The benefits and challenges of pre-consent in a multi-site, pediatric sickle cell intervention trial

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ED	Emergency Department
MAGiC	Magnesium in Crisis
LAR	Legally Authorized Representative
IRB	Institutional Review Board
SCD	Sickle cell disease

Abstract

Enrollment of patients in sickle cell intervention trials has been challenging due to difficulty obtaining consent from a legal guardian and lack of collaboration between emergency medicine and hematology. We utilized education and pre-consent in a pediatric multi-site sickle cell intervention trial to overcome these challenges. Overall, 48 patients were enrolled after being pre-consented. Variable Institutional Review Board policies related to pre-consent validity and its allowable duration decreased the advantages of pre-consent at some sites. The utility of pre-consent for future intervention trials largely depends on local IRB policies. Pre-education may also benefit the consent process, regardless of site differences.

Introduction

Intervention trials in children with sickle cell disease (SCD) hospitalized for acute pain are frequently hindered by several barriers to enrollment. These barriers have resulted in the early termination of studies due to poor enrollment, [1-3] potentially delaying advances in treatment. One barrier is the ability to obtain consent,

particularly at night and during weekends, due to limited research staff availability. [2,3] Additionally, waiting for legal authorized representatives (LARs) to be available on the inpatient floor instead of completing consent in the emergency department (ED) can delay or preclude consent. [4, 5] Another barrier is a lack of trust between families and providers [3, 6-8], which is accentuated by the lack of a relationship between emergency medicine physicians and families. Minority families in particular may have preexisting mistrust of research that can only be mitigated by a provider with whom the family shares a strong relationship. [9, 10] Stress associated with the ED environment can be tense and upsetting for families, [11] who may be unwilling or unable to focus on research studies. [12] Finally, obtaining assent in children with SCD after they received opioids may be problematic due to decreased levels of consciousness and attention. [13, 14]

Pre-consent—informed consent given in advance of an eligible ED visit—has been suggested as a way to overcome these barriers. [6, 15, 16] Children with SCD and other chronic conditions are seen, accompanied by an LAR, at regular intervals in the outpatient setting. Thus, clinic visits represent an opportunity to educate families about an ongoing study in a controlled environment, outside of the stressful ED. Pre-consent may then facilitate enrollment for inpatient clinical trials. We incorporated a pre-consent process in a multi-site, randomized clinical trial conducted within the Pediatric Emergency Care Applied Research Network (PECARN). In the Intravenous Magnesium for Sickle Cell Vasoocclusive Crisis (MAGiC) trial, [17, 18] the pre-consent process was jointly conducted by research staff from the ED and investigators in hematology who had an established relationship with patients with

SCD and their families. Here, we describe our pre-consent process, the benefits and challenges of pre-consent in the MAGiC study, and suggest key items to consider when deciding whether to pre-consent in future intervention trials. IRB approval was obtained as part of the parent trial.

Methods

In the MAGiC study, four of eight enrolling sites adopted a pre-consent process. The other four sites cited past experience, an understanding of the limits of pre-consent gained from participating sites and resource limitations as factors for declining to institute a pre-consent process.

The pre-consent process was similar across the sites. Sites worked with their Hematology clinics to identify patients likely to be eligible based on inclusion/exclusion criteria (e.g. HbSS or HbSβ^0 genotype, not on chronic transfusion therapy, no history of stroke) or frequency of recent hospitalizations. The pre-consent process was identical to the standard consent with the exception that the pre-consent introduction was given by the clinic hematologist as opposed to the enrolling research staff in the ED. In both scenarios, the introduction was followed by a full, informed-consent discussion and signing of the consent document. When a pre-consented child returned for an eligible ED visit, willingness to participate was verbally confirmed and key study procedures reviewed. All signed consents were kept in the ED so information was readily accessible.

Results

In total, all 8 sites randomized 208 patients into the trial. [8] Among the 4 pre-consenting sites, 177 (77%) of all approached patients were first approached for consent in the ED while 53 (23%) were previously pre-consented (Table I). Of the 177 patients who were not pre-consented, 72 (41%) were randomized, compared to 48 (91%) of the pre-consented patients ($p < .001$).

