

Original
Contributions

UTILITY OF INITIAL BOLUS INSULIN IN THE TREATMENT OF DIABETIC KETOACIDOSIS

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Abstract—Current guidelines for treatment of diabetic ketoacidosis (DKA) recommend administration of an intravenous bolus dose of insulin followed by a continuous infusion. This study was designed to investigate whether the initial bolus dose is of significant benefit to adult patients with DKA and if it is associated with increased complications. This was a non-concurrent, prospective observational cohort study of adult patients who presented with DKA in a 12-month period. Charts were divided into two groups depending on whether they received an initial bolus dose of insulin. Data on glucose levels, anion gap (AG), intravenous fluid administration (IVF), and length of stay (LOS) were collected. Primary outcome was hypoglycemia (need for administration of 50% dextrose). Of 157 charts, 78 received a bolus of insulin and were designated the treatment group, the remaining 79 formed the control group. Groups were similar at baseline and received equivalent IVF and insulin drips. There were no statistically significant differences in the incidence of hypoglycemia (6% vs. 1%, respectively, $p = 0.12$), rate of change of glucose (60 vs. 56 mg/dL/h, respectively, $p = 0.54$) or AG (1.9 vs. 1.9 mEq/L/h, respectively, $p = 0.66$), LOS in the Emergency Department (8 vs. 7 h, respectively, $p = 0.37$) or hospital (5.6 vs. 5.9 days, $p = 0.81$). Equivalence testing revealed no clinically relevant differences in IVF change, rate of change of glucose, or AG. Administration of an initial bolus dose of insulin was not associated with significant benefit to patients with DKA and demonstrated equivalent changes in clinically relevant endpoints when compared to patients not administered the bolus. © 2010 Elsevier Inc.

Keywords—insulin; diabetic ketoacidosis; hypoglycemia; infusions; intravenous; bolus

INTRODUCTION

Diabetes affects nearly 21 million people in the United States, about 7% of the population (1). Diabetic ketoacidosis (DKA) was listed as the first diagnosis in approximately 115,000 hospital discharges in 2003 (2). Initial intravenous (IV) bolus dosing of insulin followed by a continuous infusion (drip) is a common practice in the Emergency Department (ED) treatment of DKA, as per national guidelines (3,4). However, pediatric guidelines for DKA treatment recommend against the bolus, primarily due to concern for hypoglycemia and rapid changes in serum osmolarity leading to cerebral edema (5–8). The bolus dose is thought to be useful in overcoming the relative insulin-resistant state in DKA, and various hypotheses have been put forward to explain this (9,10). However, there seem to be no data to support the use of insulin bolus in adult patients. Specifically, there is no data on whether the bolus dose improves outcomes, shortens lengths of stay, or decreases utilization of resources. This, coupled with the fact that the bolus dose has the potential for harm, led us to design the current investigation.

The hypothesis for this investigation was that adult patients who are administered an initial bolus dose of

insulin (in addition to an insulin drip) have a higher incidence of hypoglycemia and more frequently require intravenous fluid (IVF) changes while in the ED, but have similar lengths of stay and similar rates of decrease of serum glucose and anion gap. Our objective was to demonstrate that administration of an initial bolus dose of insulin does not offer any clinically relevant benefit to adult patients with DKA, has the potential for harm, and is resource-intensive in the ED.

METHODS

Design

The study was designed as a non-concurrent, prospective, observational cohort study. We reviewed charts of all adult (aged 18+ years) patients who presented to an urban ED (90,000 visits/year) during a 12-month period extending from July 2003 through June 2004. Only those charts were included of patients assigned a diagnosis of DKA, ketoacidosis, or metabolic acidosis upon discharge from the ED (diagnosis as assigned in an electronic database of ED visits). Exclusion criteria were as follows: 1) metabolic acidosis or ketoacidosis from causes other than DKA (such as alcohol intoxication, starvation, or sepsis); 2) insulin drip not administered; and 3) sufficient data not available on review of medical record, (for example, anion gap or serum glucose not checked within 2 h of departure from ED).

The electronic chart was reviewed by the study investigators to obtain data on glucose levels (via central laboratory or point-of-care testing), anion gap determination, insulin administration, D50 administration and IVF administration. Chart review was limited to the ED course and laboratory tests checked within 2 h of departure from the ED. Baseline data (prior history of diabetes, insulin or oral hypoglycemic agent usage before arrival, and type of diabetes) were extracted from prior medical records where available.

