Resuscitation 121 (2017) 98–103

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Original paper

Association of antiplatelet therapy with patient outcomes after out-of-hospital cardiac arrest☆

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ARTICLE INFO

Article history:
Received 6 June 2017
Received in revised form
27 September 2017
Accepted 9 October 2017

Keywords:
Thrombosis
Hemostasis
Platelet inhibition
Anticoagulant
Cardiac arrest
Post-cardiac arrest syndrome

ABSTRACT

Background: Cessation of blood flow during out-of-hospital cardiac arrest (OHCA) results in microvascular thrombosis, protracted hypoperfusion after return of spontaneous circulation and damage to vital organs. We tested the hypothesis that pre-arrest antiplatelet and anticoagulant medication use would be associated with less post-arrest organ dysfunction and better outcomes.
Methods: We included OHCA patients treated from January 2005 to October 2014 at a single academic medical center. We combined our prospective OHCA registry of clinical and demographic data with a structured chart review to abstract home antiplatelet and anticoagulant medications. We fit unadjusted and adjusted regression models to test the association of antiplatelet and anticoagulant medication use with early post-arrest illness severity, survival and functionally favorable recovery.
Results: Of 1054 subjects, 295 (28%) were prescribed an antiplatelet agent and 147 (14%) were prescribed an anticoagulant prior to arrest. In adjusted models, antiplatelet agents were associated with lower post-arrest illness severity (adjusted OR 0.50 95% CI 0.33–0.77), greater odds of survival to discharge (adjusted OR 1.74 95% CI 1.08–2.80) and greater odds favorable functional outcome (adjusted OR 2.11 95% CI 1.17–3.79). By contrast, anticoagulation via any agent was not associated with illness severity, survival to discharge or favorable outcome.
Conclusion: Preventing intra-arrest and post-arrest microvascular thrombosis via antiplatelet agents could represent a novel therapeutic target to improve outcomes after OHCA.

Introduction

Over 350,000 Americans suffer a cardiac arrest outside of the hospital annually and more than 125,000 achieve return of spontaneous circulation (ROSC) and are treated in the hospital [1]. Despite advances in care, mortality in this cohort is common, with only a minority of admitted patients surviving to hospital discharge and even fewer experiencing functionally favorable recovery [2]. Initial brain and extracerebral organ injury resulting from anoxic-ischemic and reperfusion injury causes significant multisystem organ dysfunction in a majority of those with ROSC [3]. Ultimately, however, most patients' survival and recovery are limited primarily by the severity of brain injury rather than other organ failure [4,5].

Disordered thrombosis is an important and potentially modifiable mechanism of ongoing organ dysfunction after ROSC [6]. Hemostasis during cardiac arrest results in microvascular thrombosis, in turn leading to post-arrest organ hypoperfusion and areas of no-reflow that persist despite restoration of macrovascular flow [7]. The severity of both post-arrest brain and cardiopulmonary injury are strongly predictive of outcome [8,9]. Past investigational therapies to mitigate this phenomenon have focused on anticoagulant or thrombolytic agents [10–12]. Although animal work suggested that such drugs attenuate neurological damage after cardiac arrest

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.10.1016/j.resuscitation.2017.10.007

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https://doi.org/10.1016/j.resuscitation.2017.10.007
0300-9572/

[12,13], these have not translated well into human research [14,15]. Although the contribution of platelet inhibition in acute thrombosis is recognized, and their use widespread in other cardiovascular diseases, little is known about the effects of platelet inhibition on microvascular thrombosis and blood flow after cardiac arrest [16,17].

We sought to test whether current antiplatelet and anticoagulant medication use at the time of arrest were independently associated with outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA). We hypothesized that these medicines would reduce the severity of early post-arrest organ dysfunction, resulting in improved survival and functional outcomes at hospital discharge.

Methods

Setting and population

We included subjects admitted to a single academic medical center after resuscitation from OHCA from January 2005 to October 2014. Consistent with prior definitions, we considered arrests outside of the hospital setting or in the emergency department to be OHCA. We identified subjects from our prospective registry, and excluded those who were under 18 years of age as well as those who arrested secondary to trauma or a primary neurological catastrophe. At our hospital, an established Post-Cardiac Arrest Service (PCAS) coordinates these patients' care, as we have previously described in detail [18,19]. Briefly, our role includes partnering with emergency and critical care providers to ensure a consistent package of initial resuscitation and diagnostic workup, intensive care, multimodal neurological prognostication, secondary prevention and post-acute rehabilitation.