Altogether, sites pre-consented 134 patients: 48 (36%) were subsequently approached and randomized, 5 (4%) were approached but did not wish to be randomized at that time and the remaining 81 (60%) never had a qualifying ED visit during the study period. Pre-consented patients comprised 23% of all randomized patients and 40% (48/120) of randomized patients among the pre-consenting sites. Analysis by time of day revealed that , 33% (16/48) of the pre-consented patients presented between 10pm and 6am compared to 38% (27/72) of patients who were not pre-consented ($p = .641$). The percentage of pre-consented patients who were subsequently enrolled ranged by site from 24% to 56%.

A major finding reported by site research staff was IRB variability in the duration of the validity of the signed pre-consent document. At the two sites with the most stringent IRB consent requirements, signed consents expired at the annual continuing review, even if the consent had been signed only one month before. This expiration forced these sites to re-consent if not enrolled prior to the date of the continuing review. This made pre-consenting in the last quarter of the year unlikely to yield successful pre-consent. Additionally, one of these sites' IRBs invalidated all signed pre-consents if any part of the protocol was updated, even if it did not change

the consent form, while the other site invalidated all pre-consents if any part of the consent form changed. IRBs at the two remaining sites considered signed consents to be valid until the subject reached the age of majority as long as no significant changes occurred in the risks/benefits or study procedures. Finally, there were institutional differences related to the need for LAR presence at enrollment after when pre-consent. At one site, the LAR needed to be in the ED to sign an additional, shorter consent form prior to randomization (although no patients were actually unable to enroll due to this restriction), while the other three sites' enrollment was allowed without an LAR.

Among the two sites with the greatest number of pre-consented subjects, 18/70 (25.7%) patients at the site with the more stringent IRB were randomized compared to 14/32 (43.8%) of patients at the less stringent site (p = .069). Both sites had a similar proportion of their pre-consented patients randomized on nights/weekends. The number of pre-consented patients across sites reflected the size of the sickle cell program at each site.

Discussion

In a multi-site, sickle cell intervention trial, pre-consent in the clinic setting provided a means by which to address several barriers to enrollment in the ED. In this study, pre-consent facilitated enrollment in the absence of an LAR; highlighted to families the collaboration between ED and Hematology, and provided a comfortable, less stressful, setting in which to obtain consent.

When comparing randomization rates between those pre-consented and not, the proportion of pre-consented patients who were randomized was more than double that of those who were not pre-consented, with more than 90% of approached pre-consented subjects being randomized into the trial. By comparison, a recently completed treatment trial of acute SCD pain crisis by Telen MJ et al., randomized 76 patients during 31 months of enrollment across 22 sites, averaging 0.11 patients per site per month. [19] The MAGiC study randomized 208 patients during 36 months across 8 sites, averaging 0.73 patients per site per month.

Approaching families at clinic visits as part of the MAGiC pre-consent process was also a form of pre-education. The study was introduced by the hematologist and consent discussions occurred with the research staff. Even if consent was not obtained, families were educated about the study and general research concerns may have been eliminated. While pre-consent is a longer and more thorough process than pre-education, pre-consent may not be worthwhile at all sites.

Local IRB policies greatly influenced the degree to which sites were able to benefit from the pre-consent process. Although not statistically significant, the difference in randomization rates between the two sites with the most stringent and most flexible IRB consent policies highlights the importance of the IRB when evaluating the potential effectiveness of pre-consent.

We believe that pre-consent is a valuable strategy to address barriers to enrollment in sickle cell acute intervention trials. However, investigators should have a clear

understanding of the regulatory requirements adopted by their local IRBs to determine whether that particular site would benefit from a pre-consent process.

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Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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Table I. Number of subjects approached and randomized by site.

Site	Consent type	Approached,* n	Randomized, n (% of approached)
Site A	Standard	79	25 (31.6)
	Pre-consent	22	18 (81.8)
Site B	Standard	35	20 (57.1)
	Pre-consent	15	14 (93.3)
Site C	Standard	42	16 (38.1)
	Pre-consent	7	7 (100.0)
Site D	Standard	21	11 (52.4)
	Pre-consent	9	9 (100.0)
Site E	Standard	52	28 (53.8)
Site F	Standard	60	24 (40.0)

Site G	Standard	49	23 (46.9)
Site H	Standard	19	13 (68.4)

*Approached at an eligible ED visit (additional subjects approached for pre-consent at each of the four pre-consenting sites are not included because these subjects never had a subsequent eligible visit).