BRIEF REPORT

Use of a Flexible Catheter for the Administration of Subcutaneous Insulin in Diabetic Ketoacidosis: A Feasibility Controlled Clinical Trial

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ABSTRACT

BACKGROUND: Although intravenous insulin administration is the standard of care in diabetic ketoacidosis (DKA), subcutaneous insulin administration could be a suitable alternative in resource-limited settings, but pain caused by hourly insulin applications are limiting factors for using it, especially in children. We aimed to assess whether the use of a flexible subcutaneous catheter improves comfort in patients with DKA compared with the usual hourly injections' treatment. We also compared the evolution of metabolic variables in patients with DKA using both insulin administration systems.

METHODS: Randomized feasibility controlled open trial, comparing 2 ways (flexible catheter and steel needle) for the initial insulin administration in children with DKA, who were randomly selected to receive subcutaneous insulin by a flexible catheter or using standard needles. The main outcome was pain, assessed hourly and secondary outcome time to achieve ketoacidosis resolution.

RESULTS: Twenty subjects were included (10 by group). There were no differences between groups in baseline lab values (glycemia, urea, sodium, bicarbonate and pH). Pain assessment at first insulin administration was significantly lower in the intervention group (4.5 vs 0 points; $P = 0.001$). Similar differences between both treatment arms were observed in every pain assessment. There were no differences between groups regarding the time elapsed to achieve ketoacidosis resolution. (11.4 ± 4.3 vs 16 ± 8.4; $P = 0.12$). No adverse events or DKA complications were observed.

CONCLUSIONS: The use of a flexible catheter reduced the pain associated with subcutaneous insulin administration in nonsevere DKA. The flexible subcutaneous catheter could be a safe alternative for the treatment of uncomplicated DKA in resource-limited settings.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT03182569).

Dr Beaudoin conceptualized and designed the study, drafted the initial manuscript; Drs Torrents, Hamui, Tittarelli, Ibarra, and Ferraro conducted the initial analyses and reviewed and revised the manuscript; Dr Ferreira designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Diabetic ketoacidosis (DKA) is the metabolic decompensation of diabetes and includes hyperglycemia, ketonemia, glucosuria, and ketonuria.[1] In an observational European study including nearly 50 000 children with type 1 diabetes followed-up for a year, a rate of 5% to 7% of DKA was observed.[2]

Fluid replacement, insulin administration, and clinical control are essential components of DKA treatment.[3] Management of DKA by using intravenous insulin can be particularly challenging in resource-limited settings. The International Society for Pediatric and Adolescent Diabetes suggests that, in such a context, the use of subcutaneous insulin is a suitable option.[1]

The use of subcutaneous insulin in DKA treatment involves an invasive and annoying procedure: repeated insulin subcutaneous applications through a rigid needle until ketoacidosis resolution is achieved.[4] Despite being considered an effective, safe, and affordable treatment, pain caused by multiple insulin applications are limiting factors for using it, especially in children.[5,6]

Hanas et al[7] described for the first time the safety of subcutaneous catheter use, with low frequency of adverse effects and no changes in metabolic control in patients with type 1 diabetes. The use of a subcutaneous device allows insulin administration without additional needle punctures, thus improving treatment tolerance, increasing comfort, and allowing safe management of these patients.[7,8] However, no data on the use of this device or similar are reported for DKA treatment in patients with type 1 diabetes.

We aimed to assess whether the use of a flexible subcutaneous catheter improves comfort in patients with DKA compared with the usual hourly injections' treatment. We also compared the evolution of metabolic variables in patients with DKA using both insulin administration systems.

METHODS

This is a randomized feasibility controlled open trial comparing 2 ways (flexible catheter and steel needle) for the initial insulin administration in children with DKA.

