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Prevention of EP Migratory Contamination in a Cluster Randomized Trial to Increase tPA Use in Stroke (The INSTINCT Trial)

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Abstract

Objectives—Cluster randomized trials (CRTs) are increasingly utilized to evaluate quality improvement interventions aimed at healthcare providers. In trials testing emergency department interventions, migration of emergency physicians (EPs) between hospitals is an important concern, as contamination may affect both internal and external validity. We hypothesized that geographically isolating emergency departments would prevent migratory contamination in a CRT designed to increase ED delivery of tPA in stroke (The INSTINCT Trial).

Methods—INSTINCT was a prospective, cluster randomized, controlled trial. 24 Michigan community hospitals were randomly selected in matched pairs for study. Contamination was defined at the cluster level, with substantial contamination defined a priori as >10% of EPs affected. Non-adherence, total crossover (contamination + non-adherence), migration distance and characteristics were determined.

Results—307 emergency physicians were identified at all sites. Overall, 7 (2.3%) changed study sites. 1 moved between control sites, leaving 6 (2.0%) total crossovers. Of these, 2 (0.7%) moved from intervention to control (contamination) and 4 (1.3%) moved from control to intervention (non-adherence). Contamination was observed in 2 of 12 control sites, with 17% and 9% contamination of the total site EP workforce at follow-up, respectively. Average migration distance was 42 miles for all EPs moving in the study and 35 miles for EPs moving from intervention to control sites.

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Conclusion—The mobile nature of emergency physicians should be considered in the design of quality improvement CRTs. Increased reporting of contamination in CRTs is encouraged to clarify thresholds and facilitate CRT design.

Keywords

Research Methods; Emergency Medicine; Stroke; Quality Improvement

1. Introduction

In the face of a changing healthcare environment, interest in educational and quality improvement interventions that improve patient safety and outcomes continues to grow. Evaluating the impact of these interventions within the Emergency Department (ED) setting poses unique challenges, given the collaborative nature of patient care by physicians in a shift-work setting. Studying interventions targeted at a group, rather than at individuals, provides a unique way to assess the success of educational and quality improvement interventions on changing group behavior, and is well suited to the interventions targeting Emergency Physicians (EPs).

Cluster randomized trials (CRTs), also known as group- or place-randomized trials, are designed to assess interventions which operate on a group level, manipulate the physical or social environment, or cannot be delivered to individuals alone^{1, 2}. They are distinguished from randomized control trials (with individual subject randomization) by the use of the group as the unit of intervention and analysis. A group is defined by a physical, social, geographic or other connection among its members, such as the staff of a given hospital, and does not reflect their assignment (intervention vs. control) within a trial.

The CRT format can be utilized to study quality improvement and educational interventions in the ED setting by grouping physicians rather than studying individuals, as it is more feasible to provide an educational intervention to a group of physicians with shared patient-care responsibilities. Another advantage of CRTs is the ability to control for contamination between individuals within a specific group, defined as one individual's behavior change influencing another individual within a group^{1,2,3,4}. This concept of contamination is analogous to the more general concept of treatment crossover in randomized controlled trials, where individuals receive an intervention to which they were not initially randomized. Within a CRT, an individual at a site receiving the intervention who moves to a control site brings the effect of the intervention, should it exist to that control site.

The appeal of cluster randomization is that it reduces the opportunity for cross talk and observation when considering a physician-oriented intervention. If the unit of randomization was the individual physician and the hospital had physicians working alongside each other, observing each other's practice patterns, it is likely that contamination would occur with "leakage" of the intervention from the experimental to the control group. The advantage of allocating by group or site is clear when assessing educational and quality improvement interventions in healthcare.⁴ However, there are no significant studies of the CRT within the ED setting.

