Coenrolment in a randomized trial of high frequency oscillation:

Prevalence, patterns, predictors, and outcomes

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Running Head: Coenrolment in an ARDS Trial

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Abstract

Objective: Enrolment of individual patients into more than one study has been poorly evaluated. The objective of this study was to describe the characteristics of patients, researchers and centers involved in coenrolment, studies precluding coenrolment, the prevalence, patterns, predictors and outcomes of coenrolment in a randomized clinical trial (RCT).

Design, Setting, Methods: We conducted an observational study nested within the OSCILLation for Acute Respiratory Distress Syndrome (ARDS) Treated Early (OSCILLATE) Trial which compared high frequency oscillatory ventilation (HFOV) to conventional ventilation. We collected patient, center and study data on coenrolment. Multilevel regression examined factors independently associated with coenrolment, considering clustering within centers. We examined the effect of coenrolment on safety and the trial outcome.

Measurements & Main Results: Overall, 127 (23.2%) of 548 randomized patients were coenroled in 25 unique studies. Coenrolment was reported in 17 of 39 centers (43.6%). Patients were most commonly coenroled in one additional RCT (76, 59.8%). Coenrolment was less likely in older patients (odds ratio [OR] 95%CI 0.87 [0.76-0.997]), and in ICUs with >26 beds (OR 0.56 [0.34,0.94]), and more likely by investigators with >11 years experience (OR 1.73 [1.06, 2.82]), by research coordinators with >8 years experience (OR 1.87 [1.11, 3.18]) and in Canada (OR 4.66 [1.43, 15.15]). SAEs were similar between coenroled HFOV and control patients. Coenrolment did not modify the treatment effect of HFOV on hospital mortality.

Conclusions: Coenrolment occurred in 23% of patients, commonly in younger patients, in smaller centers with more research infrastructure, and in Canada. Coenrolment did not influence patient safety or trial results.

Introduction

Recruitment of eligible patients into critical care trials is challenging due to the severity of acute illness in the intensive care unit (ICU), reliance on substitute decision-makers for consent, and short time windows for randomization. The enrolment of one patient into more than one study - coenrolment - is an increasingly common approach to increase patient clinical trial participation, yet the practice has not been well studied except in research on HIV [1], resuscitation [2], thromboprophylaxis in adult critical care [3], and pediatric critical care [4]. We found no studies of coenrolment in randomized controlled clinical trials (RCTs) of mechanical ventilation.

Coenrolment offers several potential benefits, including reduced competition for similar patients among studies, avoidance of selection bias, increased likelihood of timely completion, and enhanced research cost-effectiveness. Potential disadvantages include patient or substitute decision-maker burden. Unintended interactions may develop (causing harm, or inflated or attenuated treatment effects); furthermore, modified treatment effects may reduce the power of a study unpredictably. Furthermore, bedside staff or research personnel workload may be increased. Although investigators perceive that coenrolment can be ethical and feasible [5], institutional review boards (IRBs) and protocol prohibitions can hinder such opportunities [6].

In this study, coenrolment refers to simultaneous or sequential enrolment in 2 or more studies [5]. Coenrolment in 2 studies can occur only when a patient fulfills

all inclusion criteria and has no exclusion criteria for both studies. This is distinct from factorial design studies, where all patients enrolled are randomized twice, included in both limbs of the factorial trial [7-13].

The overall objective of this study was to describe the characteristics of patients, research personnel and centers involved in coenrolment, studies permitting and precluding coenrolment, and the prevalence, patterns, predictors and outcomes of coenrolment in OSCILLATE, a RCT in patients with acute respiratory distress syndrome (ARDS) [14]. Specific aims were to analyze: 1) the proportion of eligible patients previously enrolled in a confounding study that precluded OSCILLATE randomization, and the design, affiliation, and funding of these studies; 2) the proportion of OSCILLATE patients coenroled in at least one other study, and the methods (design, consent), affiliation, funding, and timing of coenrolment; 3) the characteristics of patients, research personnel and centers coenroling versus not; 4) the effect of coenrolment on serious adverse events (SAEs) and the primary outcome of OSCILLATE.

