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Trends Over Time in Drug Administration during Adult In-Hospital Cardiac Arrest

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Abstract

Objective: Clinical providers have access to a number of pharmacologic agents during in-hospital cardiac arrest (IHCA). Few studies have explored medication administration patterns during IHCA. Herein, we examine trends in use of pharmacologic interventions during IHCA both over time and with respect to the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guideline updates.

Design: Observational cohort study.

Setting: Hospitals contributing data to the AHA Get With The Guidelines–Resuscitation database between 2001–2016.

Patients: Adult IHCA patients.

Interventions: The percentage of patients receiving epinephrine, vasopressin, amiodarone, lidocaine, atropine, bicarbonate, calcium, magnesium, and dextrose each year were calculated in patients with shockable and non-shockable initial rhythms. Hierarchical multivariable logistic regression was used to determine the annual adjusted odds of medication administration. An interrupted time series analysis was performed to assess change in atropine use after the 2010 AHA guideline update.

Measurements and Main Results: A total of 268,031 index IHCAs were included. As compared to 2001, the adjusted odds (aOR) of receiving each medication in 2016 were: epinephrine (aOR 1.5, 95%CI 1.3, 1.8), vasopressin (aOR 1.5, 95%CI 1.1, 2.1), amiodarone (aOR 3.4, 95%CI 2.9, 4.0), lidocaine (aOR 0.2, 95%CI 0.2, 0.2), atropine (aOR 0.07, 95%CI 0.06, 0.08),

bicarbonate (aOR 2.0, 95%CI 1.8, 2.3), calcium (aOR 2.0, 95%CI 1.7, 2.3), magnesium (aOR 2.2, 95%CI 1.9–2.7, $p<0.0001$), and dextrose (aOR 2.8, 95%CI 2.3, 3.4). Following the 2010 AHA guideline update, there was a downward step-change in the intercept and slope change in atropine use ($p<0.0001$).

Conclusions: Prescribing patterns during IHCA have changed significantly over time. Changes to AHA ACLS guidelines have had a rapid and substantial effect on the use of a number of commonly used IHCA medications.

Keywords

Cardiac arrest; Guideline; Atropine; Vasopressin

Introduction

In-hospital cardiac arrest (IHCA) is a relatively common and highly morbid event.(1) Advanced Cardiac Life Support (ACLS) providers commonly have access to a number of pharmacologic interventions and need to make quick decisions regarding medication administration. To assist with decision-making, the American Heart Association (AHA) publishes algorithms which can be used to guide resuscitative efforts.(2–5) These algorithms are widely taught to ACLS providers and provide recommendations regarding the selection/timing of certain medications. (6) To date, however, trends in IHCA drug administration remain unexplored and usage of those medications not explicitly included in the cardiac arrest algorithms is largely unknown.

Updates to the AHA guidelines in 2000, 2005, 2010, and 2015 have included modifications to drug administration recommendations. In the most recent 2015 recommendations, for instance, vasopressin was removed from the ACLS algorithm to increase simplicity.(3) Atropine was removed from the pulseless electrical activity (PEA) and asystole guidelines in 2010.(4) Amiodarone was introduced as a first-line antiarrhythmic for shock-refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) in 2000.(5) Delays in guideline implementation are well described and may be associated with preventable harm. (7) Given the common requirement that acute care providers receive standardized training/certification in ACLS,(6, 8) there is a unique opportunity to study the impact of this dissemination model on the assimilation of society guidelines into practice.

In the present study, we leverage the AHA Get With The Guidelines Resuscitation (GWTG-R) database to investigate trends in IHCA drug administration. We additionally seek to understand how updates to the AHA ACLS algorithm impact medication prescribing patterns, as this may shed light on the effectiveness of the ACLS training model. Finally, we aim to describe the use medications not incorporated into the AHA ACLS algorithms, so as to better direct research and educational initiatives.

