31 (25.2%)	50 (40%)
50–70	69 (56.1%)	64 (51.2%)
>70	23 (18.7%)	11 (8.8%)
Sex		
Female	40 (32.5%)	49 (39.2%)
Date of randomization		
Before Sept 1, 2020	6 (4.9%)	2 (1.6%)
Sept 1, 2020 to Feb 28, 2021	84 (68.3%)	60 (48%)
After Feb 28, 2021	33 (26.8%)	63 (50.4%)
Comorbid conditions		
Diabetes	35 (28.5%)	32 (25.6%)
Hypertension	47 (38.2%)	51 (40.8%)
Current smoker	4 (3.3%)	3 (2.4%)
COPD or asthma	8 (6.5%)	19 (15.2%)
Heart failure	3 (2.4%)	3 (2.4%)
Illness severity		
Lymphocyte count	0.82 [0.6, 1.1]	0.9 [0.68, 1.2]

(*Continued*)

Table 1. Continued

Characteristic	Deferred ($N = 123$)	Nondeferred ($N = 125$)
Creatinine	81 [66, 100]	76 [63, 93]
Systolic blood pressure	123 [114, 133]	122.5 [115, 130]
Oxygen saturation	94 [93, 96]	94 [93, 95]
FiO_2	32 [28, 36]	32 [28, 36]
S/F ratio	303 [261, 339]	305 [264, 337]
FiO_2 delivery method		
Nasal prong	109 (88.6%)	113 (90.4%)
High-flow nasal cannula	1 (0.8%)	6 (4.8%)
Face mask	12 (9.8%)	3 (2.4%)
Medication		
Dexamethasone	115 (93.5%)	121 (96.8%)
Remdesivir	34 (27.6%)	70 (56%)
Tocilizumab	0 (0%)	2 (1.6%)
Code status		
Full code	110 (89.4%)	119 (95.2%)
Do not resuscitate	5 (4.1%)	0 (0%)
Other	8 (6.5%)	5 (4%)

Abbreviations: COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; IQR, interquartile range; S/F ratio, ratio of saturation of oxygen to fraction of inspired oxygen.

Missingness for all variables was <2%.

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Table 2
Secondary outcomes and rate of adverse events among patients enrolled with deferred vs. nondeferred consent

Outcome	Deferred ($N = 123$)	Non-deferred ($N = 125$)
Secondary outcomes		
S/F ratio after 72 hours	332 [207, 423]	345 [260, 446]
Change in S/F ratio in first 72 hours (median [IQR])	7 [−58, 73]	60 [−20, 108]
Change in FiO2 (%) in first 72 hours (median [IQR])	0 [−7, 8]	−4 [−8, 4]
Days to discharge (median [IQR])	6 [4, 10]	4 [3, 6]
Discharged	114 (92.7%)	119 (95.2%)
Serious adverse events		
SAE composite	6 (4.9%)	2 (1.6%)

Abbreviations: IQR, interquartile range; SAE, severe adverse event; S/F ratio, ratio of saturation of oxygen to fraction of inspired oxygen.

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