Patients aged 5 to 18 years admitted to the Hospital Elizalde general pediatric ward for DKA from 2016 to 2018 were included. DKA was defined by the following baseline laboratory criteria: glucose >11 mmol/L (~200 mg/dL); pH <7.3 or bicarbonate <15 mmol/L; and ketonemia or ketonuria.[1]

Patients with severe DKA (pH <7.1 or bicarbonate <5 mmol/L), altered consciousness, or seizures were excluded from the study and admitted to the PICU (Fig 1).

In the intervention arm, regular insulin was administered hourly by using a flexible subcutaneous catheter. Insuflon (Unomedical; Lejre, Denmark) is a soft subcutaneous catheter (18 mm long/0.6 mm outer diameter) used for subcutaneous application of multiple drugs, including insulin.[9] It was placed before the first insulin administration, remaining in its place until ketoacidosis resolution was achieved. For successive administration of insulin, the catheter portal was punctured. Catheter dead space volume was 0.0075 mL, hence an extra single dose of 0.5 U of insulin 100 U/mL was administered before starting insulin injections. The subcutaneous catheter was removed once ketoacidosis resolution was achieved.

In the control arm, regular insulin was injected hourly by subcutaneous steel needle (28G × 0.5 in) by using a type 1 × 1 insulin syringe.[10]

The main outcome was pain, assessed by using a visual analog scale (VAS). This scale is considered a validated measure for the assessment of pain in children.[11] This VAS consists of a 10-cm line marked every cm, in which "10" meant unbearable pain and "0" meant hardly noticeable pain. Patients were asked to mark an "X" on the scale at the appropriate level of pain intensity felt after each subcutaneous insulin administration (hourly), until ketoacidosis resolution was achieved.

The secondary outcome was time to achieve ketoacidosis resolution, defined by the following laboratory values: blood glucose ≤13.8 mmol/L, pH ≥7.3, and bicarbonate ≥15 mmol/L. Blood-sampling timing and fluid replacement were based on local guidelines.[12]

Parents and patients were invited to participate in the study during the initial saline infusion; those who agreed were

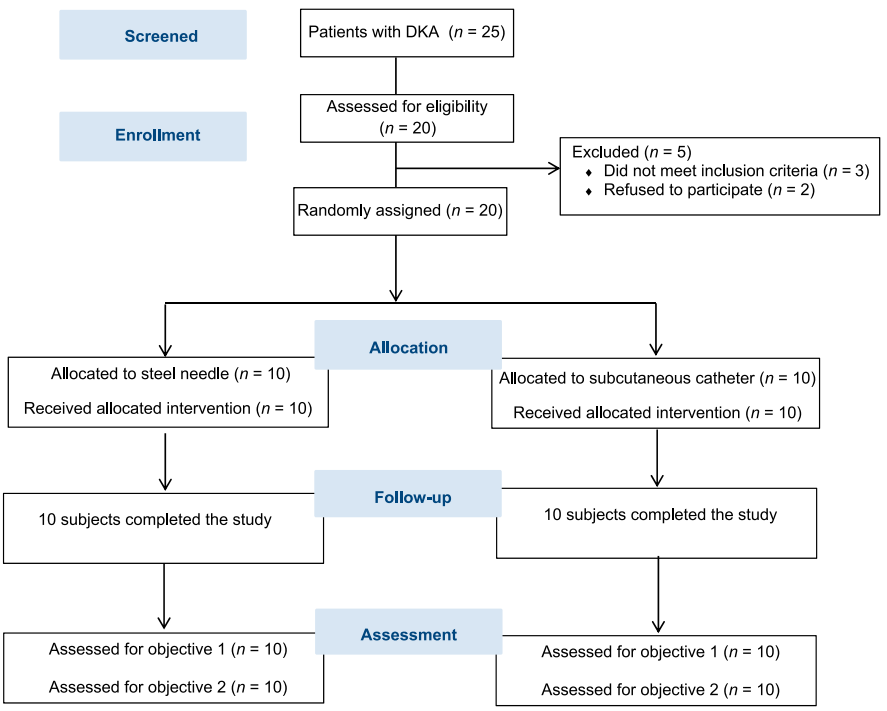

FIGURE 1 Consort flow chart of the studied patients.

