Insulin Pumps

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Introduction

THIS YEAR THERE HAVE BEEN a number of articles evaluating and optimizing the utilization of insulin pumps. A new meta-analysis by Pala et al. attempts to break down decades of past studies comparing continuous subcutaneous insulin infusion (CSII) and injection. In this more detailed analysis, they stratify studies by dosing regimen and insulins utilized, which has evolved over time. They report a consistent hemoglobin A1c (HbA1c) benefit for pumps, but it was significantly greater in past trials using regular human insulin. There is a profound need to consider other outcome measures beyond HbA1c, such as continuous glucose monitor (CGM) metrics, ease of use, and quality of life. There are several unaccounted factors in the meta-analysis, including education, automated insulin delivery analyzed by Bosi et al., and bolus speed, which was investigated by Regittnig et al. Bosi et al. found that the suspend-before-low feature on the Medtronic 640G reduced hypoglycemia in at-risk adults. Regittnig et al. observed that bolus delivery under one minute reduced postprandial hyperglycemia. These optimizations and features may affect primary outcomes in future systematic reviews.

Additional explored outcomes for CSII included weight gain, which was evaluated in insulin pump and multiple daily injection users retrospectively by Alderisio et al. Despite improved glycemic control and lower prescribed insulin doses in the insulin pump cohort, weight gain was similar over 6–10 years of follow-up. This raises the question if the mechanism of weight gain differs between the therapies. Another study by Toresson Grip et al. evaluates the costs of insulin pump therapy compared to multiple daily injections within the Swedish National Diabetes Register. As anticipated, insulin pump therapy is more costly than multiple daily injections, but unmeasured benefits must also be considered.

For those desiring pump therapy, many barriers to access still remain. Briganti et al. revealed that age need not be a limitation for pump use. In a retrospective review, they found that a population with type 1 diabetes age 50 years and over had similar outcomes to younger pump users with less weight gain and better glycemic outcomes than those 50 and over on multiple daily injections. In an effort to reduce educational barriers to access, Ehrmann et al. designed a structured insulin pump education program called INPUT (Insulin Pump Treatment). This education led to significant improvement in glycemic control while reducing severe hypoglycemia. Structured education leading to optimal utilization may increase the benefit of insulin pump therapy versus multiple daily injections. Ziegler et al. highlight the possible fatal consequences of insufficient education in a case series of six deaths from Teflon infusion sets that were found outside of the body at autopsy. Structured education and novel infusion-set design may reduce this feared risk of pump therapy.

Multiple breakthroughs in diabetes technology have advanced pump care. Klonoff et al. investigated the use of Fiasp in insulin pumps, which was found to be non-inferior to insulin Aspart with some improved measures of postprandial hyperglycemia. Another trial by Heise et al. evaluated BioChaperone insulin lispro in CSII with euglycemic

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clamp and found earlier onset of action and faster offset than Aspart or Fiasp. At the release of this 2019 ATTD Yearbook, commercial and do-it-yourself closed-loop systems will be available for insulin pumps from all major manufacturers. These systems are critically dependent on the reliable and modifiable delivery of insulin from the pump. Understanding the crucial nature of interoperability, the United States Food and Drug Administration developed the new regulatory classification of alternate controller enabled insulin pumps. Future pumps meeting criteria specified in the special controls can go through the expedited 510(k) review process for regulatory approval. These special controls include certain assurances of secure device communications, safety, and accurate and reliable insulin delivery that must be included in device labeling. This year, there were two *in vivo* studies assessing the accuracy of bolus and basal delivery in several commercial pumps by Freckmann et al. and Laubner et al. Both groups had similar findings that highlight the reproducibility of the methodology. All pumps tested appeared to have reasonable performance. Whether the subtle differences in delivery have any clinical implication requires additional investigation.

