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Use of therapeutic hypothermia among patients with coagulation disorders – A Nationwide analysis☆

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ABSTRACT

Objectives: The study aimed to assess the impact of therapeutic hypothermia (TH) on bleeding and in-hospital mortality among patients with coagulation disorders (CD).
Background: TH affects coagulation factors and platelets putting patients at risk for bleeding and worse outcomes. Effect of TH among patients with CD remains understudied.
Methods: Between 2009 and 2014, a total of 6469 cases of TH were identified using the National Inpatient Sample out of which 1036 (16.02%) had a CD. The incidence of bleeding events, blood product transfusion and in-hospital mortality was compared between patients with and without CD using one to one propensity score matching.
Results: Proportion of patients with CD increased during study duration from 13.0% to 17.4% from 2009 to 2014. Propensity matching was performed to adjust for baseline differences with 799 patients in both groups depending on presence or absence of CD. Patients with CD had a higher rate of bleeding events (13% vs. 8.5%; adjusted odds ratio 1.60; 95% confidence interval 1.16-2.23; P = 0.004), and blood product transfusion (25.0% vs. 14.1%; aOR 2.03; 95% CI 1.56-2.63; p < 0.001) compared to those without CD. There was no difference in rate of intracranial bleeding or hemorrhagic strokes between those with and without CD (3.3% vs. 3.2%; p = 0.88). There was no difference in mortality between patients with CD and those without (74.5% vs. 74.8%, aOR 0.98, 95% CI 0.78–1.23; P = 0.86).
Conclusions: Use of TH with CD resulted in more bleeding events and blood product transfusion but there was no difference in hospital mortality.

Introduction

Hypothermia has historically been associated with the development of several coagulation defects, however newer studies have challenged this long held belief [1]. The effects of hypothermia on coagulation have mostly been studied *in vitro*. Hypothermia has been shown to affect coagulation by several mechanisms affecting synthesis and kinetics of clotting enzymes or plasminogen activator inhibitors, decreasing fibrinogen levels, inducing platelet dysfunction and lowering platelet counts resulting in an increased prothrombin time, partial thromboplastin time, and clotting and bleeding times [2,3]. Temperatures lower than 33 °C are typically known to cause alterations within the coagulation cascade [4]. A majority of the clinical data associating hypothermia with worse morbidity and mortality comes from studying trauma and perioperative management [5]. On the other hand, deliberate induction of moderate therapeutic hypothermia (TH) following cardiac arrest has been shown to improve neurological outcomes [6].

Abbreviations: TH, therapeutic hypothermia; AHA, American Heart Association; CD, coagulation disorder; HCUP-NIS, Healthcare Cost and Utilization Project—Nationwide Inpatient Sample; CCS, Clinical Classification Software; AHRQ, Agency for Healthcare Research and Quality; DRG, diagnosis related group; ADP, adenosine diphosphate.

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According to a report by the AHA, an estimated 356,500 adults suffered out-of-hospital cardiac arrest during the year of 2016 [7]. Current guidelines on 'Cardiopulmonary Resuscitation and Emergency Cardiovascular Care' recommend induction of TH at a temperature of 32 °C to 36 °C for 12–24 h for all comatose patients with return of spontaneous circulation after cardiac resuscitation [8]. Reduction in metabolism and oxygen consumption within the brain, glutamate release inhibition, inhibition of apoptosis, and reduced inflammation are among the mechanisms by which TH exerts its benefits. Hypothermia is also associated with a multitude of side effects, notably, hypertension, arrhythmias, electrolyte imbalance, pneumonia, sepsis, impaired coagulation and bleeding [9].

With the background of hypothermia induced coagulation abnormalities, contraindication to use of TH among patients with significant bleeding (intracranial or non-compressible site bleeding), and demonstration of TH-related bleeding among specific cardiac populations [10], we sought to evaluate outcomes among patients with an underlying coagulation disorder (CD) who received TH during hospitalization.

Methods

Data source and study population

We conducted our analysis on hospital discharge data from the Healthcare Cost and Utilization Project—Nationwide Inpatient Sample (HCUP-NIS) from 2009 through 2014. Annually, the NIS is composed of discharge-level data from roughly 8 million hospitalizations and approximates a stratified sample of 20% of community hospitals in the United States. Core hospital stay files contain details on patient demographics (e.g., age, sex, race), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) diagnosis codes (15–30, depending on the year), Elixhauser comorbidities [11], length of hospital stay, discharge status, in-hospital mortality and total charges among other variables. Patients aged more than 16 years who received TH during hospital stay (ICD-9CM procedure code 99.81) were included in the study. Those missing mortality data or transferred out-of-hospital were excluded from the study. Death was defined in the NIS as in-hospital mortality. Bleeding event was defined by the presence of at least one the following: hemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, hemoptysis and unspecified hemorrhage. Different comorbidities were identified by using ICD-9CM diagnoses and diagnosis-related group (see Appendix). Severity of co-morbid conditions were defined using the Elixhauser comorbidity score which is a sum of the 29 Elixhauser comorbidity variables within database. The score ranges from 0 to 33, with higher scores corresponding to greater burden of co-morbid diseases.