As with any other study technique involving random assignment, there are challenges to performing a successful CRT to minimize contamination, which threatens the validity of study results^{1,2,3,4}. Utilization of the CRT approach assumes that there is limited migration and limited contact among group members from sites assigned to different treatment arms. Study validity is threatened by a variety of factors. Contamination consists of the individual physician disseminating the experimental knowledge from the experimental group to the control group. A genuine desire for improving patient care, for instance, may encourage staff at hospitals assigned to an experimental arm (intervention) who change sites to share perceived changes from an educational or quality improvement intervention with staff in a study control arm (no intervention). Non-adherence occurs when an individual physician from the control group practices in an experimental group site, but continues to follow the control protocol. Controlling for both can be a particular challenge for studies involving EPs, who may be employed at multiple hospitals or change employment to a new hospital more readily than many other physicians⁵.

In this study, we suggest methods to control contamination between treatment arms in a CRT targeted to EPs. Hospital selection was designed specifically to reduce contamination in the INcreasing Stroke Treatment through behavioral INtervention Change Tactics (INSTINCT) trial⁶. This trial tested a multi-level barrier assessment and interactive educational intervention to increase emergency department tPA use in acute ischemic stroke at 24 randomly selected Michigan community hospitals. We hypothesized that geographically isolating participating hospitals and their emergency departments in the selection process would limit emergency physician crossover and therefore limit one threat to the trial's findings. We report here the effectiveness of this approach, as this provides new data, which may benefit study design by future researchers. To our knowledge, this is the first paper to study the application of a CRT design to an EM quality improvement or educational intervention. Further, there are no prior studies in the EM literature that evaluate geographic exclusion to minimize physician crossover and contamination in a CRT.

2. Methods

2.1 Study Design

This is a secondary analysis of an observational cohort study using prospectively collected data from the INSTINCT trial. The trial was approved by The University of Michigan and local Institutional Review Boards. The design and reporting of this secondary analysis were facilitated by the STROBE statement recommendations, a reporting guideline used in observational studies⁷. We have previously described how emergency physicians were identified and surveyed during the INSTINCT trial^{5,8}.

2.2 Study Setting and Population

The INSTINCT trial selected 24 Michigan hospitals at random, in matched pairs based on stroke volume. The study was initially designed with a multi-state Specialized Programs On Translational Research In Acute Stroke (SPOTRIAS) submission and was not designed to address state level effects. Hospitals were eligible for participation in the trial if they were located in the Lower Peninsula and had 100 annual stroke discharges; < 100,000 annual

emergency department visits; were not an academic comprehensive stroke center and did not have an affiliation with the University of Michigan Department of Emergency Medicine (the coordinating center). From the list of eligible hospitals, a single site was selected. All other hospitals within a 15-mile radius of the selected hospital were then excluded from the eligible hospital list, preventing their subsequent selection. The next hospital was then chosen randomly from the remaining eligible institutions. Hospitals were paired to achieve balance between experimental and control groups on annual ischemic stroke volume, urbanization, and for profit versus not for profit status. The emergency physicians staffing the 24 recruited hospitals represented the population of interest for the study.

2.3 Study Protocol

Individual attending emergency physicians staffing each site were identified by the local site Principal Investigator (PI) at baseline (2007) and 18 months post-enrollment. Primary pediatric emergency physicians were excluded from the cohort (as tPA is not approved in patients < 18 years of age). Resident physicians were also excluded. Each physician was classified by their location at the second time point as “unchanged” (same hospital as 2007), “new” (physician not present in 2007), “departed” (physician identified in 2007, but not at follow-up) or “migrated” (physician moved to different INSTINCT hospital between time periods).

An individual moving from a hospital in the INSTINCT trial experimental arm to a hospital in the control arm represented contamination of the control. Similarly, an individual moving from a hospital in the control arm to a hospital in the experimental arm represented non-adherence.

Migration distances were determined using driving directions from Google Maps. Hospitals were considered in the same healthcare system based upon individual communication with the INSTINCT site PIs along with confirmation of the association by inspection of the hospital website.

