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Temporal compliance trends in a cluster randomization with crossover trial of out-of-hospital cardiac arrest

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Abstract

Background—Low compliance to randomized non-drug interventions can affect treatment estimates of clinical trials. Cluster randomized crossover may be appropriate for increasing compliance in the out-of-hospital cardiac arrest setting.

Purpose—The purpose was to determine whether the elapsed time from start of a non-blinded treatment period to episode enrollment date in a cluster randomized crossover trial is associated with compliance to either a period of brief CPR with electrocardiogram ECG rhythm analysis or a period of longer CPR with delayed ECG rhythm analysis in patients with out-of-hospital cardiac arrest.

Methods—The Resuscitation Outcomes Consortium PRIMED Analyze Late vs Analyze Early trial was a cluster randomized crossover trial at 10 North American regional sites. Clusters were created based on local service preference with treatment periods varying from 3 to 12 months depending on the expected enrollment rate of each randomizing unit. Episodes on the AL arm had a target of 180 seconds from CPR start to Shock Assessment and were deemed compliant if total time was between 150 and 210 seconds. Episodes on the AE arm had a target of <30 seconds from CPR start to Shock Assessment and were deemed compliant if total time was <60 seconds. We

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Conflict of Interest Statement

Robert Schmicker, Brian Leroux, Gena Sears, Ian Stiell and Sheldon Cheskes receive funding from the Resuscitation Outcomes Consortium.

Gena Sears receives funding from the Resuscitation Outcomes Consortium and sold 400+ shares of Medtronic, Inc. in March 2011.

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used logistic regression to examine the association between compliance (Yes/No) and the elapsed number of days from the start of the treatment period to the episode in the framework of generalized estimating equations, controlling for randomized treatment (Late, ref=Early) and treatment period length (ref=3, 4-5, 6, 7-11, 12 months).

Results—We had 8769 episodes in our analysis population. Overall compliance to the randomized arm was 63.5%. After adjusting for treatment arm and treatment period length, the odds of compliance for episodes occurring >300 days from treatment period start were 33% lower (OR: 0.67, 95% CI: 0.52, 0.86) than for those <60 days from treatment period start. There was no significant difference in compliance between episodes before and immediately after a cluster crossed over to the opposite arm (OR: 0.81, 95% CI: 0.57, 1.17).

Limitations—A major challenge was the lack of synchronicity between training cycles and agency crossover dates.

Conclusion—We found a significant decrease in compliance to the AL vs AE cardiac arrest intervention as the elapsed time from start of treatment period increased. We did not find a difference in compliance immediately before and after a crossover. While these results suggest that future cluster with crossover trials in the out-of-hospital setting be designed with short treatment periods and frequent crossovers, provider logistical concerns must also be considered.

Keywords

cardiac arrest; cluster design; crossover; study compliance

INTRODUCTION

Intent-to-treat (ITT) analyses, supported by the Food and Drug Administration (FDA) and National Institute of Health (NIH), are the most appropriate methods for assessing the utility of an intervention under ordinary settings.¹ Results from ITT analyses are in terms of the assigned treatment and are often more conservative than those in the ideal setting. Interventions found to be advantageous in the ideal setting may not be advantageous in the ordinary setting if implementation is challenging. As such when developing a protocol for a process of care intervention thought to be advantageous in the ordinary setting, it is important to maximize the rates of compliance by ensuring that the intervention is of minimal complexity.¹

One area that can be prone to high non-compliance is non-drug, emergency research in the pre-hospital setting. This dynamic setting is highly complex, high-pressured and has been shown to cause great stress in those that provide medical care.² Initial skills and knowledge are acquired by emergency medical providers from certification program training and then reinforced during periodic re-training programs.³ When implementing clinical trials, emergency medical providers are trained in new study-specific skills. If skill retention is most often maintained through frequent repetition, one can expect a high rate of non-compliance for skills infrequently used. Out-of-hospital cardiac arrest is a rare event⁴ that individual emergency medical providers may not encounter over the span of a year. As such, most providers may not achieve a satisfactory level of comfort with a new, and infrequently applied intervention.