Methods

We analyzed patients with moderate-severe ARDS randomized in an international clinical trial in 5 countries comparing high frequency oscillatory ventilation (HFOV) versus low tidal volume, high PEEP ventilation (control) on hospital mortality [OSCILLation for ARDS Treated Early Trial [clinicaltrials.gov NCT00474656-pilot; NCT01506401-main trial].

Nested within OSCILLATE, we conducted an observational study of coenrolment. We used prospectively collected patient and study data on coenrolment (designs, funding, and coenrolment timing [i.e., before, concurrent with, or after OSCILLATE enrolment, and each year]). We retrospectively obtained additional data on research infrastructure (personnel and research intensity), center characteristics (hospital and ICU descriptors, research ethics oversight), and coenroled studies (consenting personnel and requirements, consortia affiliation). Retrospective studies on OSCILLATE patients after trial closure weren't considered. We did not prospectively record all research conducted at all sites during OSCILLATE; however, we documented the number of additional studies at each site in 2010 for use in the regression analysis.

The OSCILLATE Steering Committee generally supported coenrolment, in keeping with principles of the CCCTG [3]. The Co-Principal Investigators (NDF, MM) of OSCILLATE discussed the possibility of coenrolment with the Principal Investigators of other trials and sought input from the OSCILLATE Steering Committee. Once consensus was reached, the other study Principal Investigators were contacted for further discussion, then the final decision about whether coenrolment was allowed or disallowed was communicated to all OSCILLATE centers. If allowed, centers handled coenrolment according to local policies; thus, some centers allowed coenrolment and others did not, some required case-by-case review, and others initially disallowed but later allowed it.

Throughout the trial, SAEs were defined as: a) any event that was fatal or immediately life threatening, permanently disabling, severely incapacitating, or required prolonged inpatient hospitalization, *or* b) any event that jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above, *and*; c) either a or b was believed, by the attending physician, to be related to OSCILLATE enrolment.

Our framework for coenrolment into 2 studies is conditional on the patient being eligible for both studies (that is, the patient fulfills all inclusion criteria and has no exclusion criteria for both studies). Therefore, a patient with elevated intracranial pressure in a trial of decompressive craniectomy versus medical management [15] was *not* a coenrolment opportunity because elevated intracranial pressure was an exclusion criterion for OSCILLATE. Two examples illustrate our decision-making. The first is a *coenrolment opportunity* - a patient enrolled in a trial of pharmaconutrition [13] who fulfilled all OSCILLATE inclusion and no exclusion criteria and was coenroled. The second is a patient enrolled in a trial of protocolized sedation with or without daily interruption of benzodiazepine and opioid infusions [16], who fulfilled all OSCILLATE eligibility criteria. In this scenario, a *coenrolment opportunity was disallowed*; these patients were not coenroled in OSCILLATE because routine sedation interruption was considered unsuitable for ARDS patients in either group.

Analysis

Continuous data are summarized as mean (standard deviation, SD) or median (interquartile range, IQR) and categorical data as proportions. We conducted univariable analyses, using t-test or Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, comparing characteristics of patients who were coenroled versus not coenroled, research coordinators who coenroled versus those who did not, and centers that coenroled versus those that did not. We evaluated whether the proportion of patients coenroled changed over the years of recruitment in Cochran-Armitage trend test. We conducted a multilevel logistic regression to examine factors independently associated with coenrolment, considering clustering of patients and research staff within centers and distinguishing patient from center characteristics. Continuous predictor variables related to investigator (e.g., years of experience), coordinator, or ICU (e.g., number of beds) characteristics were dichotomized at the median value for multivariable analysis. We examined the effect of coenrolment on SAEs and the primary outcome of hospital mortality using Chi-square test or Fisher's exact test when appropriate. We assessed coenrolment as a modifier of the effect of HFOV on mortality by including an interaction term in logistic regression adjusted for the same covariates (age, baseline acute physiology score, baseline sepsis, and duration of pre-randomization hospitalization) [14].

Ethics

OSCILLATE was approved by all participating centers' IRBs. Written informed consent was obtained from substitute decision-makers prior to randomization.