Key Articles Reviewed for the Article

Continuous subcutaneous insulin infusion can be used effectively and safely in older patients with type 1 diabetes: long-term follow-up

Briganti EM, Summers JC, Fitzgerald ZA, Lambers LNJ, Cohen ND

Diabetes Technol Ther 2018; **20**: 783–786

Efficacy of an education program for people with diabetes and insulin pump treatment (INPUT): results from a randomized controlled trial

Ehrmann D, Kulzer B, Schipfer M, Lippmann-Grob B, Haak T, Hermanns N

Diabetes Care 2018; **41**: 2453–2462

Fatalities due to failure of continuous subcutaneous insulin infusion devices: a report of six cases

Ziegler A, Williams T, Yarid N, Schultz DL, Bundock EA

J Forensic Sci 2019; **64**: 275–280

Continuous subcutaneous insulin infusion vs modern multiple injection regimens in type 1 diabetes: an updated meta-analysis of randomized clinical trials

Pala L, Dicembrini I, Mannucci E

Acta Diabetologica 2019; **56**: 973–980

Real-world costs of continuous insulin pump therapy and multiple daily injections for type 1 diabetes: a population-based and propensity-matched cohort from the Swedish National Diabetes Register

Torresson Grip E, Svensson AM, Miftaraj M, Eliasson B, Franzén S, Gudbjörnsdóttir S, Steen Carlsson K

Diabetes Care 2019; **42**: 545–552

Long-term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: a 10-year retrospective controlled study

Alderisio A, Bozzetto L, Franco L, Riccardi G, Rivellese AA, Annuzzi G

Nutr Metab Cardiovasc Dis 2019; **29**: 1110–1117

A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5)

Klonoff DC, Evans ML, Lane W, Kempe HP, Renard E, DeVries JH, Graungaard T, Hyseni A, Gondolf T, Battelino T

Diabetes Obes Metab 2019; **21**: 961–967

BioChaperone lispro versus faster aspart and insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion: a randomized euglycemic clamp study

Heise T, Meiffren G, Alluis B, Seroussi C, Ranson A, Arrubla J, Correia J, Gaudier M, Soula O, Soula R, DeVries JH, Klein O, Bode B

Diabetes Obes Metab 2019; **21**: 1066–1070

Insulin bolus administration in insulin pump therapy: effect of bolus delivery speed on insulin absorption from subcutaneous tissue

Regittnig W, Urschitz M, Lehki B, Wolf M, Kojzar H, Mader JK, Ellmerer M, Pieber TR

Diabetes Technol Ther 2019; **21**: 44–50

Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomized controlled trial

Bosi E, Choudhary P, de Valk HW, Lablanche S, Castañeda J, de Portu S, Da Silva J, Ré R, Vorrink-de Groot L, Shin J, Kaufman FR, Cohen O; SMILE Study Group

Lancet Diabetes Endocrinol 2019; **7**: 462–472

Accuracy of bolus and basal rate delivery of different insulin pump systems

Freckmann G, Kamecke U, Waldenmaier D, Haug C, Ziegler R

Diabetes Technol Ther 2019; **21**: 201–208

Comparative dose accuracy of durable and patch insulin pumps under laboratory conditions

Laubner K, Singler E, Straetener J, Siegmund T, Päh G, Seufert J

Diabetes Technol Ther 2019; **21**: 371–378

PUMPS IN PRACTICE

Continuous subcutaneous insulin infusion can be used effectively and safely in older patients with type 1 diabetes: long-term follow-up

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Diabetes Technol Ther 2018; **20**: 783–786

Background

Use of continuous subcutaneous insulin pumps in adults with type 1 diabetes has become increasingly popular, but there is very limited information on the benefit of pumps in older patients with type 1 diabetes.

Methods

This was a retrospective review of electronic medical records from the Baker Heart and Diabetes Institute Diabetes Clinic in Melbourne, Australia. Patients with type 1 diabetes, undertaking structured patient education and initiated on insulin pump or multiple daily injections between 2000 and 2016 with HbA1c data were included. Outcomes examined related

to HbA1c, blood glucose monitoring, weight, and utilization of healthcare resources.