Cluster randomization, where providers are assigned the same treatment over a defined period of time, may be appropriate for minimizing non-compliance in the out-of-hospital cardiac arrest setting compared to individual randomization, where the assigned treatment may be different with each incident. While logistically simpler, cluster randomization presents statistical challenges that result in an increase in sample size.⁵ A common method

to counter the increase in sample size, due to within cluster variance, is to include a crossover in the design.⁶ For non re-occurring events, individual patients in cluster randomization with crossover (CRC) trials do not crossover from one treatment to the next, but rather the group of patients who are in a geographical region will be eligible for another treatment based on a pre-defined time period.

The Resuscitation Outcomes Consortium (ROC) is a clinical trial network that conducts emergency medical service-based out-of-hospital research performed by licensed paramedic and fire personnel in patients with cardiac arrest or severe traumatic injuries. The ROC PRIMED Analyze Late (AL) vs Analyze Early (AE) trial examined a behavioral method of performing 3 minutes of CPR prior to ECG rhythm analysis (AL) compared with up to 60 seconds of cardio-pulmonary resuscitation (CPR) prior to electrocardiogram (ECG) rhythm analysis (AE) in adults who experienced a cardiac arrest in the out-of-hospital setting. The study was performed under a CRC design where treatment period lengths varied across regions. We evaluated whether the CRC design contributed to non-compliance by emergency medical providers. Specifically, the purpose of this study was to determine whether compliance changed over time and whether there was an initial change in compliance during the time period immediately following a crossover.

METHODS

The ROC PRIMED trial qualifies for exception from informed consent for emergency research as outlined in US FDA regulation 21CFR50.24 and the Canadian Tri-Council Agreement for research in emergency health situations (Article 2.8). The ROC PRIMED Analyze Later (AL) versus Analyze Early (AE) trial, described in detail elsewhere,⁷ compared survival to hospital discharge with Modified Rankin Score 3 between a strategy of analyze later (AL) versus a strategy of analyze early (AE). The AL vs AE trial used a cluster randomization with cluster crossover design because investigators did not feel that individual randomization was appropriate in the emergency setting. CPR is a behavioral method initiated by the medical providers upon arrival to the scene. Randomizing individual episodes through envelopes or phone calls would add unneeded on-scene complexity and dynamics to the resuscitative effort, may delay life saving treatment and enrollment may be subject to selection bias. In addition, the risk of a carryover-effect would be high if medical providers were forced to change methods on an episode-by-episode basis.

Cluster plans were created for each of 10 ROC sites based on logistical and statistical considerations. The most common plan was randomization at the agency-level, defined as a Fire Department, Emergency Medical Service (EMS) or Emergency Rescue service. Cluster sizes (the total number of episodes in a cluster after receiving both interventions) were planned to contain a similar number of episodes (<100) in an attempt to minimize the design effect.⁵ However, since agency enrollment varies in size from 1/month to 70/month across the consortium, to keep cluster size within the desired range, high enrolling agencies were encouraged to have shorter treatment periods (3 or 4 months) or to increase the number of clusters by dividing into smaller units. The latter resulted in randomization at subdivisions: AED/defibrillator, rig (an individual motor vehicle), station (a group of vehicles located in one physical location) or battalion (a group of stations). The Regional Coordinating Centers, in collaboration with the agency's Medical Directors and Administration, determined the most appropriate method for the agency. Many decisions were based on the feasibility of crossing over to a new intervention more frequently or the appropriateness of two separate rigs arriving on scene randomized to different arms of the study. The few ROC agencies that opted to randomize by rig did so with treatment periods of 12 months.