randomly assigned to each treatment arm. A blind-envelope random selection system was used, and each envelope included the treatment arm "flexible subcutaneous catheter" or "subcutaneous administration with needle," together with detailed instructions of the method to be used and a data collection form. Informed consent was attached outside the envelope. There were 5 blocks, with 4 envelopes per block (2 of each treatment arm). Envelopes inside a block were shuffled before the beginning of the recruitment and sequentially numbered in each block. The investigator picks the first envelope each time. In both arms, subcutaneous insulin administration started as soon as initial rehydration bolus finished, with 0.1 U/kg administered hourly and continued until ketoacidosis resolution was achieved. Following local guidelines, none of the patients received intravenous insulin during treatment.[12]

Analysis: Sample size was calculated assuming 65% of difference on the primary outcome between treatment arms. This value was estimated as an average of differences observed by Hanas et al[13] regarding pain, assessed with a VAS by using a flexible subcutaneous catheter versus a needle, in children and adolescents. Considering a power of 80% and a confidence level of 95%, at least 9 patients per group were required. Age and baseline laboratory values were assessed by using *t* test for independent samples to assess if groups were comparable. To describe the evolution of laboratory values in each treatment arm, *t* test for independent samples or Mann–Whitney *U* test was performed. To compare pain between groups, Mann–Whitney *U* test was used, including results from the first 6 hourly insulin doses. A *P* value $<.05$ (2-tailed) was considered as statistically significant. Data were analyzed by using Epi Info 7.2 (Centers for Disease Control and Prevention, Atlanta, GA).

The study was approved by the institutional ethics committee. To assess safety, an independent monitoring committee undertook an interim analysis when 40% of the sample was recruited.

TABLE 1 Baseline Characteristics

	Flexible Catheter ($n = 10$)	Rigid Needle ($n = 10$)	*P*
Sex			
Female	7	6	—
Male	3	4	—
Age, y	14 ± 4.3	13 ± 1.9	.69
Blood glucose, mmol/L	26.42 ± 10.21	23.48 ± 4.05	.40
Anion gap	20 ± 4.3	22 ± 2.6	.34
pH	7.16 ± 0.08	7.12 ± 0.08	.38
Urea, mmol/L	6.33 ± 1.62	5.83 ± 1.83	.60
Na^+, mEq/L	137 ± 2.7	136 ± 4.8	.54
Cl^-, mEq/L	107 ± 3.9	105 ± 4.9	.28
K^+, mEq/L	4.8 ± 0.7	4.9 ± 1	.80
HCO_3^-, mEq/L	9 ± 3.4	8.5 ± 2.8	.71

Cl^-, chlorine; HCO_3^-, bicarbonate; K^+, potassium; Na^+, sodium; —, not applicable.

TABLE 2 Outcome Measures and Insulin Administration According to Treatment Group

	Flexible Catheter ($n = 10$)	Rigid Needle ($n = 10$)	*P*
Hourly pain assessments, median			
0	0 (0–2)	4.5 (2.7–6.7)	.001
1	0	4 (2–6)	.000
2	0 (0–5)	2 (1.5–4)	.000
3	0	2 (0–6)	.009
4	0	2.5 (0.7–5)	.008
5	0	4 (1.7–5)	.002
6	0	1 (0–5)	.000
Time to resolution of DKA, h, mean	11.4 ± 4.3	16 ± 8.4	.12
Insulin, IU (IQR), kg/h, median	1.3 (1–1.6)	1.6 (1–1.4)	.31
Total insulin required, IU, mean	65 ± 32	84 ± 52	.34

IQR, interquartile range; IU, international units.

RESULTS

We included 20 subjects (10 for each arm): 13 were girls (6 in the control group) and mean age was 13 ± 3.2 years, with both groups being similar according to demographic characteristics. Sixteen patients had presented with DKA before (8 in each group). Laboratory baseline values were similar in both groups (Table 1).

