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Evidence-Based Medicine

DOES MANAGEMENT OF DIABETIC KETOACIDOSIS WITH SUBCUTANEOUS RAPID-ACTING INSULIN REDUCE THE NEED FOR INTENSIVE CARE UNIT ADMISSION?

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□ **Abstract—Background: In the last 20 years, rapid-acting insulin analogs have emerged on the market, including aspart and lispro, which may be efficacious in the management of diabetic ketoacidosis (DKA) when administered by non-intravenous (i.v.) routes. Clinical Question: In patients with mild-to-moderate DKA without another reason for intensive care unit (ICU) admission, is the administration of a subcutaneous (s.c.) rapid-acting insulin analog a safe and effective alternative to a continuous infusion of i.v. regular insulin, and would such a strategy eliminate the need for ICU admission? Evidence Review: Five randomized controlled trials were identified and critically appraised. Results: The outcomes suggest that there is no difference in the duration of therapy required to resolve DKA with either strategy. Conclusion: Current evidence supports DKA management with s.c. rapid-acting insulin analogs in a non-ICU setting in carefully selected patients.** © 2015 Elsevier Inc.

□ **Keywords—diabetic ketoacidosis; DKA; insulin; intensive care; hospitalization**

CASE REPORT

A 24-year-old man with a history of type I diabetes presents to your Emergency Department (ED) with a chief complaint of weakness. He reports that 1 month ago he lost his job and his insurance. He has been unable to afford his insulin or syringes and was trying to "stretch them out" by only using one injection per day. He ran out completely 3 days prior to arrival, and in the interim developed polyuria and polydipsia, followed by nausea, vomiting, and generalized weakness. He denies any infectious symptoms, abdominal pain, chest pain, or shortness of breath. On examination, he is mildly tachycardic and appears mildly tachypneic. Otherwise, he is afebrile and hemodynamically stable. His examination is unremarkable. His blood sugar is checked at the bedside and is 540 mg/dL, and his finger-stick ketones are high at 77 mg/dL (4.3 mmol/L).

You start by giving him a liter of normal saline (NS) while you await his chemistry results, but you're pretty sure he's in diabetic ketoacidosis (DKA). His labs come back as follows: Na 131 mEq/L, K 4.1 mEq/L, Cl 100 mEq/L, CO_2 13 mEq/L, and his anion gap is 22 mEq/L. You realize that you will need to treat his DKA, but are also aware that all of your intensive care unit (ICU) beds are full, and that you cannot send a patient to the floor on an insulin drip. The patient is also begging you to keep the cost of his care to a minimum, because he has no insurance at the moment. Given the availability of rapid-acting insulin analogs (aspart, glulisine, and lispro), you wonder if there is any place for subcutaneous (s.c.) rapid-acting insulin, as an alternative to a

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continuous infusion of intravenous (i.v.) regular insulin, in the management of mild-to-moderate DKA. You wonder if the administration of s.c. insulin in patients such as this would reduce the need for ICU admission, and hence ease your disposition in such cases.

CLINICAL QUESTION

In patients with mild-to-moderate DKA without another reason for ICU admission, is the administration of an s.c. rapid-acting insulin analog a safe and effective alternative to a continuous infusion of i.v. regular insulin, and would such a strategy eliminate the need for ICU admission?

CONTEXT

DKA is a relatively common and dangerous complication of diabetes in both children and adults, with an estimated mortality of around 13% (1,2). In 2009, seven of every 1000 diabetics were admitted to the hospital for DKA (1). The mainstay of treatment involves hydration, electrolyte monitoring, and insulin therapy, traditionally accomplished via i.v. regular insulin (3,4). Both the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes recommend a continuous infusion of i.v. regular insulin as standard of care in the management of DKA (5,6). These recommendations are based primarily on studies from the 1970s that demonstrated the superiority of regular insulin when administered via continuous i.v. infusion, compared to an s.c. or intramuscular route for initial glucose control and the prevention of hypoglycemia (7,8). The authors of these reports suggest that the delayed onset and longer half-life of s.c. and intramuscular regular insulin make these routes inadequate for the management of DKA. In the last 20 years, rapid-acting insulin analogs have emerged on the market, including aspart and lispro, which may be more efficacious in the management of DKA when administered by these non-i.v. routes (9,10). Insulin lispro, for example, has an onset of action of 10 to 20 min and reaches peak concentration within 30–90 min when administered by s.c. injection (11).

Many hospital policies dictate that treatment with continuous i.v. insulin must be accomplished in an ICU or intermediate-care setting (12,13). Recent data suggest that as the population ages, the demand for ICU beds is increasing (14,15). This, coupled with the fact that ICU admission drastically increases costs of care provides impetus for both physicians and administrators to find ways to safely reduce ICU admissions (15). Although patients in DKA are often critically ill, their care is generally regimented, and as such, those who are less ill may not require ICU-level care. Over the past decade, effort has been made to re-examine the necessity of i.v. insulin for DKA in light of the introduction of rapid-acting insulin analogs. By obviating continuous insulin infusion, it may then follow that care of these patients could take place on step-down units or in floor beds, helping to both decrease ICU utilization and reduce cost.

EVIDENCE SEARCH

A PubMed search was conducted using the advanced search builder to create the following search strategy: "(aspart OR lispro) AND ([diabetic ketoacidosis] OR DKA)." This identified 38 articles, from which the following five randomized controlled trials were identified. A search of the bibliographies of the identified articles revealed no additional clinical trials.

EVIDENCE REVIEW

Treatment of Diabetic Ketoacidosis With Subcutaneous Insulin Aspart (16)

Population. Subjects included 45 consecutive adult patients with DKA presenting to the ED at the University of Tennessee Regional Medical Center in Memphis. DKA was defined as a plasma glucose level > 250 mg/dL, a serum bicarbonate level < 15 mEq/L (mmol/L), a venous pH < 7.30, and either a positive serum ketone level at a dilution ≥ 1:4 by the nitroprusside reaction or a serum β-hydroxybutyrate level > 31 mg/dL.

Study design. Patients were randomly assigned, in a 1:1:1 fashion, to one of three treatment modalities:

1) The first group received an initial s.c. injection of 0.3 units/kg of insulin aspart, followed by 0.1 units/kg every hour until blood glucose reached 250 mg/dL. The dose was then reduced to 0.05 units/kg every hour until resolution of DKA.
2) The second group received an initial s.c. injection of 0.3 units/kg of insulin aspart, followed by a dose of 0.2 units/kg 1 h later and every 2 h thereafter, until a blood glucose of 250 mg/dL was achieved. The dose was then reduced to 0.1 units/kg every 2 h until resolution of DKA.
3) The third group received an initial i.v. bolus of 0.1 units/kg of regular insulin, followed by a continuous infusion at 0.1 units/kg/h until the blood glucose reached 250 mg/dL. The infusion rate was then decreased to 0.05 units/kg/h until resolution of DKA.

Resolution of DKA required a serum bicarbonate level > 18 mEq/L (mmol/L) and a venous pH > 7.30.

Primary outcome. Outcomes included duration of therapy and amount of insulin administered until resolution of