Clusters began enrolling patients at different times over the course of the study. Upon study initiation, clusters were randomized to either the AL or AE treatment. Clusters began enrollment in a Run-in Phase during which compliance was monitored and performance feedback given. Clusters that were able to meet compliance benchmarks as determined by the ROC Study Monitoring Committee (SMC) were advanced to the Evaluable Phase. Clusters that were unable to meet the benchmarks within 2-6 months of Run-In Phase commencement were no longer eligible to participate in the trial. Once in the Evaluable Phase, clusters retained the same randomization arm as in the Run-in Phase for a pre-specified length of time, called the treatment period length. Once the assigned treatment period was completed, the cluster switched over to the opposite treatment arm. Upon completion of both treatment arms, clusters were re-randomized by the Data Coordinating Center (Figure 1). Clusters were alerted to the assigned treatment arm as close to the date of cluster crossover as possible, usually within 1-2 months, to avoid provider bias.

For purposes of this study, the term *treatment arm* will refer to either AL or AE, the term *treatment period* will refer to the unit of time on one treatment arm and the term *treatment period length* will refer to the specific amount of time the treatment period was assigned to either treatment arm prior to crossover.

STATISTICAL METHODS

Our analysis excluded all cases in the Run-In Phase since compliance increased over time as a result of targeted efforts to meet minimum benchmarks to move into the Evaluable Phase. Clusters that initially met the benchmarks spent less time in the Run-In Phase than those that had to improve over time. Thus we were concerned that including the Run-In Phase data may bias our results. One agency had randomization performed at the AED/defibrillator level. Within this agency, each AED/defibrillator was randomized to one of the two treatment arms. The AED/defibrillator software was then programmed to provide medical providers with real time prompts to assess the rhythm after either 60 or 180 seconds of CPR, depending on the randomized treatment arm. We excluded all episodes from this agency as we felt that such active instructions during the course of care would be different and have higher compliance than those that relied on passive reminders and prior training. Our final analysis population also excluded from the Evaluable

Population all episodes with missing CPR to Shock Assessment Time, episodes that were EMS Witnessed and episodes with any study specific exclusions. Descriptive statistics were created to examine unadjusted results and trends in the analysis population over the course of the Evaluable Phase.

To examine the association between compliance and time from start of treatment period, we used logistic regression in the framework of generalized estimating equations (GEE) with compliance modeled as a binary variable. The SMC deemed episodes on the AE arm compliant if the time from initiation of CPR to shock assessment is less than 60 seconds whereas episodes on the AL arm were deemed compliant if the time was between 150 and 210 seconds. We calculated elapsed time as the difference between the start date of the respective treatment period and the episode date and created a categorical variable by cutting elapsed time by 60 day increments. We adjusted for two potential confounders: randomized treatment arm (Analyze Late, ref=Analyze Early) and treatment period length (ref=3, 4-5, 6, 7-11, 12 months). We used randomized cluster as the clustering variable in GEE, with an exchangeable working covariance structure and robust standard errors.

To examine whether there is an association between crossing over to the opposite arm and compliance, we examined episodes in the first treatment period and those in the first two weeks of the second treatment period. Episodes in clusters that did not crossover were

excluded from the analysis. We used logistic regression with similar structure as above and included a variable that represented whether the episode occurred prior to or in the two week period immediately following the crossover.

To examine whether there is a long-term trend, we examined if compliance in the first treatment period was different than compliance in the third treatment period, for those clusters that had a third treatment period. Clusters with third treatment periods were re-randomized once and had a 50% chance of having the same randomization arm during the third period as during the first. We used logistic regression with similar structure as above and included a variable that represented the treatment period.

Data manipulation were done in S-PLUS (version #6.2.1), c (2003), Insightful Corporation, Seattle, WA. Analyses were done with STATA, StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.

RESULTS

After excluding episodes as defined in the Methods Section (Run-In Phase – 25%, Defib randomization - 7%) we had 11,388 episodes in the Evaluable Phase. We then excluded any episodes with study-specific exclusions (EMS Witnessed – 11%, Written Do Not Resuscitate Orders –3%, Non-Fire/EMS Rhythm –3%, Age –2%, Others –2%) as well as those with missing time from CPR start to Shock assessment (3%). The final analysis population (Figure 2) consisted of 8767 patients across 350 clusters and 10 sites. Episodes occurred in one of 6 treatment periods, where treatment period 1-1 represented the initial post-Run-In Phase period while treatment period 1-2 represented the period after having crossed over for the first time. Treatment period 2-1 then represents the period after re-randomization and following the completion of the first two treatment periods. Table 1 shows the frequencies of each assigned treatment period length. The majority of clusters (88.6%) were either six or twelve months long.