Results

Two hundred ninety three patients fulfilled the inclusion criteria, with up to 10 years of follow-up data. Of these patients, 166 were individuals less than 50 years of age starting insulin pump therapy, 57 were 50 years or older commencing insulin pump therapy, and 70 were age 50 or over starting multiple daily injections (MDI). For those beginning pump therapy, 86.1% were started on Minimed Paradigm, 6.7% on Animas, 2.7% on Deltec Cozmo, 2.2% on Roche, and 2.2% were undocumented. In this group glycemic outcomes were similar in older compared with younger patients. The older participants tended to check blood sugar more frequently ($P=0.006$) and had less weight gain ($P=0.018$). Among the patients 50 and over, use of CSII was associated with a greater drop in HbA1c ($P<0.001$), less hypoglycemia on meter glucose ($P=0.008$), greater frequency of blood sugar checks ($P<0.001$), and greater health-care utilization ($P<0.001$) compared with MDI.

Conclusions

Pumps can be used effectively and safely in patients 50 and older with type 1 diabetes. In this study, the older population had similar outcomes as younger patients using pumps with less weight gain and better glycemic outcomes versus MDI in older patients.

Comment

The majority of individuals with type 1 diabetes are adults, and longer exposure to hyperglycemia increases the risk of microvascular and macrovascular disease. Diabetes technology, which has demonstrated efficacy, should not be limited to only the younger population. Prior retrospective studies by Matejko (1) and Yeoh (2) showed a similar glycemic benefit of insulin pump therapy for those 50 and over compared with those less than 50 years of age.

The present study reproduces the findings comparing pump therapy by age. In addition, they compare those age 50 or over on MDI against those starting insulin pump therapy with similar baseline characteristics (present age, age at diagnosis, diabetes duration, gender, socioeconomic status, years of follow-up, HbA1c, meter hypoglycemia, and weight). The findings reveal that pump therapy was associated with a greater drop in hemoglobin A1c, less hypoglycemia, increased meter glucose checks, and increased visits with healthcare professionals (on average 5.5 visits per year in insulin pump group versus 3.8 visits per year in the injection group) compared with multiple daily injections.

The findings must be taken in the context of the retrospective observational design. Correlation is hypothesis generating but cannot establish causality. The authors also point to a selection bias due to the funding needed for insulin pump use in the Australian health system and access to clinical care. The patients started on insulin pump likely demonstrated motivation and the physical and cognitive skills needed to operate a pump. However, the older patients on multiple daily injections had similar socioeconomic status at baseline to those patients started on insulin pump. The findings emphasize that age alone should not deter providers from offering pump therapy.

Efficacy of an education program for people with diabetes and insulin pump treatment (INPUT): results from a randomized controlled trial

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Diabetes Care 2018; **41**: 2453–2462

This manuscript is also discussed in the article on Practical Implementation of Diabetes Technology: Real-World Use, page S-119.

Background

Meta-analysis reveals statistically significant reductions in HbA1c with insulin pump therapy. More frequent use of pump features (e.g., bolus calculator and temporary basal rates) are also associated with better glycemic control. Use of these features requires structured education to provide individuals

with the necessary knowledge. No structured education program providing insulin pump training has been rigorously assessed. A structured insulin pump education program called INPUT (Insulin Pump Treatment) was developed to address these problems. This program is based on self-management and empowering participants to use their insulin pump effectively and overcome emotional and motivational obstacles.