Pain assessment at first insulin administration was significantly higher in the control group (4.5 vs 0; $P = .001$). Similar differences between both treatment arms were observed in every pain assessment (Table 2).

There were no differences in insulin requirement between the experimental and the control groups (1.3 vs 1.6 U/kg per hour; $P = .31$).

Also, there were no differences between groups regarding the time elapsed to achieve ketoacidosis resolution (11.4 ± 4.3 vs 16 ± 8.4 hours; $P = .12$).

No adverse events related to the flexible catheter use (local infection, kinked catheter, etc) or to DKA complications (cerebral edema, metabolic disorders, etc) were observed in either group.

DISCUSSION

We found that children with DKA receiving subcutaneous insulin by a flexible catheter showed less pain than those using standard needles.

Pain in pediatrics is a meaningful issue. The International Association for the Study of Pain defines it as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage or described in terms of such damage." This definition connects pain to both sensory systems: physiology and the neurobiology of emotions related to previous experience.[14]

Needle fear ("needle phobia") and injection pain are still major problems related to insulin administration.[6] Pain and anxiety caused by insulin administration in patients with type 1 diabetes have been studied. Humphrey et al[15] reported "high levels of distress" in ∼50% of the 223 children and adolescents during insulin applications.

Patient awareness of injection discomfort has been studied extensively, revealing that it is related to needle length, needle diameter, and injection context. Even as needle length and diameter are continually improved through new technology, a reproducible awareness of injection pain persists on the basis of visual stimulus of the needle itself and level of anticipated pain among patients.[16]

Hanas et al[13] showed that the use of subcutaneous catheters reduces not only pain, assessed with the same VAS score used by us, but also preinjection anxiety in children with type 1 diabetes, as compared to standard needles.

Despite the fact that pain management in patients with diabetes by using subcutaneous catheters has been studied, there is no information related to subjects with DKA in which the injection frequency is higher.[8,13] Regardless, intravenous insulin is accepted as the standard of care in DKA treatment,[1] subcutaneous rapid-acting insulin in DKA was evaluated, revealing safety and effectiveness both in adults[5,17,18] and children.[4,19,20] Moreover, in several middle-low income countries, like most of those in Latin America, "there are few PICU beds in public hospitals, which are usually occupied by children who demand ventilatory support; therefore, most of the (nonsevere) patients with DKA will be managed in general emergency wards."[21]

Della Manna et al[19] describe the subcutaneous lispro administered every 2 hours until capillary blood glucose levels neared 13.8 mmol/L, like our local guidelines. That study reveals the effectiveness of subcutaneous insulin in DKA but also reflects the difficulty in administering insulin injections as frequent as every 2 hours.[19]

Within the strengths of our study, we must take into account that we used the best research design (randomized controlled trial), and all subjects received fluids together with insulin in a standardized manner, according to local guidelines.[12]

On the other hand, our study has potential limitations to be considered. The study was not powered to examine the effect of the subcutaneous device on the safety and efficacy of DKA treatment. The primary outcome (pain) was based on the patient's response (VAS) and could be considered subjective, but despite not being blinded, this tool was proven useful in assessing pain in different research settings.[22–24] We also did not include patients with severe DKA (pH <7.1) because there is concern regarding subcutaneous insulin absorption in these individuals, but even in low-resource scenarios, those patients are usually managed in PICUs by using intravenous insulin administration.[25] Finally, this is an open-label study, but considering the intervention and the primary outcome, it would have been difficult to make it blinded.

In our study, we provide information on the safety, efficacy, and feasibility of the use of a flexible subcutaneous catheter as an alternative to reduce pain related to repeated injections of insulin in nonsevere DKA treatment. On the basis of these promising results, lager studies should be performed to confirm our findings.

CONCLUSIONS

The use of a flexible catheter reduced the pain associated with subcutaneous insulin administration in nonsevere DKA. The flexible subcutaneous catheter could be a safe alternative for the treatment of uncomplicated DKA in resource-limited settings.

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