Prior approval was obtained from the Institutional Review Board.

Definitions

Insulin drip was defined as a continuous IV administration of regular human insulin. Patients who received an IV or subcutaneous (SC) dose of insulin in addition to the drip on presentation to the ED were defined as having received an *insulin bolus*. Diagnosis of *DKA* was defined as an anion gap metabolic acidosis with increased serum glucose and beta-hydroxybutyrate levels, necessitating an insulin drip. *Hypoglycemia* was defined as need for IV

administration of a 50-g/dL solution of dextrose (D50). *IVF change* was defined as change in the IVF solution from normal saline (NS) to 5% dextrose in half-normal saline (D5.45) or 5% dextrose in water (D5W).

Treatment

All patients were treated at the discretion of the emergency physician (EP). At our institution, adult patients diagnosed with DKA are routinely started on an insulin drip at 0.1 units/kg/h. Administration of an initial bolus dose of 10 units (0.1–0.15 units/kg) of regular insulin is per the prerogative of the EP. All patients receive an IV bolus of NS followed by continuous infusion. Supplemental electrolyte administration is also determined by the EP. Continuous IV glucose administration (in the form of an IVF change to D5.45 or D5W) is started once the blood glucose level reaches 200–300 mg/dL. All patients diagnosed with DKA receive continuous monitoring of cardiac rhythm, blood pressure and pulse oximetry, 1–2 hourly point-of-care glucose measurements, and central laboratory serum electrolyte concentration determination every 4–6 h. Patients remain in the ED until they may be safely transported to their assigned inpatient room. The insulin drip is discontinued once the anion gap metabolic acidosis has resolved and a long-acting form of insulin has been administered.

Data Analysis

Charts were divided into two groups based on whether they were given an initial bolus dose of insulin. Baseline data are compiled in Table 1. Our primary outcome of interest was the incidence of hypoglycemia. Other endpoints were: 1) need for IVF change, 2) rate of decrease in serum glucose and anion gap levels, and 3) length of stay in the ED and the hospital.

The data were summarized and examined for possible differences between the bolus and control groups. For discrete variables, frequencies were examined and tests of association performed. In most cases, results were obtained through chi-squared tests. For two of the variables (hypoglycemia and history of insulin use) data were sparse in two cells, therefore Fisher's exact test was substituted. Basic statistics were tabulated for all of the continuous variables. In some cases (e.g., hospital length-of-stay), a variable could have been treated as continuous or ordinal. It was decided to treat these as continuous, as the number of possible values was fairly large and there were no obvious deviations from normality. *t*-Tests were run to examine differences between groups. In most cases, pooled variances were assumed.

Table 1. Baseline Characteristics

| | Bolus Group n = 78 | Control Group n = 79 | <i>p</i> Value |
|---------------------------------------|-----------------------|-------------------------|-------------------|
| Age (years) | 41 ± 15.9 | 40 ± 15.0 | 0.63 |
| Male (%) | 41 (52.6%) | 36 (45.6%) | 0.38 |
| History of diabetes? (%) | 60 (77.9%) | 65 (82.3%) | 0.50 |
| Type 2 diabetes (%) | 24 (42.9%) | 21 (32.8%) | 0.26 |
| Prescribed OHA before arrival (%) | 8 (13.3%) | 9 (13.9%) | 0.93 |
| Prescribed insulin before arrival (%) | 55 (91.7%) | 61 (93.9%) | 0.74 |
| Initial glucose level (mg/dL) | 690 ± 291 | 644 ± 281 | 0.31 |
| Initial anion gap (mEq/L) | 29.1 ± 8.2 | 29.3 ± 8.3 | 0.90 |

Values are reported as mean ± SD.
OHA = oral hypoglycemic agent.

Formal tests for equality of variance were performed and in two cases (hospital length-of-stay and total IVF), there was evidence of unequal variance, so the Satterthwaite method was substituted. All statistical tests were two-sided and performed at the 0.05 level of significance.

For equivalence testing, clinical thresholds were pre-defined as a minimum change in magnitude that would be considered clinically relevant. For example, we postulated that if the bolus group and control group differed in their IVF requirement by 500 mL or more, that difference would be clinically relevant. Similar thresholds were set for rate of change of glucose (25 mg/dL/h), rate of change of anion gap (1.0 mEq/L/h), ED length of stay (2 h), and hospital length of stay (1 day). Testing for equivalence was performed by computing the 95% confidence interval (CI) around the difference between means of the two groups, and comparing this to a clinically significant threshold. This approach has been described previously (11,12).