Predictors

Our primary predictors of interest were anticoagulant or antiplatelet medication use immediately prior to the arrest. We considered patients to be exposed to these medications if they had an active and pharmacy-filled prescription (e.g. a 30 day medication supply filled in within 30 days of presentation, a 90 day supply filled within 90 days, etc) of at least one anticoagulant or antiplatelet medication, respectively, at the time of their arrest. We classified alteplase, argatroban, bivalirudin, apixaban, dabigatran, rivaroxaban, dalteparin, enoxaparin, fondaparinux, unfractionated heparin, and warfarin as anticoagulants. We classified anagrelide, ASA, cilostazol, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticlopidine, ticagrelor, tirofiban, triflusal, and vorapaxar as antiplatelet agents. As a surrogate measure of medical and pharmacy access prior to arrest, we also determined whether each patient was prescribed any medication as a binary measure. We performed a structured chart review to derive these data from the electronic medical record. We used multiple sources within the EMR in this search including emergency department and admission physician and nursing documentation. In addition to this documentation, it is our institutional policy that an emergency department-based pharmacist reconciles all admitted patients' medication lists via direct contact with families, nursing home records, outpatient clinic documentation, and by directly contacting the outpatient pharmacy used by the patient to obtain last fill dates. We treated these exposures as binary predictors and made no adjustment according to dose or number of each agents prescribed (e.g. single vs dual antiplatelet therapy). We abstracted standard clinical and demographic data from our registry: age, sex, initial shockable rhythm, witnessed arrest, layperson cardiopulmonary resuscitation (CPR), and emergent cardiac catheterization [20]. "Cardiac etiology" of cardiac arrest was defined as arrest due to acute coronary syndrome, primary cardiac dysrhythmia, structural heart disease or either left or right ventricular failure, which we determined using a structured chart review.

Outcomes

Our primary outcome of interest was post-arrest illness severity, which we operationalized using each patients' prospectively assigned Pittsburgh Cardiac Arrest Category (PCAC). PCAC is a validated, 4-level ordinal predictor of outcome based on severity of neurological and cardiopulmonary injury after cardiac arrest [3,9]. We assign PCAC prospectively based on the best neurological and cardiopulmonary function in the first 6 h after ROSC. Briefly, levels of PCAC are:

I – Mild or no brain injury, awake;

II – Moderate brain injury without severe cardiopulmonary dysfunction;

III – Moderate brain injury with cardiopulmonary dysfunction; and,

IV – Severe brain injury with loss of some or all brainstem reflexes.

As secondary outcomes, we examined dysfunction of separate organ systems. Because PCAC incorporates both neurological and cardiopulmonary failure, as a separate analysis we analyzed it as a 3- level outcome, grouping Category II and III patients together. We also examined measures of cardiopulmonary dysfunction, including post-arrest ejection fraction, PaO2 to FiO2 ratio, and peak troponin level.

Additional secondary outcomes were survival to hospital discharge and favorable functional status at hospital discharge. We defined a favorable functional outcome based on discharge disposition, with discharge to home or to acute rehabilitation considered good outcomes and discharge to a skilled nursing facility, long-term acute care facility, hospice or death considered unfavorable functional outcomes [21].

Statistical analysis

We summarized baseline characteristics and report means with standard deviations (SD). In our main analysis, we tested the association between outpatient antiplatelet/anticoagulant medications and PCAC. First, we used unadjusted ordinal logistic regression to test the association between each predictor and PCAC, and standard unadjusted logistic regression to predict survival to discharge and functionally favorable outcome. Then, we built adjusted models to predict each outcome that included medication and other predictors with univariable associations significant at a level of $P \leq 0.1$. Using this method, our final model predicting PCAC included age, shockable rhythm, and witnessed status, in addition to antiplatelet and anticoagulant medication use. Our models predicting outcome at hospital discharge included age, shockable rhythm, witnessed status, and cardiac catheterization as covariates.

Because accurate information about arrest etiology was only available for the subset of the cohort presenting after February 2012, we ran separate models with (n = 1054) and without (n = 466) this predictor and compared the stability of the odds ratios between models. In a *post hoc* analysis, we adjusted for any current medication use as a binary predictor. Our intent was to address a potential confounding effect of access to pre-arrest medical care whereby antiplatelet medication use might simply be a marker of better access. We forced this covariate in each final adjusted model, and compared the effects for antiplatelet and anticoagulant medication usage with and without this adjustment. Finally, we used rank sum tests to compare peak troponin, left ventricular ejection fraction and PaO2:FiO2 ratio between categories of antiplatelet or antico-