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Clinical Paper

Evaluation of glucose management during therapeutic hypothermia at a Tertiary Academic Medical Center☆,☆☆

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ABSTRACT

Study aim: Alterations in metabolic function during therapeutic hypothermia (TH) decrease responsiveness to insulin and increase the risk of hyperglycemia. Glycemic control is associated with improved outcomes in selected patients; however, glycemic management strategies during TH are not defined. The objective of this analysis was to evaluate the glycemic metrics and IV insulin administration in critically ill patients during the cooling and rewarming phases of TH.

Methods: Data from 37 patients who received at least 6 h of therapeutic hypothermia for cardiac arrest between January 2007 and January 2010 were retrospectively evaluated, 14 (37.8%) of whom had diabetes.

Results: The mean blood glucose was 9.16 ± 3.22 mmol/L and 6.54 ± 2.45 mmol/L; $p < 0.01$ during cooling and rewarming, respectively. Twelve (32.4%) patients experienced at least one hypoglycemic event, defined as a blood glucose <4 mmol/L. Nineteen (51.4%) patients experienced at least one hyperglycemic event, defined as a blood glucose >11.11 mmol/L and 15 (40.5%) patients received IV insulin therapy. Patients on IV insulin had a higher incidence of diabetes (9 vs. 5; $p < 0.05$), higher admission blood glucose (13.89 ± 6.13 vs. 11.03 ± 4.65 mmol/L; $p = 0.11$), and a higher incidence of hyperglycemia (14 vs. 2; $p < 0.01$) and hypoglycemia (8 vs. 4; $p < 0.05$). Of the patients on IV insulin, mean insulin requirements during cooling and rewarming were 15.2 ± 16.1 and 7 ± 12.5 units/h, respectively.

Conclusion: TH is commonly associated with hyperglycemia, hypoglycemia, and the use of IV insulin therapy. Further research is needed to determine optimal glycemic management strategies to prevent hyper- and hypoglycemia in patients during the different phases of TH.

1. Introduction

Based on two clinical trials published in 2002 that demonstrated therapeutic hypothermia (TH) improves neurologic outcomes and overall survival following cardiac arrest (CA), TH has been incorporated into clinical practice guidelines in the United States and Europe as a class I (highest) recommendation.[1,2] TH is thought to have multiple protective mechanisms including, but not limited to, a reduction in cerebral metabolism, glucose utilization and oxygen consumption.[3]

Alterations in metabolic function during the cooling period of TH decrease responsiveness to insulin and increase the risk of hyperglycemia.[3] Sustained hyperglycemia during TH has been associated with increased mortality.[4] Alternatively, during the rewarming phase of TH, there is increased responsiveness to insulin and therefore a higher risk of hypoglycemia.[3] Hypoglycemia in critically ill patients has been associated with increased mortality, however, not specifically in relation to TH.[5] Due to increased insulin resistance during cooling, high dose IV insulin infusions are often required during TH, thus leading to the potential for increased risk of hypoglycemia during rewarming.[6]

Recommended target glucose concentrations for critically ill patients continue to evolve. Position statements by American College of Endocrinology (ACE) and American Diabetes Association

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(ADA) recommend initiation of a safe continuous IV insulin protocol for most critically ill patients if the glucose value exceeds 10 mmol/L, however management strategies during therapeutic hypothermia (TH) are not defined.[7] Current evidence suggests that higher blood glucose levels during the first 24 h following CA may be associated with worse functional neurologic recovery, however, only one of these trials assessed patients undergoing TH.[8,9]

The 2010 American Heart Association (AHA) Guidelines for Post-Cardiac Arrest Care include a class IIb recommendation for targeting moderate glycemic control following return of spontaneous circulation (ROSC).[10] Additionally, the European Resuscitation Council (ERC) Guidelines for Resuscitation 2010 recommend maintaining blood glucose at less than or equal to 10 mmol/L as well as avoiding hypoglycemia.[11] Neither the AHA nor the ERC guidelines identify specific strategies to achieve this target. The aim this analysis is to evaluate the glycemic metrics and IV insulin administration in critically ill patients during the cooling and rewarming phases of TH after cardiac arrest.

2. Methods

A retrospective review of patients who received therapeutic hypothermia after cardiac arrest between January 2007 and January 2010 at Brigham and Women's Hospital, Boston, MA, was conducted. Patients prescribed TH were identified using a hospital database. Patients were excluded if they were less than 18 years old, underwent less than 6 h of TH, were assessed for TH without receiving therapy, were cooled during cardiac surgery, or did not have complete medical records available. Data was evaluated for a total of 36 h from initiation of TH.