Results

Hospitals were largely teaching institutions (38, 97.4%), with a mean (SD) of 566 (248) hospital beds. Most ICUs were closed (37, 94.9%), with a mean (SD) of 33 (20) beds. Centers enrolled patients in OSCILLATE for a mean (SD) of 2.7 (1.7) years. Multicenter trial experience was considerable for research coordinators (8.6 [4.6] years) and site investigators (12.2 [5.5] years). On average, 1.5 (1.6) full-time equivalent (FTE) dedicated research personnel per site were working during each site's enrolment period. The response rate for retrospective data on workload was 37/39 (94.5%).

Aim 1. Confounding studies that precluded coenrolment

We considered all 548 randomized patients and 574 eligible non-randomized patients in 39 participating centers in 5 countries. Of 574 eligible non-randomized patients, the reason for non-enrolment was prior enrolment in a study not permitting coenrolment for 24 (4.2%) patients in 10 studies (Table 1).

Aims 2 and 3. Characteristics of coenrolments

Overall, 127 of 548 (23.2%) randomized patients were coenroled in 25 unique studies [160 coenrolment events] (Table 2). There is overlap among studies between Tables 1 and 2 because for certain studies, coenrolment was allowed in some but not other OSCILLATE centers, and coenrolment was initially disallowed

for some studies but then subsequently allowed (e.g. REDOXS [13], PROWESS-SHOCK [17]). Coenrolment was reported in 17 of 39 centers (43.6%), and 3 of 5 (60.0%) countries. Among 127 coenroled patients, the median (interquartile range [IQR]) number of additional studies into which one patient was coenroled was 1 (1,1) [maximum of 4] (Table 3). Of 26 patients coenroled in 2 or more additional studies, the commonest combination was 1 additional RCT and 1 additional prospective comparative study (non-randomized comparison) (23.1% of patients) followed by RCT and prospective audit (19.2% of patients). The most common design among the 160 coenrolment events was RCTs (100, 62.5%), observational studies (total 60 [prospective comparisons (21, 13.1%), prospective audits (34, 21.5%), qualitative studies (4, 2.5%) and retrospective audits (1, 0.6%)].

Two centers had explicit coenrolment guidelines. Of 160 coenrolment events, 149 (93.1%) required informed consent. Of these, consent was obtained before OSCILLATE (30, 20.1%), concurrent with OSCILLATE (37, 24.8%), or after OSCILLATE enrolment (82, 55.1%). The proportion of patients coenroled did not increase annually (p=0.72), In 2010, there were a median of 2 (1-3) additional observational studies and 4 (2-6) RCTs concurrently recruiting per site.

Aim 3. Characteristics of patients, research personnel, and centers

We compare patients, research personnel (research coordinators and site investigators) and centers engaged in coenrolment versus not, in Table 4. In univariable analysis, patients who were coenroled did not differ from those not

coenroled regarding age, sex, illness severity as measured by APACHE-II score, and body mass index. Patients in the HFOV group (63/275, 22.9%) were just as likely to be coenroled as the control group (64/273, 23.4%).

There were no differences in numbers or discipline of research personnel, or the primary persons obtaining consent in centers coenroling versus not coenroling. However, research coordinators who coenroled had more multicenter trial experience than those who did not (p=0.02).

Univariable analysis showed that centers coenroling versus those not coenroling were of similar size, were just as likely to have participated in the OSCILLATE pilot phase, and were participating concurrently in a similar number of observational studies. However, centers coenroling were participating in more RCTs than centers not coenroling [median 4 (4-6) versus 2.5 (2-5), p=0.04], and had participated in OSCILLATE for significantly longer [median 4.8 (2.1-5.0) versus 1.9 (1.0-2.9) years, p=0.005], and had more experienced research coordinators [median 11 (10-13) versus 6 (4-10) years of experience, p=0.02].