All statistical analyses were performed using Statistical Analysis Software, Version 9.1 (SAS Institute Inc.; Cary, NC).

RESULTS

There were 321 charts that met the inclusion criteria, and 164 met one or more of the exclusion criteria. The most common reasons for exclusion were: acidosis not due to diabetic ketoacidosis ($n = 112$) and incomplete documentation ($n = 25$). A total of 157 charts were analyzed. Figure 1 illustrates the details of patient flow through the study.

Seventy-eight patients were determined to have received an initial bolus dose of insulin and the remaining ($n = 79$) were analyzed in the control group. The two groups were similar at baseline with respect to age, sex

distribution, initial serum glucose level, initial anion gap, insulin or oral hypoglycemic agent usage before arrival, and past medical history and type of diabetes. Table 1 details the baseline characteristics. Data on the type of diabetes were not available for five charts, and no prior data were available for one chart. These charts were excluded from the analysis for relevant baseline variables only.

More charts in the bolus group developed hypoglycemia (5 patients, 6%) as compared to the control group (1 patient, 1%). This difference was not found to be statistically significant (p -value of the comparison was 0.12). The relative risk of hypoglycemia in the bolus group was 5.06 (95% CI 0.61–42.36). For our secondary outcomes, the bolus group did not show a significantly increased requirement for IVF change (23 patients [30%] vs. 20 patients [25%], respectively, $p = 0.56$). There were no statistically significant differences between the two groups in terms of total amount of IVF administration in the ED (2450 ± 934 vs. 2522 ± 1172 mL, respectively, $p = 0.67$), starting insulin drip rate (6.6 ± 1.7 vs. 6.5 ± 1.5 units/h, respectively, $p = 0.70$), rate of change of serum glucose in the ED (60.1 ± 38.2 vs. 56.0 ± 45.4 mg/dL/h, respectively, $p = 0.54$), rate of change of anion gap in the ED (1.9 ± 1.2 vs. 1.9 ± 1.4 mEq/L/h, respectively, $p = 0.66$), serum glucose level on discharge from the ED (319 ± 217 vs. 327 ± 233 mg/dL, respectively, $p = 0.81$), anion gap on discharge from the ED (17.4 ± 6.5 vs. 17.8 ± 7.4 mEq/L, respectively, $p = 0.75$) length of stay in the ED (7.9 ± 5.0 vs. 7.2 ± 4.1 h, respectively, $p = 0.37$) and length of stay in the hospital (5.6 ± 5.3 vs. 5.9 ± 6.9 days, respectively, $p = 0.81$).

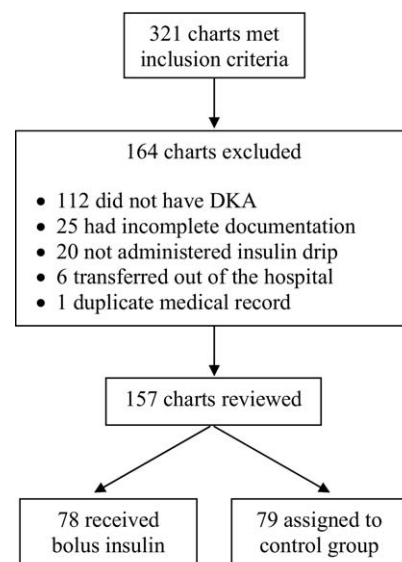


Figure 1. Patient flow through study.