Materials & Methods

Data Source

The GWTG-R database is a large, prospectively collected, quality-improvement registry of IHCA events sponsored by the AHA. Hospitals participating in the registry submit clinical information and outcomes for consecutive patients using an online Patient Management Tool (Quintiles, Cambridge, Massachusetts). The design, data collection, and quality control of the repository have been described previously.(9, 10) Data are collected prospectively on all IHCAs who do not have prior do-not-resuscitate orders.

This research was classified as non-human research by the Beth Israel Deaconess Medical Center Institutional Review Board.

Study Population

Index adult IHCA events in the GWTG-R database were included. Events from the years 2000 (the year of the start of the registry) and 2017 (for which data entry was ongoing at the time of analysis), events listed as occurring in a pediatric area, events missing hospital-level information, and events without chest compressions were excluded.

Medication Exposures & Definitions

The GWTG-R database includes medications provided following pulselessness and prior to return of spontaneous circulation (ROSC) or death. These medications include epinephrine, vasopressin, amiodarone, lidocaine, calcium, magnesium, atropine, dextrose, and bicarbonate. Timing of drug administration is only collected for epinephrine and vasopressin. Shockable rhythm is defined as pulseless VT/VF and non-shockable rhythm is defined as PEA or asystole.

Updates to AHA ACLS Guidelines & Prescribing Patterns

We hypothesized that changes to the AHA ACLS algorithms would have an effect on medication prescribing patterns in the year following guideline update. Specifically, we *a priori* planned to assess changes in atropine use after 2010 and vasopressin use after 2015. These time points and medications were selected to reflect major deletions from the algorithm.

Statistical Analysis

Descriptive statistics were used to characterize the study population. Continuous variables are reported as medians with interquartile ranges. Categorical variables are reported as counts with frequencies. Rates of use for each medication were calculated for each year and then presented graphically over time.

For each of the above medications of interest, multivariable logistic regression with generalized estimating equations (GEE) and an exchangeable variance-covariance structure was used to assess the relationship between event year and medication. For these analyses, year was considered as a categorical variable (2001 used as a reference). Covariates in the GEE model, chosen by the authors as those most likely to be associated with prescribing

patterns, are listed in Supplemental Table e1 (see Supplemental Table e2 for variable definitions).

To assess the effect of guideline updates on atropine prescribing patterns, we performed interrupted time series analyses using segmented linear regression with GEE. For large datasets, linear regression is valid even for binary outcomes and often provides more easily interpretable results.⁽¹¹⁾ The model included all covariables described above, in addition to variables estimating the pre-intervention trend, change in level following the intervention, and the post-intervention trend. To reflect the timing of the updated guideline publication in October 2010, the pre-intervention time included all of the year 2010.⁽⁴⁾ As our cohort only included one year after 2015, segmented regression could not be performed to assess changes in vasopressin use. Instead, the reference year in the multivariable GEE was changed to 2015 and the annual adjusted odds ratio (aOR) for receiving vasopressin was assessed with respect to the updated reference year.

Events in which data was missing for any of the included covariates were excluded (22.1% of all cases, Supplemental Table e3). As a sensitivity analysis, multiple imputation was performed using chained equations and under the assumption that data were missing at random. A total of 20 unique datasets were created and the models re-created in each dataset. The results for each model were then combined across datasets. As not all hospitals contributed data throughout the study period, unadjusted trends in medication use were also assessed in post-hoc sensitivity analyses wherein the cohort was limited to only those hospitals contributing data on at least 5 IHCAs per year throughout the study period. *p*-Values <0.05 were considered statistically significant. All statistics were performed using STATA, version 14 (College Station, TX, StataCorp LP, USA).