We analyzed the trends in use of TH within the overall study population and among patients with a CD. We additional examined the trends in hospital mortality within patient subsets depending on the presence or absence of an associated CD. The primary outcome of our study was difference in hospital mortality. Secondary outcomes included any bleeding event and transfusion of blood products. Outcome comparisons were made between patients with a CD (Elixhauser comorbidity variable:CM_COAG) to those without. The AHRQ comorbidity software assigns CM_COAG as a comorbidity by strictly restricting its search to those secondary diagnoses that are not directly related to principal diagnosis/DRG assignment for each patient. It excludes complications that might have originated during the hospitalization as a result of diagnostic or therapeutic interventions. Details on types of coagulopathy, frequency of occurrence and related events can be seen in Appendix.

Statistics

Demographics and baseline characteristics were summarized using descriptive statistics. Continuous data was expressed as mean ± one standard deviation and analyzed using the student's *t*-test. Pearson's chi-square test was used for analysis of categorical variables. Trend analyses were performed using the Mantel-Haenszel test of trend and analysis of variance test for categorical and continuous variables, respectively. Propensity score matching was used to identify a cohort of patients with similar characteristics to those with CDs to assess for differences in primary and secondary outcomes. Propensity score matching was performed using a 1:1 matching protocol without replacement and caliper width 0.01 of SD of the logit of propensity score using CM_COAG as treatment variable. The groups were matched on 47 different variables including patient demographics, admission characteristics, hospital characteristics, year of admission, comorbidities and associated risk score as shown in Table 1. All study measures were compared between cases and non-cases before and after matching. We repeated the propensity matched analysis among patients with an associated cardiac arrest to compare differences hospital mortality within that population. Results were considered statistically significant for p values <0.05. IBM SPSS statistics version 23.0 (Armonk, NY) was used to perform data analysis.

Results

Trends in use of therapeutic hypothermia

Among those receiving TH, the proportion of patients with an underlying CD increased from 13.0% in the year 2009–17.4% at end of the study duration in the year 2014 as seen in Fig. 1 ($p_{trend} < 0.001$). The number of patients receiving TH included in the study also increased during the study duration from a total of 609 cases in year 2009–1,377 cases by 2014. In-hospital mortality among patients receiving TH increased from 2005 to 2014 among patients with (55.7% to 79.6%; $p_{trend} < 0.001$) and without (53.8% to 74.1%; $p_{trend} < 0.001$) CDs. The mean Elixhauser comorbidity score in the overall population increased (2.99–3.71; $p_{trend} < 0.001$) during the study period as shown in Fig. 2.

Baseline characteristics

From a total of 6469 cases receiving TH included in the analysis, 1036 (16.02%) cases had a CD and 5433 (83.98%) did not. The Appendix provides detailed information on the breakdown of coagulation studied and incidence of bleeding events and in-hospital mortality depending on type of disorder. Prior to matching, patients with a CD receiving TH had similar age (59.2 ± 16.9 vs. 60.0 ± 16.2 years; p = 0.13), and gender distribution (63.5% vs. 62.9% males; p = 0.72) to those without a CD. Patients with a CD had a higher proportion of patients who were African American or Hispanic, and lower proportion of Caucasian patients than those without CD. Overall additional patient and hospital characteristics revealed similarities in rate of weekend admissions, insurance payer information, hospital region, bedsize or location and teaching status within the two groups. Mean cost of hospitalization and length of stay were significantly higher among patients with a CD ($149,702 vs. $127,143; p < 0.001 and 7.7 vs. 6.7 days; p = 0.001), respectively. The rates of diabetes, hypertension, dyslipidemia, chronic pulmonary disease and peripheral vascular disease were similar in both groups. Patients with CDs were less likely to be current or prior smokers (26.1% vs. 29.3%; p = 0.03), more likely to be associated with alcohol abuse (11.1% vs. 8.7%; p = 0.01) and had similar rate of drug abuse compared to patients without CDs.