Subcutaneous Insulin in the Treatment of Diabetic Ketoacidosis in the Pediatric Population

Lauren A. Ljunghag
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Abstract

Background: Diabetic ketoacidosis or DKA is an acute and fatal disease that is highly prevalent in the pediatric population. The current gold standard of treatment is continuous intravenous regular insulin (CIRI), which requires admission to the intensive care unit (ICU) and is a substantial cost to the patient. Alternate routes of insulin administration, such as subcutaneous (SQ) insulin, do not require ICU admission. If SQ insulin is found to be safe and efficacious for the treatment of DKA, this treatment modality could replace continuous IV regular insulin, and therefore decrease the need for ICU admission and cost of stay.

Methods: An exhaustive search of available medical literature was performed using MEDLINE – Ovid, MEDLINE - PubMed, Web of Science, Google Scholar, and CINAHL. Keywords included: diabetic ketoacidosis or DKA, subcutaneous insulin, intravenous insulin, and pediatric. Eligible studies were assessed using the GRADE criteria.

Results: Two articles met inclusion criteria and were included for this systematic review. One study was a retrospective chart review and the other a randomized controlled clinical trial. The retrospective chart review looked at 76 instances of DKA and found that median time to DKA resolution was 10.3 hours using SQ insulin. The controlled clinical trial randomly assigned 30 patients to receive CIRI and 30 patients to receive SQ insulin. Patients receiving SQ insulin took up to 6 hours longer to achieve full DKA resolution as compared to the CIRI group. However, in both studies, patients that were treated with SQ insulin experienced no increase in adverse outcomes including hypokalemia, hypoglycemia, cerebral edema, or death.

Conclusion: Subcutaneous insulin, regular or fast acting, can be used as a safe and effective treatment of DKA in pediatric patients. Providers should consider administration of SQ insulin every 4 hours if using regular insulin and every 2 hours if using fast-acting insulin analogs until DKA resolution.

Keywords: Diabetic ketoacidosis, subcutaneous insulin, and pediatric patients

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Subject Categories
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Biography

Lauren Ljunghag is a native of Colorado and attended the University of Colorado at Boulder where she received a Bachelor of the Arts in Integrative Physiology. While at CU, she worked as a research assistant in a behavioral genetics research lab. After completion of her undergraduate degree, Lauren became a certified nurse assistant at the Children’s Hospital Colorado.
Abstract

**Background:** Diabetic ketoacidosis or DKA is an acute and fatal disease that is highly prevalent in the pediatric population. The current gold standard of treatment is continuous intravenous regular insulin (CIRI), which requires admission to the intensive care unit (ICU) and is a substantial cost to the patient. Alternate routes of insulin administration, such as subcutaneous (SQ) insulin, do not require ICU admission. If SQ insulin is found to be safe and efficacious for the treatment of DKA, this treatment modality could replace continuous IV regular insulin, and therefore decrease the need for ICU admission and cost of stay.

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**Results:** Two articles met inclusion criteria and were included for this systematic review. One study was a retrospective chart review and the other a randomized controlled clinical trial. The retrospective chart review looked at 76 instances of DKA and found that median time to DKA resolution was 10.3 hours using SQ insulin. The controlled clinical trial randomly assigned 30 patients to receive CIRI and 30 patients to receive SQ insulin. Patients receiving SQ insulin took up to 6 hours longer to achieve full DKA resolution as compared to the CIRI group. However, in both studies, patients that were treated with SQ insulin experienced no increase in adverse outcomes including hypokalemia, hypoglycemia, cerebral edema, or death.

**Conclusion:** Subcutaneous insulin, regular or fast acting, can be used as a safe and effective treatment of DKA in pediatric patients. Providers should consider administration of SQ insulin every 4 hours if using regular insulin and every 2 hours if using fast-acting insulin analogs until DKA resolution.

**Keywords:** Diabetic ketoacidosis, subcutaneous insulin, and pediatric patients
Acknowledgements

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Table of Contents
Biography .................................................................................................................................................. 2
Abstract .................................................................................................................................................... 3
Acknowledgements ................................................................................................................................... 4
Table of Contents ..................................................................................................................................... 5
List of Tables ............................................................................................................................................. 6
List of Abbreviations ............................................................................................................................... 6
BACKGROUND ........................................................................................................................................ 7
METHODS ............................................................................................................................................... 8
RESULTS ............................................................................................................................................... 9
DISCUSSION .......................................................................................................................................... 12
CONCLUSION ......................................................................................................................................... 14
References .............................................................................................................................................. 16
Table I: Quality Assessment of Reviewed Article with GRADE ........................................................... 18
Table II: Summary of Characteristics of the Reviewed Studies ............................................................. 18
Table III: Summary of Findings ............................................................................................................... 18
List of Tables