Results

Study Population

A total of 268,031 IHCA events occurring in 712 hospitals were included (see Figure 1 for cohort selection). The number of arrests per year recorded in the database increased over time from 7,333 events in 2001 to a maximum of 22,603 events in 2015. The median age of patients was 67 (IQR 56–78) years, 42% were female, and most events had a non-shockable initial rhythm (82%). The duration from event recognition to ROSC/death, decreased over time from a median of 20 (IQR 12–31) minutes in 2001 to 13 (IQR 5–26) minutes in 2016 (*p*<0.0001, Supplemental Figure e1). A total of 12,366 (4.6%) patients received no intra-arrest medications.

Vasopressors

Epinephrine was used in 235,360 (87.8%) arrests, including 32,756 (73.7%) arrests with an initial shockable rhythm and 185,530 (92.7%) arrests with an initial non-shockable rhythm. Since 2001, epinephrine has been used in between 71.7% and 77.2% of arrests with an initial shockable rhythm and between 92.1% and 93.6% of arrests with an initial non-shockable rhythm (see Figure 2a). Patients in 2016 had greater odds of receiving epinephrine

during their arrest than patients in 2001 (aOR 1.52, 95%CI 1.28, 1.80, $p<0.0001$, see Figure 2b).

Vasopressin was used in 27,487 (10.3%) arrests, including 4,203 (9.5%) arrests with an initial shockable rhythm and 21,666 (10.8%) of arrests with an initial non-shockable rhythm. Use of vasopressin increased between 2001 and 2007 then largely remained stable until rates of use declined in 2015 and 2016 (see Figure 2a). Using 2015 as the reference year, odds of vasopressin use were lower in 2016 (aOR 0.38, 95%CI 0.33, 0.45, $p<0.0001$, see Figure 2b).

Antiarrhythmics

Amiodarone was used in 46,456 (17.3%) arrests, including 19,563(44.0%) arrests with an initial shockable rhythm and 24,386 (12.2%) arrests with an initial non-shockable rhythm. The rate of amiodarone use increased over time between 2001 and 2016 (see Figure 3a). After multivariable adjustment, patients in 2016 had greater odds of receiving amiodarone during their arrest than patients in 2001 (aOR 3.39, 95%CI 2.90, 3.96, $p<0.0001$; see Figure 3b).

Lidocaine was used in 19,423 (7.2%) arrests, including 9,863 (22.2%) arrests with an initial shockable rhythm and 8,521 (4.3%) with an initial non-shockable rhythm. The rate of lidocaine use decreased over time between 2001 and 2016 (see Figure 3a). After multivariable adjustment, patients in 2016 had lower odds of receiving lidocaine during their arrest as compared to patients in 2001 (aOR 0.19, 95%CI 0.16, 0.22, $p<0.0001$; see Figure 3b).

Atropine

Atropine was used in 139,332 (52.0%) of arrests, including 16,488 (37.1%) with an initial shockable rhythm and 112,826 (56.4%) with an initial non-shockable rhythm. Rates of atropine use were similar between 2001 and 2010 before declining between 2011 and 2016 (see Figure 4a). After multivariable adjustment, patients in 2016 had lower odds of receiving atropine during their arrest as compared to patients in 2001 (aOR 0.07, 95%CI 0.06–0.08, $p<0.0001$; see Figure 4b). In the interrupted time series analysis, there was a downward step-change in the intercept and downward slope change when comparing the pre and post-intervention period in both those with an initial shockable rhythm (intercept change 26.1%, 95%CI 20%–32.7%, $p<0.0001$, slope change 3.1%/year, 95%CI 2.8%–3.4%, $p<0.0001$) and those with an initial non-shockable rhythm (intercept change 23.6%, 95%CI 19.5%–27.7%, $p<0.0001$, slope change 7.3%/year, 95%CI 6.7%–7.6%, $p<0.0001$). (see Supplemental Figure e2). This finding persisted after adjustment ($p<0.0001$) and was similar when quarterly time intervals were used in place of years (see Supplemental Figure e3).

