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Clinical paper

Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest☆

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ABSTRACT

Background: Withdrawing life-sustaining therapy because of perceived poor neurological prognosis (WLST-N) is a common cause of hospital death after out-of-hospital cardiac arrest (OHCA). Although current guidelines recommend against WLST-N before 72 h (WLST-N < 72), this practice is common and may increase mortality. We sought to quantify these effects.

Methods: In a secondary analysis of a multicenter OHCA trial, we evaluated survival to hospital discharge and survival with favorable functional status (modified Rankin Score ≤3) in adults alive >1 h after hospital admission. Propensity score modeling the probability of exposure to WLST-N < 72 based on pre-exposure covariates was used to match unexposed subjects with those exposed to WLST-N < 72. We determined the probability of survival and functionally favorable survival in the unexposed matched cohort, fit adjusted logistic regression models to predict outcomes in this group, and then used these models to predict outcomes in the exposed cohort. Combining these findings with current epidemiologic statistics we estimated mortality nationally that is associated with WLST-N < 72.

Results: Of 16,875 OHCA subjects, 4265 (25%) met inclusion criteria. WLST-N < 72 occurred in one-third of subjects who died in-hospital. Adjusted analyses predicted that exposed subjects would have 26% survival and 16% functionally favorable survival if WLST-N < 72 did not occur. Extrapolated nationally, WLST-N < 72 may be associated with mortality in approximately 2300 Americans each year of whom nearly 1500 (64%) might have had functional recovery.

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Conclusions: After OHCA, death following WLST-N < 72 may be common and is potentially avoidable. Reducing WLST-N < 72 has national public health implications and may afford an opportunity to decrease mortality after OHCA.

Introduction

Cardiac arrest is the most common cause of death in the United States, with an estimated 326,000 out-of-hospital cardiac arrest (OHCA) victims assessed by emergency medical services (EMS) annually.[1] Between 50 and 89% of OHCA patients with return of spontaneous circulation (ROSC) die in the hospital.[2,3] Fear of survival with severe brain injury or belief that aggressive care is futile prompt some clinicians and proxies to choose withdrawal of life-sustaining therapy (WLST). WLST because of perceived neurological injury and assumed poor prognosis (WLST-N) is the most common proximate cause of death after OHCA.[4,5]

Current evidence-based guidelines recommend delaying WLST-N for at least 72 h after ROSC because, prior to this time, no clinical sign or test precludes a favorable neurological outcome and clinical examination is not reliable before that time point.[6–8] Even thereafter, the most accurate neurological predictors still do not have perfect specificity for predicting poor outcome,[10] and patients who remain comatose on post-arrest day 3 may still awaken and have favorable recoveries.[11] Despite this, WLST-N before 72 h (WLST-N < 72) is common.[5,12] Premature WLST-N after OHCA may increase mortality, reduce favorable neurological outcomes and confound the results of clinical trials.

In order to estimate the mortality resulting from premature WLST-N, we conducted a secondary analysis of a large randomized controlled trial (the Resuscitation Outcomes Consortium (ROC) PRIMED trial), which enrolled OHCA subjects at 151 hospitals across North America. During the trial, published guidelines differed from current guidelines and suggested that certain combinations of prognostic signs might be sufficient to preclude favorable outcome as early as 24 h after OHCA.[9] We quantified the incidence and timing of WLST-N and WLST-N < 72 in the ROC PRIMED cohort, then used a propensity-matched cohort to estimate the effect of WLST-N < 72 on outcome. Our primary hypothesis was that predicted survival in those exposed to WLST-N < 72 is greater than nil. Our secondary hypothesis was that there is between-hospital practice variation in WLST-N after adjustment for case mix.

Methods

Study design and patients

This is a secondary analysis of the ROC PRIMED trial (clinicaltrials.gov NCT00394706), conducted June 2007 to October 2009. Results of this trial, which tested the use of an impedance threshold device compared to a sham device and early versus late rhythm analysis and defibrillation in OHCA, have been reported.[13,14] No difference in outcomes was identified for either comparison. Subjects were ≥18 years old with EMS-treated OHCA. Excluded were OHCA arrests due to trauma or exsanguination, pregnant patients, and prisoners. In the present analysis, we included only the subgroup of subjects who had ROSC, were treated at any participating hospital and survived at least 60 min after hospital arrival.

Primary exposures and outcomes

Consistent with current guidelines, we defined WLST-N < 72 as WLST-N occurring within 72 h after arrest. Since the date, but not time, of WLST-N was recorded, we conservatively defined "WLST-N < 72″ as occurring within 2 calendar days after arrest. Therefore, exposure to WLST-N < 72 ranged between 61 min to 72 h after ROSC, but some patients categorized as exposed to WLST-N on or after day 3 might actually have been exposed between 49 and 72 h after ROSC and been misclassified. Research coordinators recorded the date and cause of death for all subjects in one of the following four categories: (1) "subject is unstable and continued life support is impossible or futile (including multiple system organ failure, recurrent cardiac arrest without ROSC, and intractable shock);" (2) "subject meets criteria for brain death;" (3) "subject is stable but care is withdrawn or limited because of non-neurological considerations (including underlying terminal illness, pre-existing advanced directives or surrogate's understanding of the subject's wishes);" or (4) "subject is deemed to have a poor neurological prognosis and care is withdrawn or limited resulting in death" (WLST-N). Of note, to guide neurological prognostication and the decision for WLST-N, the ROC PRIMED Manual of Operations recommended at a minimum "daily neurological assessment of [the] subject" with "two complete assessments at least 24 h apart" demonstrating "no improvement in neurological status over 3 days" and/or "ominous [electroencephalographic] or evoked potential evaluations." These recommendations were consistent with, but less specific than, the 2006 American Academy of Neurology consensus guidelines.[9] The Manual of Operations was distributed to EMS providers participating in the ROC PRIMED trial, but was not actively distributed to inpatient providers. EMS agencies were the unit of study in ROC PRIMED, and so subjects were transported to a range of hospitals including academic and non-academic centers. The ROC PRIMED trial team had no direct oversight of inpatient care of WLST practices and inpatient providers received no formal training as part of the study.

Primary outcomes were survival to hospital discharge and survival to discharge with favorable functional status at the time of discharge (modified Rankin Score (mRS) ≤ 3). We defined survival to hospital discharge as transfer to rehabilitation, a skilled nursing facility or home residence. mRS was assigned at hospital discharge using a standard instrument.

Covariates

In the present study, we selected a priori biologically plausible covariates for adjusted analyses. Demographic factors were age, gender, race or ethnicity, and residential status prior to arrest, which we categorized as home, rehabilitation, assisted living, nursing home or unknown. Elements of past medical history abstracted from the hospital record included presence or absence of coronary artery disease, past myocardial infarction (MI), congestive heart failure, past coronary artery bypass grafting, diabetes, dialysis dependence, illicit drug or alcohol use, cancer or terminal illness. Arrest-specific covariates were presenting rhythm, categorized as shockable (ventricular tachycardia, ventricular fibrillation, or shock administered by an automatic defibrillator), pulseless electrical activity, asystole, "no shock advised" by an automatic defibrillator, and unknown; intervals from 911 call to professional cardiopulmonary resuscitation (CPR) and from CPR initiation to ROSC; bystander CPR; presence of ST-elevation MI; and arrest