Table I: Quality Assessment of Reviewed Article with GRADE
Table II: Characteristics of Reviewed Studies
Table III: Summary of Findings

List of Abbreviations

CIRI: Continuous Intravenous Regular Insulin
DKA: Diabetic Ketoacidosis
DM: Diabetes Mellitus
ICU: Intensive Care Unit
SQ: Subcutaneous
Subcutaneous Insulin in the Treatment of Diabetic Ketoacidosis in the Pediatric Population

BACKGROUND

Diabetic ketoacidosis (DKA) is an acute and life-threatening complication of diabetes mellitus that frequently requires hospitalization in the pediatric and adult population. This condition results from a relative and absolute deficiency of circulating insulin, combined with increased levels of the counterregulatory hormones including catecholamines, glucagon, and growth hormone.\textsuperscript{1-3} Outcomes of this condition involve severe hyperglycemia, metabolic acidosis due to ketone formation, and intracellular dehydration caused by hypertonicity in the blood vessels.\textsuperscript{1}

Criteria for DKA in the pediatric population includes blood glucose > 200 mg/dL, bicarbonate < 15 mmol/L, venous pH < 7.3, ketonemia, and ketonuria.\textsuperscript{4} There are different severities of DKA, mild, moderate, and severe, that are based on the degree of acidosis.\textsuperscript{1} Mild DKA has a venous pH <7.3, moderate DKA has a venous pH < 7.2, and severe DKA has a venous pH < 7.1. DKA can be attributed to several causes including lack of treatment due to unknown status of diabetes, missed or incorrect dose of insulin in a known diabetic, illness or traumatic event in a diabetic, or non-compliance with diet in a diabetic patient.

After determining the patient is indeed in DKA based on laboratory criteria, the goals of treatment include correction of dehydration, correction of acidosis and ketosis, restoration of blood glucose to near normal levels, identification and treatment of the precipitating event, and avoidance of the treatment complications that can arise.\textsuperscript{1} Treatment begins with 1-2 hours of fluid resuscitation at a rate of 10 mL/kg/hour with normal saline to try to restore peripheral perfusion, and then insulin administration is initiated.\textsuperscript{5} Options for insulin modalities include
continuous intravenous regular insulin (CIRI), subcutaneous (SQ) regular insulin or subcutaneous fast-acting insulin. Continuous intravenous infusion of low-dose regular human insulin is the current standard of care for DKA as stated by the American Diabetes Association (ADA)\(^6,7\) and the International Diabetes Federation and the International Society for Pediatric and Adolescent diabetes (ISPAD).\(^5,6\) Endocrinologists prefer IV insulin to SQ injections to treat DKA in order to avoid the delay in onset of action due to slower uptake of insulin in the SQ form, and to take advantage of the short half-life of IV insulin. Both of these drug properties of IV insulin allow for more flexible and rapid dose adjustment.\(^6\) However, IV infusions are associated with higher hospitalization costs and resource requirements as compared to SQ injections.\(^8\) Within most medical centers across the United States, treatment of DKA with CIRI involves admission to the ICU due to intensity of treatment, as well as hospital policies that prevent the use of CIRI outside of ICU setting.\(^8-10\)

With the high cost that comes with CIRI due to required ICU admission and continuous monitoring, a systematic review\(^6\) has assessed the safety and efficacy of subcutaneous insulin as a replacement to CIRI for treatment of DKA in adults. This study was done comparing treatment of DKA with SQ Lispro to CIRI. The authors, Vincent and Nobecort, concluded that administration of SQ Lispro every 1-2 hours is a feasible alternative to CIRI. While treatment with SQ insulin can be considered for adults, DKA is also a highly prevalent condition in children. This review will be addressing if subcutaneous insulin is a safe and efficacious treatment of DKA exclusively in the pediatric population.

METHODS

An exhaustive search of literature was performed using MEDLINE-Ovid, MEDLINE-PubMed, Google Scholar, CINAHL, and Web of Science. Keywords included: diabetic
ketoacidosis or DKA, subcutaneous insulin, intravenous insulin, and pediatric. Inclusion criteria included patients under the age of 18, human studies, and studies in English. Studies were excluded if they used an insulin bolus during treatment. Bibliographies of studies and relevant articles were searched to find further sources. Relevant studies were assessed for quality using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE).\textsuperscript{11}

**RESULTS**

The initial literature search yielded 12 articles for review. After screening abstracts for eligibility, 2 articles were selected that met inclusion criteria. One study\textsuperscript{12} used a randomized controlled clinical trial and the other study\textsuperscript{13} used a retrospective chart review design. See Tables I, II, and III.