Methods

This was a German multicenter, randomized, parallel trial with a 6-month follow-up evaluating the impact of INPUT on glycemic control, behavior, and psychosocial status. Those with diabetes on insulin pump therapy, age 16–75 years with HbA1c 7.5–13%, who had received prior structured diabetes education, were included. Exclusion criteria were diabetes for less than 1 year, severe disease preventing regular participation, pregnancy, severe cognitive impairment, treatment of a psychiatric disorder or dialysis-dependent kidney disease. Participants were randomized to INPUT program or to usual care. Education included information on adapting basal rates, programming different basal profiles, and adjusting prandial insulin administration. The primary outcome was change in HbA1c from baseline to 6 months. Secondary outcomes were changes in behavioral and psychosocial measures and incidence of severe hypoglycemia.

Results

Recruitment occurred in April 2016; 520 individuals were approached and 268 participants were randomized to the INPUT group ($n=135$) or control group ($n=133$). Baseline measures of age, sex, education, body mass index (BMI), diabetes type, diabetes duration, HbA1c, frequency of blood glucose measurements, structured diabetes education, duration of pump therapy, onset of pump therapy, therapy regimen at last education, number of complications, and severe hypoglycemia were equivalent between groups. HbA1c improved in the INPUT group (8.33 ± 0.8 vs 8.04 ± 0.9 ; $P < 0.0001$) but not in the control group (8.33 ± 1.0 vs 8.27 ± 1.0 ; $P = 0.11$). The between-group difference in HbA1c reduction was also significant ($P = 0.0029$). Severe hypoglycemia was more common in the control group (incidence rate ratio 3.55 [95% CI 1.50–8.43]; $P = 0.0041$).

Conclusions

The INPUT education program led to a significant improvement in glycemic control while reducing severe hypoglycemia in insulin pump users.

Comment

Systematic review and meta-analysis have revealed statistically significant but marginal improvements in glycemic control of around 0.3% (3,4). One addressable concern is that structured education is lacking, holding back the potential of this diabetes technology. The authors of the present study designed an educational intervention known as INPUT and then performed a randomized clinical trial to assess efficacy at 6 months.

The primary outcome measure of the trial was change in HbA1c, which was -0.3% in the INPUT cohort.

Given that this is the same HbA1c reduction associated with transition from multiple daily injections to insulin pump, this is a very exciting finding. Indeed, this came with a reduction in hypoglycemia, diabetes distress, depressive symptoms and increased diabetes self-management, satisfaction with pump use, and diabetes-specific empowerment.

Conferring self-efficacy is perhaps the most significant duty of any diabetes program. The multitude of tools now available are only useful if those utilizing them are empowered. A thorough understanding of what pumps can and cannot do helps set realistic expectations. As we rapidly develop increasingly complex systems, structured education techniques will need to keep pace.

Fatalities due to failure of continuous subcutaneous insulin infusion devices: a report of six cases

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J Forensic Sci 2019; **64**: 275–280

Background

Malfunctions of any component of the insulin pump can result in insufficient insulin delivery and, if not recognized promptly, can lead to ketoacidosis. In this report, the authors describe six fatalities due to one such malfunction—the failure of plastic cannulas of CSII devices to penetrate the skin and deliver insulin—resulting in fatal diabetic ketoacidosis (DKA).

Methods

The cases are derived from four different death investigation systems in the United States. For each case, scene and autopsy findings are presented, as well as selected toxicology and histology findings.

Results

Case 1: A 73-year-old woman with a history of type 1 diabetes was discovered dead in her residence. The deceased was found to be wearing an insulin pump, with the insulin infusion cannula applied to the right abdomen. Inspection of the infusion site revealed a bent plastic cannula that left an indentation in the intact skin surface. Incision of the skin revealed the absence of subjacent hemorrhage. The adhesive patch appeared to be wet. The final five glucose readings recorded blood glucose of >400 mg/dL (>22.2 mmol/L). At these times, the device indicates 3.90, 4.00, 1.10, 3.20, and 4.00 units of insulin were administered, respectively. Vitreous fluid glucose >500 mg/dL (>27.7 mmol/L).