Figure 3 shows unadjusted compliance to the randomized treatment arm by the treatment period length. The highest compliance rates occurred in clusters with 6 month treatment periods (AE – 73.7%, AL – 67.5%) but varied across all treatment periods. The overall compliance rate was 63.5% (AE – 65.3%, AL – 61.5%). Figure 4 shows unadjusted compliance to the randomized treatment arm by the elapsed time between the start of treatment period and episode date. The highest rates of AE compliance occurred in the 61-120 day period (68.3%) while the highest rates of AL compliance occurred in the 0-60 day period (63.4%).

After adjusting for treatment arm (AL, ref=AE) and treatment period length (ref=3, 4-5, 6, 7-11, 12 months), elapsed time from the start of the treatment period to episode date is significantly associated ($\chi^2(5)=11.8$, $p=0.04$) with compliance when cluster was used as the clustering variable. This significance is driven by the odds of compliance for episodes >300 days from treatment period start date in comparison to episodes <60 days from treatment period start (OR: 0.67, 95% CI: 0.52, 0.86) (Table 2). In the same model, randomized treatment period length ($\chi^2(4)=23.6$, $p<0.01$) was found to be significantly associated with compliance.

In a sensitivity analysis, elapsed time from the start of the treatment period to episode date is significantly associated ($\chi^2(5)=13.5$, $p=0.02$) with the absolute deviation from the intervention target when adjusted for the same covariates as above. The significant is driven by the increase in absolute deviation for episodes >300 days from treatment start date in comparison to episodes <60 days from treatment period start (11.3, 95% CI: 0.5, 22.2) (Table 3).

Three hundred and nine (309) clusters crossed over at least once to the opposite arm. Within this subgroup of clusters, 236 episodes fell within a two-week period after the first assigned crossover date. After adjusting for treatment arm, treatment period length and elapsed time, the odds of compliance were not significantly lower (OR: 0.81, 95%CI: 0.57, 1.16) in the first two weeks after crossover in comparison to before the crossover (Table 4).

In a subgroup of episodes from clusters that were re-randomized after having completed two full treatment periods (n=31 clusters, 1445 episodes), there was not a significant association when comparing compliance in third treatment period to the first treatment period (OR: 1.00, 95% CI: 0.98, 1.01) when adjusted for elapsed time, treatment period length and treatment arm.

DISCUSSION

In a cluster randomized crossover trial comparing two strategies of CPR in the out-of-hospital emergency setting, we found a significant association between elapsed time from start of treatment period to episode date and compliance to the assigned treatment arm. Specifically, episodes occurring >300 days after their respective treatment period start had 33% lower odds of compliance compared to episodes <60 days after treatment period start.

One possible explanation for this result is the minimal number of cardiac arrest cases seen per year by individual out-of-hospital emergency providers. Across the ROC network, we estimate that 36,000 medical providers⁸ treat 20,500 patients with cardiac arrests each year.⁴ This suggests, that the average medical provider may likely treat one cardiac arrest per year. Medical providers gain familiarity with standard American Heart Association (AHA) resuscitation guidelines through repetition. The same familiarity may not be achievable with new research protocols if they are not reinforced through training or performed often enough. In our study this appears to be especially true if the cardiac arrest occurs 300 days or more from the start of the treatment period.

By adjusting for treatment period length in our model we accounted for the fact that not all clusters would be able to treat an event 300 days from the initial start date. Our results show that treatment period length is significantly associated with compliance, with episodes in clusters with 6 and 12 month treatment periods having 40% and 21% greater odds of compliance than those in clusters with 3-month treatment periods, regardless of the actual number of elapsed days from the start of the treatment period. This suggests that agencies that opted for 6 and 12-month treatment periods had a higher baseline compliance rate than those with 3 month treatment period.

In a subgroup of episodes occurring in clusters that completed at least two full treatment periods we did not find a significant difference in compliance between episodes in the first treatment period and the third treatment period. This result suggests that compliance does decrease over time, but only inside of treatment periods and not across treatment periods.