**Della Manna et al**

This was a randomized clinically controlled trial\textsuperscript{12} that compared the efficacy of treating DKA with a subcutaneous fast-acting insulin analog, humalog (Lispro), to the standard of treatment, continuous regular intravenous insulin (CIRI). This clinical trial took place from June 2001- June 2003. Sixty patients were randomly selected to receive either SQ Lispro or CIRI for treatment of DKA. Thirty patients were selected for each treatment modality. Median age of patients in SQ insulin group was 11.3 and median age in CIRI group was 12.1 years. All patients met required DKA criteria: venous pH <7.3, blood glucose $\geq$ 16.6 mmol/L (300 mg/dL), bicarbonate < 15 mmol/L, ketonuria greater than “++.” After a standard 1-2 hours of fluid resuscitation, insulin was started at a dosage of 0.15 units/kg every 2 hours in the SQ Lispro group, and 0.1 unit/kg/hour in the CIRI group. At a blood sugar of 13.8 mmol/L (250 mg/dL), administration of SQ Lispro was extended to 0.15 units/kg every 4 hours and patients in the CIRI
group were taken off IV insulin and transferred to SQ regular insulin at a dose of 0.15 units/kg every 4 hours.\textsuperscript{12}

Outcomes considered in the study were the rate at which blood glucose declined, the time taken for patient’s DKA to resolve, volume of IV fluids, amount of insulin administered, number of hypoglycemic events, number of events of cerebral edema, and number of deaths. Serum potassium was reported 24 hours following the blood glucose reaching 250 mg/dL in each group. Criteria for DKA resolution included the patient having the ability to eat and be mentally alert, a venous pH >7.3, bicarbonate >15 mmol/L, and anion gap < 16 mmol/L.\textsuperscript{12}

The mean decrease in capillary glucose for the SQ Lispro group and CIRI group was 2.9 mmol/L/hour and 2.6 mmol/L/hour, respectively. The total time taken for blood glucose to decrease to 13.8 mmol/L, or 250 mg/dL, was around 6 hours in both the SQ and CIRI groups. Following this, the CIRI group had full DKA resolution within 6 hours, while the SQ group had full DKA resolution within 12 hours. The total amount of IV fluid replacement in the SQ group was 44 +/- 17.9 mL/kg for a mean period of 4.4 +/- 2.3 hours and in the CIRI group the amount of IV fluid administered was 42.7 +/- 17.4 mL/kg for a period of 4.5 +/- 2.2 hours. Amount of insulin required to resolve DKA in the SQ Lispro group was 0.28 +/- 0.19 units/kg, whereas in the CIRI group insulin required was 0.37 +/- 0.24 units/kg. Number of hypoglycemic events was six in the CIRI group and four in the SQ Lispro group. Serum potassium levels 24 hours after blood glucose of 250 mg/dL was reached were 3.68 +/- 0.55 in the CIRI group, and 4.05 +/- 0.44 in the SQ group. There were no events of cerebral edema or death in this trial. There was no required escalation of care in SQ group, which was measured by need to move patients to the ICU, or need to switch from SQ Lispro to CIRI.\textsuperscript{12}
Limitations of this study include the inability to blind providers to which treatment is being administered. This study did not report the differences between the SQ and CIRI group in frequency and severity of hypokalemic events during DKA treatment. Also, in this study an unaccounted for variable was introduced which was the administration of bicarbonate to patients who has bicarbonate levels < 5.0 mmol/L.\textsuperscript{12}

\textbf{Cohen et al}

Through retrospective chart analysis from the years 2007 – 2010, this study\textsuperscript{13} evaluated the safety and efficacy of subcutaneous (SQ) regular insulin for the treatment of diabetic ketoacidosis in children. Average age of patients was 11.6 (+/- 4.0 years). The study included 76 episodes of DKA, all of which were treated with scheduled doses of SQ regular insulin. After the standard 1-2 hours of fluid resuscitation, SQ insulin was administered every 4 hours at a dose of 0.8 units/kg/day. This dose was adjusted on a sliding scale based on patient’s blood glucose at the time of insulin administration. All patients met required DKA criteria: venous pH < 7.3, blood glucose > 200 mg/dL, bicarbonate < 15 mmol/L, ketonuria, and ketonemia. Only patients with a pH $\geq$7.0 were treated with subcutaneous insulin.\textsuperscript{13}