Electrolytes and Others

The rates of use of bicarbonate, calcium, magnesium, and dextrose have all increased over time (see Figure 5a with rates of medication use stratified by initial rhythm). As compared to the year 2001, patients in the year 2016 had higher odds of receiving bicarbonate (aOR 2.01, 95%CI 1.77, 2.27, $p<0.0001$), higher odds of receiving calcium (aOR 1.99, 95%CI 1.72, 2.30, $p<0.0001$), higher odds of receiving dextrose (aOR 2.76, 95%CI 2.25–3.39, $p<0.0001$),

and higher odds of receiving magnesium (aOR 2.23, 95%CI 1.89–2.65, $p < 0.0001$, See Figure 5b).

Results of analyses following multiple imputation are included in the data supplement (see Supplemental Table e4) and are similar to the complete case analysis. When restricting the analysis to hospitals providing data for the entire period ($n = 27,081$ from 21 sites), trends in medication use were consistent with those in the full cohort (see Supplemental Figures e4–e7). The results of the segmented regression analysis for atropine were likewise similar to those in the full cohort, although the magnitude was reduced (see Supplemental Table e5).

Discussion:

Temporal trends in medication use during IHCA have not been comprehensively described but are essential in order to evaluate current practice, better understand implementation science in resuscitation medicine, and guide future ACLS guideline updates. In this study, the use of epinephrine, amiodarone, bicarbonate, calcium, magnesium, and dextrose were found to have increased over time. The increased use of some medications comes despite shorter arrest durations. Lidocaine, atropine, and vasopressin have declined in use since 2001, 2010, and 2015 respectively. These findings are robust to multivariable adjustment controlling for hospital, patient, and arrest-level factors.

The AHA ACLS training model, with the near-universal requirement of hospital-based healthcare professionals in the United States participating in IHCA response to maintain certification biannually,(6, 8, 12, 13) allows for rapid dissemination of guideline updates. The effect of the ACLS training model on medication prescribing patterns is perhaps most saliently reflected by atropine use. Atropine was removed from the ACLS algorithm in 2010—not necessarily due to new high-quality evidence of ineffectiveness/harm, but rather as a result of a review of existing literature.(4) Nevertheless, the proportion of patients receiving atropine declined substantially each year between 2011 and 2016 and fell nearly 50% within 2 years of the update. These results are similar to those seen in an OHCA population.(14)

Further demonstrating the effect of guideline change on clinical practice, the proportion of patients receiving amiodarone increased by nearly 50% between 2001 and 2002 following the inclusion of amiodarone as a first-line treatment of shock-refractory VF and pulseless VT in 2000.(5) While data prior to 2001 were not included in the present study, the use of amiodarone was likely low given that intra-arrest use was rarely reported until the late 1990s.(15–18) The change in clinical practice is particularly notable given that the landmark study by Kudenchek et al. was published in 1999; just one year prior to the ACLS update. (18) Furthermore, amiodarone use steadily increased over time while lidocaine use fell following stronger language in the guidelines favoring amiodarone over lidocaine (2, 4), and finally the removal of lidocaine from the VF/pulseless VT pictorial algorithm (though remained in the text) in 2010.(4) The slower decline in lidocaine use after 2010, as compared to the decline in atropine use over the same period, may be due to a more gradual de-emphasis of lidocaine in the guidelines and the continued presentation of lidocaine as an alternative to amiodarone in the guideline text.

Vasopressin was introduced as part of the ACLS cardiac arrest algorithm in 2000, at which time it was thought that it “may be a more effective pressor agent than epinephrine.” (5, 19–21) Our data show a consistent increase in vasopressin use after the 2000 update. (5) In 2005 and 2010, vasopressin was deemphasized in the ACLS algorithm and was removed in 2015 based on evidence showing no benefit over epinephrine and to limit complexity.(22–25) These changes are again reflected in our data, with the proportion of patients receiving vasopressin falling from 10.9% in 2015 to 4.7% in 2016. It is notable, however, that vasopressin use began to decline a year prior to the 2015 guideline update, suggesting a potential role of external factors—including increases in medication cost.(26)