Table 2. Main Results

| | Bolus Group | Control Group | p Value | Equivalence Testing: Comparison of CI against Clinical Threshold | | |
|----------------------------------|-------------|---------------|---------|--|----------------|-----------|
| | | | | δ_{means} | 95% CI | Threshold |
| Hypoglycemia (%) | 5 (6.4%) | 1 (1.3%) | 0.12 | | | |
| IVF change (%) | 23 (29.5%) | 20 (25.3%) | 0.56 | | | |
| Total IVF (mL) | 2450 ± 934 | 2522 ± 1172 | 0.67 | -72 | -406 to +263 | 500 |
| Starting insulin drip rate (U/h) | 6.6 ± 1.7 | 6.5 ± 1.5 | 0.70 | | | |
| ED LoS (h) | 7.9 ± 5.0 | 7.2 ± 4.1 | 0.37 | +0.7 | -0.8 to +2.1 | 2.0 |
| Hospital LoS (days) | 5.6 ± 5.3 | 5.9 ± 6.9 | 0.81 | -0.2 | -2.2 to +1.7 | 1.0 |
| Final glucose (mg/dL) | 319 ± 217 | 327 ± 233 | 0.81 | | | |
| Final anion gap (mEq/L) | 17.4 ± 6.5 | 17.8 ± 7.4 | 0.75 | | | |
| Δ glucose (mg/dL/h) | 60.1 ± 38.2 | 56.0 ± 45.4 | 0.54 | +4.1 | -9.1 to +17.3 | 25.0 |
| Δ anion gap (mEq/L/h) | 1.9 ± 1.2 | 1.9 ± 1.4 | 0.66 | -0.09 | -0.50 to +0.32 | 1.00 |

Values are reported as mean ± SD. For equivalence testing, the difference between means is noted as mean_{bolus} - mean_{control}. IVF = intravenous fluids; ED = Emergency Department; LoS = length of stay; Δ = rate of change of; CI = confidence interval; δ = difference between.

Equivalence Testing

The 95% CIs around the difference between the mean of the bolus group and the control group were determined to be: total IVF (-406-+263 mL), rate of change of glucose (-9.1-+17.3 mg/dL/h), and rate of change of anion gap (-0.50-+0.32 mEq/L/h). All of these fell within our clinical thresholds (as defined previously), and all of these cross zero, indicating that the bolus group did not significantly differ from the control group. The 95% CIs for ED length of stay (-0.8-+2.1 h) and hospital length of stay (-2.2-+1.7 days) crossed zero but extended beyond our clinical thresholds. The point estimate of ED length of stay favored longer ED stays (by 0.7 h) in the bolus group and longer hospital stays (by 0.2 days) in the control group.

Results are summarized in Table 2.

DISCUSSION

Insulin administration and fluid and electrolyte management form the mainstay of treatment for DKA, and EDs across the country have developed protocols in line with national guidelines for management of the same. The American Diabetes Association recommends “an intravenous bolus of regular insulin at 0.15 units/kg body wt, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h” as insulin therapy for adult patients with DKA (5). They go on to state that “An initial insulin bolus is not recommended in pediatric patients.”

The rationale behind use of bolus insulin in treatment of DKA is unclear. With the invention of insulin in 1922, it rapidly became the treatment of choice for DKA (13). Subsequent studies seemed to indicate that larger doses of insulin were more effective (14,15). Later studies in

the 1970s proposed that the more “physiologic” 0.1 units/kg/h dose was effective in controlling DKA (16-19). Ensuing randomized controlled trials established the same dose as having lesser incidence of hypoglycemia with similar rates of resolution of hyperglycemia and ketosis (20-22). A landmark randomized trial in 1977 compared IV, SC, and intramuscular (IM) administration of insulin utilizing a bolus “primer” dose followed by an infusion (23). They found similar outcomes in all three groups, but noted a significantly greater need to repeat the primer dose to obtain an “acceptable response” (10% glucose decrement in the first hour) in the SC and IM groups compared to the IV group. This was explained by the fact that the IV route led to higher serum levels of insulin, which was beneficial in causing a more rapid fall in serum glucose and ketone bodies. However, this beneficial effect could not be detected after the first 2 h of therapy. Subsequently, it was shown that the primer dose (0.44 units/kg) could be administered as an IV bolus or as half IV and half IM or SC with similar results (24).

The use of bolus insulin is thought to be useful to overcome a certain amount of insulin resistance that has been found to exist in the DKA state, when compared to well-controlled type 1 diabetes (9,10,25-27). The hyperosmolar state has been shown to contribute to this resistance, and replacement of fluids and electrolytes has been shown to make cells more responsive to insulin (25,28). This raises the question of what benefit the bolus dose of insulin provides, if careful management of fluid and electrolyte issues is a priority. The pediatric literature seems to recognize this, with guidelines published by the American Diabetes Association and the European Society for Paediatric Endocrinology recommending an IV drip without the bolus dose of insulin (5,6). A bolus dose of insulin has been shown (in pediatric groups) to accelerate the early decline in serum glucose without altering

time to normoglycemia—this could be considered an undesirable effect with higher potential for cerebral edema (8). Another prospective study found no difference in decline of serum glucose level or serum osmolality after the first hour, and similar times to achieve normoglycemia (29).