Outcomes considered in this study were the time taken for resolution of DKA, number of hypokalemic events, number of hypoglycemic events, number of events of cerebral edema, and number of deaths. This study also looked at differences of these outcomes between patients with known diabetes versus new onset diabetes and those with mild DKA versus moderate or severe DKA. Criteria met for DKA resolution included the patient having the ability to eat and be mentally alert, a venous pH $>7.3$, and bicarbonate $>15$ mmol/L.\textsuperscript{13}

Results illustrated DKA resolution in median time of 10.3 hours (Range 5.5 – 14.2 hours). Hypokalemia was considered at serum potassium levels $\leq$ 3.5 mEq/L. There were 14
hypokalemic events with average serum potassium of 3.1 mEq/L. No ECG abnormalities were experienced by any of the patients during hypokalemic events. There was one recorded mild hypoglycemic event. No events of cerebral edema or death occurred. There were no instances in which patients required escalation of care, that being, transfers to the ICU, or addition of CIRI during treatment of DKA.\textsuperscript{13}

Limitations included small sample size and a retrospective study design, which doesn’t allow for a controlled clinical setting or the insurance of correct timing and dose administration of insulin. Also, the study lacked comparison to continuous intravenous regular insulin, the standard of treatment of DKA.\textsuperscript{13}

**DISCUSSION**

DKA is the most frequent cause of hospitalization among children and adolescents with type I diabetes. The current gold standard of treatment is continuous intravenous regular insulin, which requires admission to the ICU and continuous monitoring. CIRI uses an extensive amount of hospital resources and results in high admission costs to the patient. The two studies\textsuperscript{12,13} included looked at treatment of DKA with subcutaneous insulin, which would limit the need for ICU admission in the pediatric population. Both studies looked at time taken for full DKA resolution, number of hypoglycemic events, number of events of cerebral edema, number of deaths, and number of times escalation of care was required (refer to Table III). Both of the studies concluded that full DKA resolution could be obtained with SQ insulin administration effectively with no increase in incidences of hypokalemia, hypoglycemia, cerebral edema, or death.

For the Della Manna et al study,\textsuperscript{12} when comparing the CIRI group to SQ Lispro group, DKA resolution was not reached for up to 6 hours longer in the SQ Lispro group. However, this
may be attributed to the fact that SQ Lispro administration was extended to every 4 hours after a blood glucose of 250 mg/dL was reached. Thereafter, a slower rate of decline in blood glucose was observed. Based on the duration of action of SQ Lispro, the researchers from this study state continuing SQ Lispro injections at a lower dose every 2 hours may have quickened DKA resolution. The Cohen et al study recorded an average time of 10.3 hours for resolution of DKA with the use of SQ regular insulin, which was comparable to times found in the Vincent and Nobecourt review. This review, which looked at studies that compared SQ insulin Lispro to CIRI for the treatment of DKA in the adult population, found that there was “no statistically significant or clinically relevant differences in the speed of blood glucose decline or the resolution of DKA symptoms between the SQ insulin and CIRI groups.” Based on the two studies included in this review, this carries down to the pediatric population.

Two different types of insulin were administered for each study, which poses an inconsistency between the studies. The Della Manna et al study used subcutaneous Lispro, a fast-acting insulin analog, and the Cohen et al study used subcutaneous regular insulin. The difference between the two types of insulin is the onset of action, which is around 1-20 minutes in SQ Lispro, and 1 hour in SQ regular insulin, and the duration of action, which is 3-4 hours for SQ Lispro and 4-6 hours for SQ regular insulin. Based on these properties, administration of SQ Lispro was initiated at the frequency of every 2 hours in the Della Manna et al study, and administration of SQ regular insulin was every 4 hours in the Cohen et al study. The same outcome of safe and effective DKA resolution was illustrated with both types of SQ insulin.

Limitations of the Cohen et al study include having relatively small sample size for an observational study. Also, specifically with this retrospective chart review study, only patients who had a pH of ≥ 7.0 were treated with SQ insulin, if the pH was lower than this they were
treated with CIRI. This did not allow for assessment of efficacy and safety of SQ regular insulin in the truly severe cases of DKA. In regards to Della Manna et al study, the providers were not blinded to allocation of treatment; however, due to differing methods of treatment of each group, intravenous in the ICU vs SQ injections not in the ICU, provider blinding seems difficult. Although, the study lacked blinding, all data was objective laboratory results and the need for provider blinding was extraneous. CIRI and SQ groups had comparable demographics and starting laboratory values for this study.

