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Clinical Paper

Quality of CPR: An important effect modifier in cardiac arrest clinical outcomes and intervention effectiveness trials☆

Demetris Yannopoulos[a,*], Tom P. Aufderheide[b], Benjamin S. Abella[c], Sue Duval[a], Ralph J. Frascone[a], Jeffrey M. Goodloe[d], Brian D. Mahoney[e], Vinay M. Nadkarni[f], Henry R. Halperin[g], Robert O'Connor[h], Ahamed H. Idris[i], Lance B. Becker[b], Paul E. Pepe[j]

[a] University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455, United States
[b] Medical College of Wisconsin, 9200 West Wisconsin, Milwaukee, WI 53226, United States
[c] University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, United States
[d] University of Oklahoma School of Community Medicine, 1145 S. Utica Ave, 6th Floor, Tulsa, OK 74104, United States
[e] Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415, United States
[f] University of Pennsylvania and Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, United States
[g] Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287, United States
[h] University of Virginia, P.O. Box 800699, Charlottesville, VA 22908, United States
[i] University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States
[j] University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8579, United States

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ABSTRACT

Objectives: To determine if the quality of CPR had a significant interaction with the primary study intervention in the NIH PRIMED trial.
Design: The public access database from the NIH PRIMED trial was accessed to determine if there was an interaction between quality of CPR performance, intervention, and outcome (survival to hospital discharge with modified Rankin Score (mRS) ≤3).
Setting: Multi-centered prehospital care systems across North America.
Patients: Of 8719 adult patients enrolled, CPR quality was electronically recorded for compression rate, depth, and fraction in 6199 (71.1%), 3750 (43.0%) and 6204 (71.2%) subjects, respectively. "Acceptable" quality CPR was defined prospectively as simultaneous provision of a compression rate of 100/min (±20%), depth of 5 cm (±20%) and fraction of >50%. Significant interaction was considered as $p < 0.05$.
Intervention: Standard CPR with an activated versus sham (inactivated) ITD.
Measurements and main results: Overall, 848 and 827 patients, respectively, in the active and sham-ITD groups had "acceptable" CPR quality performed ($n = 1675$). There was a significant interaction between the active and sham-ITD and compression rate, depth and fraction as well as their combinations. The strongest interaction was seen with all three parameters combined (unadjusted and adjusted interaction p-value, <0.001). For all presenting rhythms, when "acceptable" quality of CPR was performed, use of an active-ITD increased survival to hospital discharge with mRS ≤3 compared to sham (61/848 [7.2%] versus 34/827 [4.1%], respectively; $p = 0.006$). The opposite was true for patients that *did not* receive "acceptable" quality of CPR. In those patients, use of an active – ITD led to significantly worse survival to hospital discharge with mRS ≤3 compared to sham (34/1012 [3.4%] versus 62/1061 [5.8%], $p = 0.007$).
Conclusions: There was a statistically significant interaction between the quality of CPR provided, intervention, and survival to hospital discharge with mRS ≤3 in the NIH PRIMED trial. Quality of CPR delivered can be an underestimated effect modifier in CPR clinical trials.

1. Introduction

Interventions that create circulation and restore a stable heart rhythm during the first minutes of cardiopulmonary resuscitation (CPR) are critical for achieving survival after out-of-hospital cardiac arrest (OHCA), a leading cause of death in adults.[1–4] The American

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* Corresponding author.
E-mail address: yanno001@umn.edu (D. Yannopoulos).

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Heart Association (AHA) guidelines for CPR have recommended prompt delivery of chest compressions to limit the time of no or low flow and now have underscored the importance of recognizing, delivering and even measuring quality compression parameters to alter the outcomes from OHCA positively.[1–5]

The predominate determinants of blood flow generation during CPR that have been identified are chest compression rate, depth, and fraction (percentage of CPR time when chest compressions are being delivered without interruption).[6–11] Accordingly, as chest compressions (and the chest compression-decompression cycle) are performed primarily to generate blood flow, survival outcomes would likely depend upon the quality of CPR delivered.[5]

Other than timely defibrillation, there has been limited progress in confirming the effectiveness of other interventions that can improve outcomes beyond conventional closed chest CPR in the clinical setting.[1,4] Despite robust laboratory findings and positive results in smaller-scaled human trials, most highly promising cardiac arrest therapies have not been demonstrated to have clinical benefit when studied in large-scale, effectiveness trials.[12–14]

The National Institutes of Health (NIH) sponsored Resuscitation Outcomes Consortium (ROC) PRIMED trial was an example of such a trial.[13,14] The PRIMED trial evaluated an impedance threshold device (ITD) as a resuscitative adjunct during standard, manual CPR in a multi-center, randomized clinical trial (RCT).[14] Despite positive outcomes in preclinical and smaller clinical trials, however, no differences in survival to hospital discharge with favorable neurological function were identified when patients were randomized to receive active versus sham ITD devices in this large, effectiveness RCT.[14]

Since the design, implementation and completion of the PRIMED trial, evolving data and broader concerns regarding the interaction of CPR quality and outcomes have raised the issue of sub-optimal CPR performance as being a potential unrecognized effect modifier in resuscitation research and patient outcomes.[5] In turn, this concern raised the speculation that the effect of the ITD may have been masked by the quality of CPR performed. Few data exist to confirm the potential modifier effect of CPR quality on outcomes in any clinical resuscitation trial.