In multivariable analyses (Table 5), coenrolment was less likely in older patients (odds ratio [OR] 0.87, 95%CI 0.76-0.997 for each 10 year increase) and in larger ICUs (OR 0.56 [0.34, 0.94] for those with >26 beds [median] versus ≤26 beds). However, coenrolment was more likely in centers with experienced investigators (OR 1.73 [1.06, 2.82] for those with >11 years [median] versus ≤11 years experience), in centers with experienced research coordinators (OR 1.87 [1.11,

3.18] for those with >8 years [median] versus ≤8 years experience) and in Canada compared to elsewhere (OR 4.66 [1.43, 15.15]).

Aim 4. Effect of coenrolment on outcomes

Among patients coenroled in other studies, rates of SAEs were similar between the HFOV (2 of 63, 3.2%) and control (1 of 64, 1.6%, p=0.62) groups and similar to the main trial findings (HFOV: 7 of 275 [2.5%] versus control: 1 of 273, [0.4%]; p=0.07). Also, SAE rates were similar between patients who were coenroled (3 of 127, 2.4%) versus not coenroled (5 of 417, 1.2%), p=0.40).

The primary outcome of OSCILLATE, including coenroled patients (relative risk of hospital mortality with HFOV, 1.33; 95% CI 1.09 to 1.64; p=0.005), did not change when patients coenroled in any other studies were excluded (relative risk 1.26, 95%CI 1.01-1.58, p=0.04, n=421) and when patients coenroled only in other RCTs were excluded (relative risk 1.27, 95%CI 1.02-1.58, p=0.03, n=455).

The percentage of patients coenroled was comparable in HFOV [63 of 275 (22.9%)] and control [64 of 273 (23.4%)] groups. Adjusted for treatment group, coenrolment status, age, the acute physiology component of the APACHE II score, pre-randomization duration of hospitalization, and sepsis, the p-value of interaction between coenrolment and treatment for hospital mortality in the logistic regression was 0.64, showing that coenrolment did not modify the treatment effect (OR [95%CI] among coenroled and non-coenroled: 2.01 (0.85, 4.76) and 1.59 (1.01, 2.50), respectively).

Discussion

One quarter of patients in this ARDS trial were coenroled in at least one other study - commonly another RCT. Coenroled patients within OSCILLATE had a similar illness severity as those who were not coenroled. We found no differential coenrolment across the 2 arms of this unblinded trial. Coenrolment did not increase the risk of SAEs. The largest number of co-enrolments with any individual RCT was 25 patients (<5% of patients in OSCILLATE, and smaller percentages in the coenroled RCTs listed in Table 2), making the probability that coenrolment had impacts on the treatment effect in OSCILLATE or other trials unlikely. Indeed, our analysis suggested that coenrolment did not modify the treatment effect of HFOV.

We also found that the absolute number of patients coenroled was greatest in Canada, reflecting the extensive enrolment of Canadian patients in the trial. However, the proportion of coenroled patients was highest in the single enrolling center in Saudi Arabia (16 of 44, 36%), followed by Canadian centers (107 of 410, 26%) and the United States (4 of 76, 5%). Given relatively few centers outside Canada, results are non-representative of national practice elsewhere.

Multivariable analysis suggested that younger patients were significantly more likely to be coenroled than older patients, which may reflect more intensified pursuit of research opportunities for younger patients, or greater concern about

coenrolment in the elderly. Smaller ICUs were significantly more likely to coenrol than larger ICUs, perhaps reflecting their research efficiency. Centers with more experienced research coordinators and investigators were more likely to coenrol, suggesting heightened vigilance for, and comfort with, coenrolment.

Our study highlights the lack of a universal approach to coenrolment. Coenrolment decisions permissible by steering committees of each study were subsequently subject to approval at each center, only some of which allowed coenrolment. For other study combinations, coenrolment was originally not considered, and hence did not occur initially with PROWESS-SHOCK [17] or REDOXS [13]. After discussion with relevant stakeholders, it was later allowed for both studies, and either occurred [13] or didn't [17]. Regarding another combination, an early coenrolment in SLEAP [16] was an oversight, as this was eventually disallowed. Therefore, coenrolment early in a trial's recruitment, or in centers without an established approach, may occur on a case-by-case basis and evolve. Although no centers had official IRB policies at the time of this study, 2 centers had IRB-approved coenrolment guidelines and the CCCTG guidelines [18] may have been operational in some centers. Centralized research governance and ethical approval such as exists in the UK [19] could potentially reduce coenrolment variability, harmonize approaches, enable timely recruitment, and decrease fixed trial costs.