The lack of data supporting the use of bolus insulin prompted us to design the present study. An observational chart-review design, with sample size based on presentation in a 12-month period, was chosen for convenience. Inclusion criteria were designed to capture a large number of patients with metabolic acidosis, and exclusion criteria were used to narrow the population to DKA patients. The equivalence of baseline characteristics and administered therapies suggests equal distribution of potential confounding factors between the groups. Our results are compatible with the published pediatric literature, effectively demonstrating that the bolus insulin did not increase the rate of decline of serum glucose or correction of the anion gap.

Equivalence testing was done in an attempt to add clinical relevance to our results. Thresholds were established with the logic that if the change in the value of a particular variable (purportedly caused by administration of the bolus insulin) fell within this threshold, the EP would not consider the change clinically relevant. For example, if the change in anion gap per hour varied less than ± 1.0 mEq/L/h between the two groups, an EP would consider this change to be clinically insignificant. After calculating the 95% CI of the difference between the means of the two groups, this interval was compared to the threshold to determine if the difference would exceed our pre-determined thresholds. Using the same example, the difference in the rate of change of anion gap between the two groups had a 95% chance of lying between -0.5 and $+0.32$ mEq/L/h, values well within our threshold. Our results did support the equivalency of the two groups, with the rate of change of serum glucose and anion gap falling within our thresholds. The ED and hospital length of stay did exceed our thresholds; however, the point estimates of the same varied in opposite directions, favoring longer ED stays in the bolus group and longer hospital stays in the control group.

We hypothesized that the patients receiving an initial bolus dose of insulin would have a higher incidence of hypoglycemia, which we could detect as increased administration of D50 to these patients. A trend toward this was noted in our data, but it did not reach statistical significance. From a review of the literature, we had expected an accelerated early drop in serum glucose levels in the bolus group, which would prompt the EP to initiate an IV glucose infusion (D5W or D5.45). Less than a third of patients required IVF changes, and the two groups were similar in this respect. High initial serum

glucose may have contributed to this outcome; furthermore, the bolus insulin was found to be less efficacious than initially expected. It is possible that our sample size (convenience sample based on enrollment in a 12-month period) was insufficient to detect a difference in the rare outcome of hypoglycemia. However, given the fact that the two groups had an equivalent rate of decline in serum glucose, we believe that the initial bolus dose of insulin has been shown to be minimally efficacious in this regard.

LIMITATIONS

The major drawback of this study was the non-randomized cohort design, hence no standard protocol was utilized for treatment of DKA patients. Assignment to bolus vs. control group was therefore dictated by EP preference, and this may have introduced an undetermined confounding factor. However, we did find that relevant baseline characteristics were equally distributed within the two groups, as noted in Table 1. The groups were also treated equally, as demonstrated by equivalent amount of IVF administered and similar insulin drip rates (Table 2). Our inclusion criteria of enrolling patients who were given a diagnosis of DKA by the EP has the potential of missing a number of eligible cases who would have been included if the study was performed prospectively. However, due to the broad search criterion used to identify charts, we feel that the number of missed cases is not significant.

We chose a surrogate definition for hypoglycemia (administration of D50, rather than an actual serum glucose level), because patients displaying clinical signs or symptoms of hypoglycemia when on an insulin drip are often presumptively treated for hypoglycemia in our ED and may not have a serum glucose measurement. This may have significantly affected the incidence of hypoglycemia as reported in this study.

Our data analysis is limited to ED endpoints, and hospital length of stay may be more significantly affected by the patient's Intensive Care Unit course. Finally, the total amount of IVF administered to the patient was not charted accurately in some patients, and the data used are based on rate of administration and length of stay; although this could have significantly affected the outcome, such bias would be equally distributed between the two groups.

CONCLUSION

In this study, administration of an initial bolus dose of insulin (in addition to an insulin drip) was not associated

with significant benefit to adult patients with DKA and demonstrated equivalent changes in clinically relevant endpoints, when compared to patients not administered the bolus. Further randomized controlled trials are required before a firm recommendation can be made regarding use of bolus insulin in treatment guidelines for DKA.

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