2.4 Outcome Measures

The primary outcome measure was the number of control hospitals with “substantial contamination.” This was defined a priori as >10% contamination of emergency physicians within a cluster. This was based on a consensus discussion of the INSTINCT trial leadership, because no specific quantitative guidance existed regarding an acceptable level of contamination within a CRT. While contamination is infrequently reported in CRTs, a prior review of health behavior interventions observed that contamination ranged from 0–65% in eight studies focused on patient level health educational interventions³. Secondary outcome measures included total contamination (number of EPs changing from intervention to control hospital within the total study population), total non-adherence (number of EPs changing from control to intervention sites within the total study population), total crossover (contamination + non-adherence) and migration distance.

2.5 Data Analysis

Descriptive statistics were calculated for all measures and are reported with median and absolute range or proportions with absolute count as appropriate. Contamination for an individual control hospital was calculated by determining the proportion of the total emergency physician staff at the follow-up time period, which had been identified as on staff at an intervention hospital in 2007. Data management and analysis were conducted using SAS 9.2 (Cary, NC). As the sample size for this secondary analysis was fixed by the design of INSTINCT (24 hospitals), we did not conduct a prospective power analysis for this observational study.

3. Results

307 emergency physicians were identified at all sites over both time periods. The median age of the EPs was 44 (absolute range 40–67). The characteristics of the physicians and hospitals are given in table 1. Overall, seven EPs (2.3%) changed study sites. One EP moved between control sites, leaving six (2.0%) total crossovers. Of these, two (0.7%) moved from intervention to control (contamination) and four (1.3%) moved from control to intervention (non-adherence). Contamination was observed in two of the 12 control sites, with 17% and 9% contamination of the total site EP workforce, respectively. Based on the predefined primary outcome of this analysis, only the hospital with 17% contamination achieved the definition of >10% contamination, therefore one out of twelve INSTINCT hospitals experienced contamination, or 8.3% (95% CI 1.5 – 35.3%). Two of six crossovers occurred between hospitals within the same health system. Average migration distance was 42 miles for all EPs in the study and 35 miles for EPs moving from intervention to control sites (Figure 1).

4. Discussion

To our knowledge, this is the first study to address application of a CRT to an EM quality improvement or educational intervention, and is the first study to address methods to control contamination in a CRT targeted towards EPs. Hospital selection was specifically designed to reduce contamination and data from this study may benefit future investigators who wish to employ a similar study design. In retrospect, taking into consideration emergency physician contract groups would have been an additional step to limit potential contamination. Such groups often have physicians who work in multiple hospitals.

The vast majority of EPs remained at their original assigned site. Migration distances far exceeded the 15-mile separation distance used in the study design (average migration distance of 42 miles). The 15-mile separation distance was chosen by consensus to minimize contamination, as there was no prior data to use as a guideline.

We hypothesize that an increased population density may have contributed to the increased frequency of migration as the majority of the changes occurred within southeast Michigan rather than within other, less densely populated portions of the state (Figure 1). The existence of regional hospital networks for sites included in the INSTINCT trial may have further contributed to increased migration rates for sites in the southeast portion of the state.

Given that 2 of 6 crossovers occurred within the same health system, this may be an additional factor influencing likelihood of EP crossover. Two of the included sites had observed contamination rates (17% and 9%), however, substantial contamination was low using the predetermined threshold (1 of 12 control sites). Only 2 of the 307 physicians in the study moved from intervention to control sites, therefore the difference in total contamination at the 2 affected sites is primarily a reflection of cluster size at those sites rather than EP crossover.

Given the overall low rate of EP migration, it may be possible to minimize contamination at the outset by placing hospitals within a health system within the same study arm. Based upon our findings, an exclusion zone of 45 miles would have further reduced crossovers. Larger exclusion zones may be challenging to incorporate into study design and may require inclusion of hospitals over a larger geographic region. It may also be possible to limit contamination by choosing study sites with more individuals in each cluster to minimize the impact of an individual physician changing sites. The applicability of this approach may be limited by study goals and primary outcomes. If the primary outcome of the study is to evaluate interventions at community hospitals, then exclusion of smaller sites may decrease the study's external validity.