The TH guideline at Brigham and Women's Hospital addresses multiple components of care during TH, one of which is glycemic control. Our institution has a paper-based, multiplication-factor IV insulin protocol for critically ill patients; however, several provisions to this protocol have been made for patients undergoing TH. Specifically, in patients undergoing TH, our institution recommends initiating IV insulin when the blood glucose is >11.11 mmol/L. Blood glucose assessment is then performed from an arterial line every hour during cooling and rewarming and every 30 min during rewarming for those patients requiring IV insulin infusions. Additionally, the guideline recommends a maximum rate of infusion of 50 units/h and stopping the insulin infusion when the blood glucose falls below 11.11 mmol/L. The glycemic target for the IV insulin protocol was updated in 2009 in response to the AACE/ADA Consensus Statement.[7]

The following glycemic metrics were collected: proportion of patients requiring IV insulin infusions, rates of hyperglycemia (defined as a blood glucose greater than 11.11 mmol/L) and hypoglycemia (defined as a blood glucose less than 4 mmol/L), insulin requirements, and mean blood glucose during cooling and rewarming. Both point of care glucose and arterial blood glucose were utilized for analysis. Additional outcomes assessed include ICU and hospital LOS as well as ICU and hospital mortality.

2.1. Statistical analysis

Patient demographics, treatment characteristics, and outcomes were described using measures of central tendency or proportions with measures of variance as appropriate. An a priori subgroup was identified based upon use of continuous infusion IV insulin at any point during the cooling process. Baseline demographics, including known diabetes, hypoglycemic and hyperglycemic events, and mortality were compared in patients who did or did not require IV insulin.

Proportions, means, and medians were compared using the Student *t*-test, Mann–Whitney *U*-test, and the Fisher exact test, where appropriate. All *p*-values were two-tailed and statistically significant at an alpha of ≤ 0.05. The protocol was reviewed and approved by the Brigham and Women's Hospital/Partners Institutional Review Board prior to data collection.

3. Results

Fifty-five patients were identified between January 2007 and January 2010. Of the identified patients, a total of 18 were excluded: 2 patients that underwent less than 6 h of TH; 14 patients were assessed to receive TH, but it was never initiated; 1 patient was cooled during cardiac surgery; and 1 patient had incomplete medical records. A total of 37 patients were included in the final analysis. Baseline demographics for these patients are presented in Table 1. Most common etiology of CA was ventricular fibrillation (41%) followed by PEA (32%). The mean time to ROSC was 15 min and 59.5% of patients received bystander CPR. Fourteen of the 37 patients of patients had a history of diabetes (37.8%). The mean length of the cooling phase of the protocol was 22.1 ± 4.9 h prior to patient rewarming.

Baseline blood glucose values were 13 mmol/L in the patients who required IV insulin and 11.86 mmol/L in the patients who did not require IV insulin. During the observed time period, the mean point-of care blood glucose was 9.16 ± 3.22 mmol/L during cooling and 6.54 ± 2.45 mmol/L during rewarming ($p < 0.01$). In those patients who had a history of diabetes, the mean point-of care blood glucose was higher during cooling and lower during re-warming.

Of the 37 patients included in the analysis, 15 patients (40.5%) were initiated on a continuous IV insulin infusion while undergoing TH. The mean time to initiation of IV insulin was 6.3 ± 6.8 h from presentation and the mean duration of continuous IV insulin infusion was 20.1 ± 9.8 h. Nine of the 14 patients with a history of diabetes required an insulin drip. Additionally, 6 of the 23 patients with no documented history of diabetes required an insulin drip.

Table 1
Baseline demographics.

Variable	Overall ($n = 37$)
Age, years[a]	59.3 ± 17
Weight, kg[a]	90.4 ± 30.7
Baseline temperature, °F[a]	96.3 ± 2.8
Heart rate, bpm[a]	96 ± 25.2
Serum creatinine[a]	1.7 ± 1.6
Male, *n* (%)	22 (59.5)
Ethnicity, *n* (%)	
Caucasian	18 (48.6)
African American	7 (18.9)
Hispanic	3 (8.1)
Other	2 (6.9)
Unknown	9 (24.3)
PMH, *n* (%)	
Diabetes	14 (37.8)
Asthma/COPD	10 (27)
Coronary artery disease	13 (35.1)
Congestive heart failure	13 (35.1)
IV drug use	6 (16.2)
Alcohol use	7 (18.9)
Arrest, *n* (%)	
Out of hospital	32 (86.5)
Witnessed	29 (78.4)
Bystander CPR	22 (59.5)
Time to ROSC, min[a]	15 (8–17.5)
Coronary catheterization	11 (29.7)
Time to ROSC, min[b]	15 (8–17.5)

[a] Data presented as mean ± SD.
[b] Data presented as median (interquartile range).