While the AHA does not recommend the routine use of bicarbonate, calcium, and magnesium during ACLS outside of certain situations (e.g. magnesium in torsades de pointes) (2–5, 27, 28), our study found an increase in their use between 2001 and 2016. Bicarbonate was used in nearly 50% of all IHCAs in 2016. This is notable given recent bicarbonate shortages.(29) Dextrose use also rose, despite evidence suggesting that the administration of dextrose during IHCA is associated with worse outcomes.(30) That use of bicarbonate, calcium, dextrose, and magnesium appears to be increasing over time may be related to the fact that these medications are not listed on the ACLS graphical algorithm (aside from magnesium in the 2005 VF/VT algorithm), that recommendations surrounding the use of these medications have not changed, and/or that there remain certain indications for their use (i.e. calcium for hyperkalemia). Understanding the situations in which these medications are being used during IHCA may be helpful in directing future research.

Delays in the implementation of clinical guidelines into routine patient care are well described in other medical fields, and longer delays may be associated with harm.(7, 31, 32) Resuscitation science, generally, is no exception with many investigators highlighting uneven implementation of new science.(33–36) The data presented here arguably show a more rapid uptake of updated ACLS medication guideline recommendations into practice than might be expected. We hypothesize that this more rapid uptake is related to the AHA ACLS training model and the quick decision making required during IHCA which promotes an algorithmic response. Nevertheless, while ACLS guideline changes appear to have an effect on prescribing practices overall, some clinicians continue to use medications in ways that are not congruent with current guidelines. For instance, approximately 20% of patients with initial non-shockable rhythms received atropine in 2016. These findings may be related to individual interpretation of the existing literature as opposed to incomplete guideline penetration, but clearly there is a knowledge gap which could be addressed with a more granular approach (e.g. provider surveys) to studying prescribing patterns.

Our study was limited in that the GWTG-R registry only collects the initial recorded rhythm of each arrest and does not account for changes in rhythm during IHCA. In addition, we did not assess the relationship between drug administration and patient outcomes in this study due to lack of time-to-administration data for most medications and the related risk of bias. (37) Our analysis was limited to hospitals participating in GWTG-R, which may be more responsive to AHA guidelines and limits international generalizability. Discontinuous years of GWTG participation may have resulted in hospital-level variation with respect to

medication prescribing. Finally, we were unable to assess other factors that may have influenced the use of medications such as cost/availability.

Conclusions:

Significant temporal variability exists in the use of various pharmacologic interventions during IHCA. Updates to AHA ACLS guidelines were associated with rapid and substantial changes to certain IHCA medication prescribing patterns. This information can be used to understand current practice and guide future AHA ACLS updates and implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Cohort selection

Figure 2:

a) Rates with 95% confidence intervals of epinephrine and vasopressin use over time.

Dashed vertical lines indicates years new guidelines were published. b) Adjusted odds with 95% confidence intervals of receiving epinephrine and vasopressin each year with respect to the year 2001 [reference]

Figure 3:

a) Rates with 95% confidence intervals of amiodarone and lidocaine use over time. Dashed vertical lines indicates years new guidelines were published. b) Adjusted odds with 95% confidence intervals of receiving amiodarone and lidocaine each year with respect to the year 2001 [reference]

Figure 4:

a) Rates with 95% confidence intervals of atropine use over time overall and by initial rhythm. Dashed vertical lines indicates years new guidelines were published. b) Adjusted odds with 95% confidence intervals of receiving atropine each year with respect to the year 2001 [reference]

Figure 5:

a) Rates with 95% confidence intervals of electrolyte and other medication use over time. Dashed vertical lines indicates years new guidelines were published. b) Adjusted odds with 95% confidence intervals of receiving electrolytes and other medications each year with respect to the year 2001 [reference]