The use of subcutaneous insulin for the treatment of DKA could reserve the hospital resources that are used to treat DKA with CIRI and lower cost of admission for the patient. In a study that looked at difference of cost when treating DKA with CIRI in the ICU, as compared to SQ insulin on the non-ICU floor, the ICU was associated with 39% higher hospitalization charges, which was an average difference of about $5,600 per case. A pediatric emergency department in Brazil follows identical protocol as the United States for fluid and electrolyte administration, as well as laboratory monitoring in DKA patient, but has been treating pediatric patients with SQ Lispro since 1996 due to limitations of resources, and reports no incidences of cerebral edema or deaths. If subcutaneous insulin is just as safe and effective, and poses no increased risks for the patient, this method should be a strong consideration for treatment of DKA in the pediatric population.

**CONCLUSION**

Subcutaneous insulin should be considered for the treatment of DKA in pediatric populations. It has been demonstrated safe and effective at resolving this condition. In seems advantageous to the patient, and to hospital resources, to look at alternate treatment options to replace continuous intravenous regular insulin for the treatment of DKA. ICU beds and staff
should be saved only for those medical conditions that cannot be treated safely outside this environment. In order to achieve this, future studies need to be done that focus on comparing different types of subcutaneous insulin to find which option provides the safest and most effective manner in which to treat DKA.
References


### Table I: Quality Assessment of Reviewed Article with GRADE

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Della Manna et al 12</td>
<td>RCT</td>
<td>Limitations: Not Serious</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indirectness: Not Serious</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inconsistency: Not Serious</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecision: Not Serious</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias: Unlikely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen et al 13</td>
<td>Retrospective</td>
<td>Limitations: Not Serious</td>
<td>None</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indirectness: Not Serious</td>
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<td>Inconsistency: Not Serious</td>
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<td></td>
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<td>Publication bias: Unlikely</td>
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</table>

*a* Lack of blinding, no downgrade applied due to objectivity of outcomes

*b* Small sample size

### Table II: Summary of Characteristics of the Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of patients</th>
<th>Median Age</th>
<th>Type of Insulin</th>
<th>Dose of Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Della Manna et al 12</td>
<td>Controlled Clinical Trial – randomized</td>
<td>N = 60 30: IV insulin 30: SQ lispro</td>
<td>Lispro: 11.3 +/- 3.6 IV Insulin: 12.1 +/- 3.3</td>
<td>Subcutaneous Lispro (fast-acting insulin analog) compared to continuous intravenous regular insulin</td>
<td>SQ Lispro – 0.15 units/kg injected q2h until BG is 13.8 mmol/L then 0.15 units/kg injected q4h CIRI – 0.1 units/kg/hour until BG is 13.8 mmol/L then 0.15 units/kg of regular insulin injected q4h</td>
</tr>
<tr>
<td>Cohen M et al 13</td>
<td>Retrospective chart review</td>
<td>76 DKA episodes</td>
<td>11.6 +/- 4.0</td>
<td>Subcutaneous Regular Insulin</td>
<td>0.8 units/kg/day – this amount is divided by 6 for q4hour dosing then a sliding scale was used based on blood glucose level prior to insulin injection</td>
</tr>
</tbody>
</table>

### Table III: Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes measured to show DKA resolution</th>
<th>Blood Glucose Decline</th>
<th>Time to DKA resolution</th>
<th>Number of patients requiring escalation of care: ICU bed or switch from SQ to CIRI</th>
<th>Average Potassium Levels</th>
<th>Hypoglycemic events</th>
<th>Number of deaths/cerebral edema events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Della Manna et al 12</td>
<td>1. Blood Glucose &lt;13.8 mmol/L. 2. pH &gt;7.3 3. Bicarbonate &gt;15 mmol/L</td>
<td>IV Insulin: -2.9 mmol/L/hour SQ Lispro: -2.6 mmol/L/hour</td>
<td>IV Insulin: &lt; 6 hours after BG &lt; 13.8 mmol/L (250 mg/dL) SQ Lispro: &lt; 12 hours after BG &lt; 13.8 mmol/L (250 mg/dL)</td>
<td>0</td>
<td>IV Insulin – 3.68 mEq/L (+/- 0.55) SQ Insulin – 4.05 mEq/L (+/- 0.44)</td>
<td>IV Insulin – 6 SQ Insulin – 4</td>
<td>0</td>
</tr>
<tr>
<td>Cohen M et al 13</td>
<td>1. Ability to eat 2. Venous pH &gt; 7.3 3. Bicarbonate &gt;15 mmol/L</td>
<td>Not recorded</td>
<td>Average of 10.3 hours (5.5 to 14.2 hours)</td>
<td>0</td>
<td>14 patients experienced hypokalemia – average K+ during hypokalemia 3.1 mEq/L</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>