Case 2: Deceased discovered on the bedroom floor. A trend of increasing blood glucose levels, ranging from 423 to

550 mg/dL (23.5 to 30.5 mmol/L), with the final reading simply indicating “HI.” Examination of the insulin infusion cannula revealed that the plastic cannula was lying on top of the skin and not inserted into the subcutaneous tissue. A small area of epidermal excoriation was noted under the cannula tip; however, incisional evaluation of the site revealed no evidence that the skin was punctured. Microscopic examination revealed subnuclear vacuoles in the renal tubular epithelium, consistent with Armanni–Ebstein lesions. Postmortem toxicology revealed urine glucose >2,000 mg/dL (>111 mmol) and ketones 40 mg/dL (6.8 mmol/L) by dipstick, and peripheral blood acetone of 67 mg/dL (11.5 mmol/L) by gas chromatography.

Case 3: A 52-year-old man with a history of diabetes (type unspecified), asthma, and hypertension was found deceased in his residence. Upon examination, the plastic cannula of the insulin infusion set was noted to be kinked and lying on the surface of the skin. Microscopic examination revealed subnuclear vacuoles in the renal tubular epithelium, consistent with Armanni–Ebstein lesions. Postmortem toxicology revealed urine glucose of 1000 mg/dL (55.5 mmol/L) and ketones 15 mg/dL (2.5 mmol/L) by dipstick and peripheral blood acetone 35 mg/dL (6.0 mmol/L) by gas chromatography.

Case 4: A 44-year-old man with a history of type 2 diabetes was found deceased in his residence. Upon examination of the insulin infusion cannula, it was revealed that the plastic cannula was bent and lying on the skin surface. A skin puncture was under the adhesive patch immediately adjacent to the cannula tip, suggesting that the cannula may have been properly placed initially and was subsequently dislodged. Microscopic examination revealed subnuclear vacuoles in the renal tubular epithelium, consistent with Armanni–Ebstein lesions. Postmortem toxicology revealed urine glucose >2,000 mg/dL (>111 mmol/L) by dipstick and peripheral blood acetone of 15 mg/dL (2.5 mmol/L) by gas chromatography.

Case 5: A 60-year-old woman with a history of diabetes mellitus (type unspecified) was found dead at home. Careful removal of the insulin infusion cannula revealed the plastic cannula was slightly bent and lying on the surface of the skin, with no evidence of skin penetration. Urine dipstick at the time of autopsy showed 15 mg/dL (2.5 mg/dL) ketones and 1,000 mg/dL (55.5 mmol/L) glucose. Microscopic examination of the kidneys revealed subnuclear vacuoles in the proximal convoluted tubular epithelium, consistent with Armanni–Ebstein lesions.

Case 6: A 37-year-old man with a history of type 1 diabetes, hypertension, hyperlipidemia, and smoking complained of flu-like symptoms and general weakness for approximately a week before being found dead in his apartment by his roommate. Removal of the insulin infusion cannula revealed a plastic cannula bent at a 90° angle, lying flat against the unbroken skin, resulting in a furrow on the skin surface. Subnuclear vacuoles in the renal tubular epithelium, consistent with Armanni–Ebstein lesions, were noticed upon microscopic examination of the kidney tissue. Analysis of vitreous fluid found glucose of 1,031 mg/dL (57.2 mmol/L). Blood acetone level was 46.2 mg/dL (7.9 mmol/L).

Conclusions

In five of the six cases, the malfunction was identified to be failure of the insulin infusion cannula to puncture the skin; in one case (Case 4), it appeared that the cannula had initially punctured the skin to some extent, but it was unclear if the

cannula had failed to insert fully or had inserted and subsequently dislodged. In addition, in five of six cases, including Case 4, the cannulas were bent or kinked, and in one case (Case 2) the cannula appeared straight but was not inserted through the skin. All cases involved plastic cannulas. Four of the six cases involved perpendicularly inserted cannulas, all of which were bent or kinked. Of the two angled cannulas, one (Case 3) was bent and another (Case 2) had failed to insert. In all cases, cannula malfunction resulted in the failure of insulin infusion, which then resulted in fatal ketoacidosis. All fatalities occurred in the residences of the patients and were unwitnessed.