Coenrolment has been investigated in 2 pediatric ICU studies. Harron and colleagues [4] evaluated coenrolment for the CATCH trial (CATheters in CHildren) [20] comparing impregnated versus standard central venous catheters to reduce bacteremia, and the CHIP trial (Control of Hyperglycaemia in Paediatric intensive care) [21] comparing tight versus standard glucose control. Of 5 ICUs participating in both trials, 3 disallowed coenrolment. The fourth ICU didn't record approaches or refusals, but did coenrol one child. In the fifth ICU, of 35 parents approached for both trials, 17 consented to both, 13 consented to one, and 5 declined both. Consent rates during coenrolment were 29/35 (82%) and 18/35 (51%) for CATCH and CHiP respectively, compared with 78% and 51% for a single trial. Coenrolment was interpreted as not jeopardizing recruitment or overwhelming parents [4].

Coenrolment has been investigated in 2 adult ICU studies. Burns et al characterized consent encounters and outcomes in a national one-month prospective observational study in 23 ICUs [6]. Coenrolment was permitted in 19/23 (83%) of ICUs and occurred in 11 studies on 50 occasions involving 20/119 (17%) patients. Research staff were unable to obtain consent for 129 patients; in 19 (15%) instances, the trials prohibited coenrolment. In a 67-center thromboprophylaxis trial (PROTECT) [22], the proportion of patients coenroled (19%) [3] was similar to OSCILLATE (23%). Factors associated with coenrolment in PROTECT differed, including illness severity, consent by substitute decision-maker (versus patient), greater experience of person

obtaining consent, larger center size, and enrolment into the main trial rather than pilot.

Limitations of this report include possible under-reporting of patients already in another study who were eligible for OSCILLATE but for whom coenrolment was not pursued. We did not capture surrogates who were not approached for coenrolment, or when coenrolment was offered but declined. We did not characterize persons eliciting informed consent or whether there was IRB, industry, or investigator prohibition. Our characterization of research intensity may be affected by recall bias; we acknowledge that shared positions, summer students and managers may have existed.

Strengths of this study are the focus on ARDS patients in whom the risks may theoretically be high. This pre-planned longitudinal observational study nested within a randomized trial examined precluding studies, the prevalence, patterns, and outcomes associated with coenrolment. We analyzed predictors using multilevel regression to take into account clustering of patients and research personnel within centers.

Coenrolment is not recommended in a clinical trial protocol in the SPIRIT checklist [23], or in a clinical trial report in the CONSORT checklist [24]. Without empiric evidence that coenrolment increases the risk of bias or affects the generalizability of findings, reporting cannot be mandatory. However, enhanced

transparency would include the rationale for coenrolment, the approach taken, the proportion of coenroled patients in each arm and into which other studies, and the consequences, if known, on the results.

The impact of coenrolment on interviews of substitute decision-makers to explore decisional burden versus appreciation for opportunities would be useful. In one center, consent rates for coenrolment encounters were reportedly similar to single study consent encounters [25], but further research is warranted. Observational studies or registries in centers with considerable coenrolment experience would illuminate pros and cons and population-specific concerns [26], as well as efficiencies such as modular consent forms [27].

Guidelines for coenrolment would raise awareness among investigators, IRBs, funders and regulators. Coenrolment documents may reflect research consortia policies [18,28], whereas the UK National Institute of Healthcare Research Comprehensive Clinical Research Network produced a guideline encouraging coenrolment in the ICU [19]. International coenrolment data remain sparse among countries contributing to global critical care research [29].

Conclusions

Coenrolment occurred in one quarter of patients enrolled in this ARDS trial, most commonly in another randomized trial. Coenrolment was more common in younger patients, in smaller centers with more research infrastructure, and in

Canada. Coenrolment did not jeopardize patient safety or modify the treatment effect in this international trial. Careful monitoring and reporting of co-enrolment is warranted in the ICU setting.

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