Based upon the fundamental physiology of closed chest CPR and the ITD itself, the participating authors here, including independent investigators not involved in the PRIMED trial, hypothesized that there would be a significant and clinically important interaction between outcome and the respective individual CPR quality parameters of chest compression rate, depth, and fraction, as well as the overall combination of all three parameters.[5]

Although, traditionally, secondary analyses of study data have been viewed with skepticism and often dismissed without consideration, the value of this function, even as an important hypothesis-generating scientific activity, has become increasingly important in the realm of RCT data.[15] For example, a recent study published in the Journal of the American Medical Association highlighted the notion that re-analysis of RCT data may help the scientific community assess the validity of reported trial results, particularly when the re-analysis involved prospectively collected blinded data (RCT) as well as the addition of independent expert authors not involved in the original trial. In several cases of such re-analyses, the conclusions and subsequent medical practices were altered.[15]

The ITD trial not only involved an RCT with a blinded intervention and prospectively collected data, including CPR quality parameters from numerous centers, but it was also an NIH-supervised multi-center trial with study groups and other comparative data well-matched.[14] As previously noted, even in otherwise well-designed resuscitation trials with well-matched groups and implementation, effect modifiers, such as ventilatory parameters, well-controlled in the laboratory, may not be recognized and controlled in the clinical setting.[12,16,17] Thus, in clinical trials, such modifiers may mask the effects of a study intervention on outcomes, making their recognition potentially important for clinical practice.

To test the hypothesis that quality of CPR was an outcome modifier in the ROC PRIMED Trial, investigators evaluated if there was a statistically significant interaction between the three different components of chest compression quality (rate, depth, and fraction) and their combinations, the tested interventions, and the original primary study outcome, survival to hospital discharge with a Modified Rankin Scale Score (mRS) $\leq$3 (favorable neurological function).

2. Materials and methods

2.1. Ethics approval, data source and investigators

The ROC PRIMED database was acquired from the NIH under the NIH Data Sharing Policy, three years following publication.[14] This de-identified database was re-analyzed independently from the ROC by the authors of the current study, including biostatisticians at the University of Minnesota, investigators who participated in the ROC PRIMED Trial and resuscitation researchers from institutions not participating in the ROC PRIMED Trial. The authors had no identifiable conflict of interest with the current investigation. The study was exempted from review by the University of Minnesota Institutional Research Board.

2.2. Population selection and study eligibility criteria

Detailed rationale and methodologies for the ROC PRIMED trial have been published.[12,14] The study was a prospective, randomized, double-blind, multi-center North American effectiveness trial performed by EMS personnel under an FDA Investigational Device Exception. Adult subjects found in OHCA were randomly assigned and treated with either a sham (un-activated) or active ITD (−16 cm resistance; manufacturer, Advanced Circulatory Systems, Inc., Roseville, MN).[14]

Sham and active devices were indistinguishable to rescuers. The first qualified EMS provider placed the ITD between the ventilation bag and the patient's airway device. All other resuscitative measures followed individual EMS agency standard operating procedures,[13,14] Participating EMS agencies generally followed the concurrent 2005 AHA Guidelines for CPR and Emergency Cardiovascular Care with occasional local variation in out-of-hospital treatment.

2.3. Data collection

All participating EMS agencies implemented an electronic system for monitoring individual components of CPR during the trial. CPR quality parameters were electronically recorded in subjects immediately following application of the defibrillation electrodes using thoracic impedance recorded from external defibrillation electrodes or via an accelerometer interface between the rescuer's hands and the patient's chest using commercially available defibrillators.[14] Electronic capture of the quality of CPR performed included chest compression rate, depth, and fraction. These data were used in a run-in phase to determine when sites qualified to start enrollment in the pivotal phase of the study. Although CPR quality was also monitored during the pivotal phase of the study, sites were not required to discontinue patient entry if they did not meet CPR quality benchmarks. Quality of CPR data linked to individual cardiac arrest subject records from the pivotal phase of the ROC study were available to the current authors from the NIH-provided database.[14]