This appears to be consistent with our finding that compliance in the two week period immediately following the initial crossover is not significantly lower than in the entire previous treatment period. We hypothesized that compliance after the crossover would be worse because of a carryover effect, which may be relevant in high density regions where medical providers see multiple cardiac arrests but irrelevant in low density regions where cardiac arrest is rare. However, the carryover effect did not appear to be an issue in our study.

This unexpected finding could be the result of increased communication between agencies and their medical providers. ROC clinical sites employed multiple strategies simultaneously

to inform medical providers of the appropriate randomization arm upon crossover. These strategies include in-house slide-shows or web-based modules and reminders posted to the dashboard of rigs, defibrillator cases or in common work areas. Each appears to have helped maintain compliance at similar rates across treatment periods.

In the primary analysis for the trial, Stiell et. al did not find a significant association between randomized treatment arm and survival to hospital discharge with Modified Rankin Score

3. The trial was designed in a way to encourage high compliance rates within clusters, knowing that high rates of non-compliance in an ITT analysis can push the effectiveness estimates towards zero. There was concern that the overall compliance rate of 63.5% may have been a factor in the null result. However, in a secondary analysis based on the actual treatment received, the treatment estimates were also not significant, suggesting that the high rates of non-compliance were not solely responsible for the non significant effectiveness estimates in this trial.⁹

Even though it is fortunate that a degree of non-compliance did not affect the significance of our effectiveness estimate, it is preferred to design future studies to increase compliance. Any change in study design, however, must be measured against emergency provider logistical concerns. Expressed concerns about the design were the difficulty in scheduling re-training programs, and the feasibility of posting reminders in stations and vehicles upon crossover to the new intervention. The latter was labor intensive and often outside job descriptions for many medical providers. As partners in research, investigators need to consider feedback from the medical providers and design a study that is statistically sound, practical to implement and meaningful.

A major challenge in conducting the trial was the lack of synchronicity between training cycles and crossover dates. All participating agencies trained their medical providers to the two treatment arms prior to commencement in the study (in some instances more than once due to delayed regulatory approval). However, due to set training cycles, time and personnel limitations, very few provided physical re-training immediately prior to crossover dates. While most agencies had reminder materials posted throughout stations and rigs, many providers would have to implement a new intervention that they were physically trained on months prior.

In future trials of emergency medicine research with crossover, it may be wise to schedule the study start and crossovers to be in sync with retraining at the agencies. This will require flexibility between not just study investigators and medical providers but with regulatory bodies as well. This represents a complex interweaving of entities, which may be difficult to implement. However, if investigators are able to plan trial start around what are sometimes fixed training schedules, it would help increase retention of new, trial specific skills and improve study compliance.

An additional challenge was the inability to determine how compliance was affected by provider feedback. During the Evaluable Phase, the SMC provided regular feedback on compliance data to the sites. Site investigators and Medical Directors then provided those data to the providers in attempt to reinforce both the study intervention and overall good clinical practice. It is unclear the extent to which this helped compliance.

A major strength of the ROC PRIMED trial was the heterogeneity of EMS agencies which makes results more appropriate and robust for agencies of all sizes and in all locations. No two EMS agencies are the same. The ROC PRIMED trial included agencies that differ in location (urban vs rural), oversight (public vs private) and service level (ALS vs BLS vs both) such that the primary effectiveness estimates should be generalizable.

In addition to the heterogeneity of agencies, individual providers within agencies differed in terms of both training (ALS vs BLS) and experience. However, all providers received the same training, had to meet the same benchmarks and received the same feedback. We feel that by standardizing key provider criteria that we were able to control for individual provider characteristics.