Alternatively, the impact of an individual physician upon contamination rates may further emphasize the importance of minimizing EP crossover in initial study design, as a single EP crossover from intervention site to control site can cause significant contamination if the cluster size is small. If a small number of EPs were to migrate and cause contamination at several control sites, this could have a substantial impact on trial validity and interpretation of study outcomes. For instance, had there been more significant contamination in the INSTINCT trial with resulting increased tPA use at control sites, the final results could have demonstrated a diminished difference in usage between control and intervention sites, leading to a type II error in interpretation of the results⁸.

The impact of non-adherence on the behavior of other individuals at an intervention site is subject to debate; nevertheless it is still desirable to minimize these crossovers as well given their possible impact on final results and interpretation of outcomes. The number of EPs with non-adherence in the INSTINCT trial was small, however in larger numbers (particularly if crossover occurred later in the trial) this may also have attenuated the increase in tPA use and impacted trial results. Given the overall low number of turnover events (defined as any physician departure, arrival, or movement between INSTINCT hospitals), we were unable to identify any physician demographics or hospital characteristics which were associated with contamination or turnover⁵.

4.1 Limitations

This study examined only physical migration and crossover and did not assess other forms of contamination or non-adherence that may threaten study validity. It is likely the opportunity for such contamination is reduced given the imposed geographic separation but the data to prove this supposition is not available. The number of clinicians employed at additional hospitals not included in the INSTINCT trial is unknown, as is the rate of possible contamination had the 15 mile exclusion limit not been utilized in this study. Further, the

10% threshold for contamination defined in this study, although chosen a priori, has not been validated as clinically meaningful. We were able to evaluate the 15 mile exclusion distance within the confines of the INSTINCT trial, however the ideal exclusion distance has not been determined and may differ depending on geographic location and population density and other factors including what proportion of a state's population lives in a specific metropolitan area. Finally, we only evaluated the presence of the individual physicians and their movement within the study at two time points, approximately two years apart and additional movements could have occurred before, between, and after these measurements.

5. Conclusions

The mobile nature of emergency physicians should be considered in the design of quality improvement CRTs. Use of a 15-mile exclusion zone in hospital selection for this CRT was associated with very low levels of substantial cluster contamination (1 of 12 control sites) and total crossover. Degree of cluster contamination is impacted by cluster size, and choosing larger clusters may further minimize the impact of an individual who changes sites. Based upon the above data, assignment of hospitals from a single health system to a single study group or an exclusion zone of 45 miles would have further reduced crossovers. To our knowledge, no prior study has yet quantified what constitutes a sufficient distance to avoid cross-contamination in a CRT. Further studies may be needed to clarify physician or hospital characteristics associated with higher turnover rates. Increased reporting of contamination in CRTs is encouraged to clarify thresholds and facilitate CRT design.

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Figure 1.
EP Migratory Contamination in the INSTINCT Trial

Table 1**Characteristics of Hospitals and Emergency Physicians**

Characteristics	n	(%)*
Hospital Level (n=24)		
<u>Inpatient Beds</u>		
< 100	4	(17)
101 – 250	11	(46)
251 – 500	6	(25)
> 500	3	(13)
<u>Annual ED Volume (adult)</u>		
< 20,000	7	(29)
20,001 – 40,000	8	(33)
40,001 – 60,000	8	(33)
60,001 – 80,000	1	(4)
<u>Teaching hospital</u>	11	(46)
Physician Level		
n	(%)*	
<u>Female</u>	59/254	(23)
<u>Race or ethnic group</u>		
White	216/239	(90)
Non-white	23/239	(10)
Black	7/239	(3)
Asian	5/239	(2)
Hispanic	7/239	(3)
Other	4/239	(2)
<u>Education</u>		
EM residency training	220/255	(86)
Specialty board certification†		
Emergency medicine	231/255	(91)
Internal medicine	1/255	(0)
Family practice	8/255	(3)
Pediatrics	0/255	
None	9/255	(4)
Other	6/255	(2)
<u>Year of EM residency completion</u>		
1977 – 1986	14/193	(7)
1987 – 1996	80/193	(41)
1997 – 2006	99/193	(51)