To our knowledge, this is the only analysis to look at compliance in an out-of-hospital emergency trial with cluster randomization and crossover. Our analysis is unique as we were able to combine objective data on compliance with subjective data on the feasibility of intervention implementation. In future out-of-hospital cardiac arrest trials, a CRC design may be appropriate as it offers a compromise between statistical efficiency and logistical ease. Our results suggest that in such studies, treatment periods should be short and crossovers numerous in order to increase compliance with the implementation of the intervention. In future studies, the definition of short treatment periods should not only be based on statistical merit alone, but should also include logistical considerations. This may equate to 3 month crossover periods, but it also may equate to 6 month crossover periods if the former is unsustainable. Ultimately, the design that best balances both statistical and logistic concerns may be best for the long-term viability of the study.

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Figure 1.
Treatment periods for clusters of differing treatment period length, assuming the same start date and time for each cluster

Figure 2.

Study Flow Chart. Period 1-1 represents the first treatment period after initial randomization. Period 1-2 represents the treatment period after the first crossover. Period 2-1 represents the first treatment period after re-randomization.

Figure 3.
Intervention Compliance Rate by Randomized Treatment Period Length

Figure 4.
Intervention Compliance Rate by Elapsed Days from Treatment Period Start

Table 1

Treatment Period Length and Frequency

Length (mo.)	# of Clusters	Median Subjects per Cluster (IQR)	Median Number of Crossovers (IQR)
3	1	108.2 (--)	5.0 (--)
4-5	16	64.0 (59.1, 91.2)	0.5 (0, 2.3)
6	107	39.6 (8.4, 52.7)	0.0 (0.0, 1.0)
7-11	23	66.0 (57.5, 74.5)	0.0 (0.0, 0.0)
12	203	7.0 (4.0, 13.0)	1.0 (1.0, 1.0)

Table 2**Odds Ratios for Elapsed Time vs Intervention Compliance**

Covariate	OR (95% CI)
Elapsed Days from Treatment Period Start	
60 days	REF.
61-120 days	1.00 (0.88, 1.13)
121-180 days	1.01(0.89, 1.14)
181-240 days	0.90 (0.74, 1.10)
241-300 days	0.90 (0.73, 1.12)
>300 days	0.67 (0.52, 0.86)
Treatment Period Length	
3 months	REF.
4-5 months	0.97 (0.64, 1.47)
6 months	1.40 (1.07, 1.84)
7-11 months	0.61 (0.46, 0.82)
12 months	1.21 (1.03, 1.42)
Treatment Arm AE	REF.
Treatment Arm AL	0.84 (0.69, 1.03)

AE = Analyze Early; AL = Analyze Later

Table 3

Estimates for Elapsed Time vs Absolute Deviation from Intervention Target

Covariate	β (95% CI)
Elapsed Days from Treatment Period Start	
60 days	REF.
61-120 days	-3.54 (-10.92, 3.82)
121-180 days	-6.10 (-15.3, 3.07)
181-240 days	-1.48 (-11.21, 8.23)
241-300 days	3.63 (-6.43, 13.69)
>300 days	11.34 (0.47, 22.21)
Treatment Period Length	
3 months	REF.
4-5 months	-9.16 (-16.21, -2.11)
6 months	-15.00 (-22.64, -7.37)
7-11 months	2.71 (-13.17, 18.59)
12 months	-7.01 (-12.52, -1.49)
Treatment Arm AE	
Treatment Arm AL	-1.96 (-8.65, 4.74)

AE = Analyze Early; AL = Analyze Later

Table 4

Odds Ratios for Crossover vs Intervention Compliance

Covariate	OR (95% CI)
After Crossover	0.81 (0.57, 1.16)
Elapsed Days from Treatment Period Start	
60 days	REF.
61-120 days	0.98 (0.80, 1.20)
121-180 days	0.99 (0.80, 1.23)
181-240 days	0.82 (0.66, 1.01)
241-300 days	0.82 (0.65, 1.04)
>300 days	0.61 (0.46, 0.80)
Treatment Period Length	
3 months	REF.
4-5 months	0.32 (0.24, 0.44)
6 months	0.86 (0.63, 1.18)
7-11 months	0.32 (0.24, 0.43)
12 months	0.67 (0.54, 0.82)
Treatment Arm AE	REF.
Treatment Arm AL	0.79 (0.63, 0.98)

AE = Analyze Early; AL = Analyze Later