Comment

These cases highlight the most severe complication of insulin pump therapy: death due to diabetic ketoacidosis resulting from non-delivery of insulin. Five out of six cases also demonstrated the Armani–Ebstein lesions: a histological change in the kidney consisting of subnuclear vacuolation of the proximal tubules. It has been most associated with diabetic ketoacidosis but not specific to diabetes mellitus (5,6).

It is not entirely clear from these reports why the users did not seek medical help before this unfortunate outcome occurred, as one could argue that these are all preventable deaths. It appears that all the cases occurred while the user was alone without family members or friends present. One possible intervention would be infusion sets with a steel cannula for the at-risk population. Case reports like these may help identify risk factors such as living alone and latency between significant hyperglycemia and infusion-set change.

It is not clear what training the deceased received before and during CSII therapy to avoid these fatal sequelae. Management of hyperglycemia and sick days are a critical part of education before and during CSII therapy. Users are advised to keep backup insulin pens or syringes with them at all times. If the unexplained hyperglycemia and ketones do not improve after one pump correction users are advised to give an injection and change insulin infusion set or patch pump. These cases should remind all healthcare professionals dealing with CSII the critical importance of education about managing hyperglycemia, monitoring and treatment of ketones, and the need to keep backup supplies at all times, as well as seeking early medical help if glucose and ketone levels are not improving. In clinical practice, we find that it is not enough to provide this training once, at the start of the CSII therapy. It should be discussed throughout the CSII therapy follow-up.

Whether CSII is associated with higher rates of DKA is somewhat controversial. Due to the lack of long-acting depot insulin, cessation of insulin delivery can lead to more rapid insulin deficiency, and rapid onset of DKA in CSII treated patients. Data from a large study of children and adolescents <20 years of age (Germany, Austria, Luxemburg, and Switzerland) has shown lower rates of DKA with pump than MDI (7). Data from the U.S. T1D Exchange Registry also shows no increase in DKA rates with pump (8). A study from Denmark found no overall

difference in DKA rates among pump and MDI users but higher DKA rate with pump use was found in small clinics (9). Among pump users, DKA was highest in the first year after starting pump.

Continuous subcutaneous insulin infusion vs modern multiple injection regimens in type 1 diabetes: an updated meta-analysis of randomized clinical trials

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Acta Diabetologica 2019; **56**: 973–980

Background

Meta-analyses of clinical trials comparing insulin pump therapy with traditional insulin injections usually show a small, but significant advantage of pumps with respect to HbA1c and risk of severe hypoglycemia. Pumps carry a small theoretical risk of ketoacidosis, secondary to malfunction or catheter occlusion. Given advances in technology, this study aims to update previous meta-analyses comparing pump therapy with multiple daily injections in subjects with type 1 diabetes.

Methods

All randomized clinical trials of 12 weeks or longer comparing pump therapy with injections in people with type 1 diabetes were included. If a single trial was included more than once, the paper containing more adequate information was considered the principal publication. Specific subgroup analyses were designed to compare pump therapy versus multiple daily injections. An exploratory analysis was also performed to verify the effect of pumps in insulin-naïve individuals with type 1 diabetes.

Results

In trials with rapid-acting insulin analogs, the advantage of pump therapy (ΔHbA1c : -0.29 [-0.46 , -0.13]) was significantly smaller ($P=0.02$) than in trials with regular human insulin (ΔHbA1c : -1.93 [-1.84 , -0.42]). Lispro (ΔHbA1c : -0.25 [-0.48 , -0.02]) provided similar results to Aspart (ΔHbA1c : -0.29 [-0.49 ; -0.09]). NPH (ΔHbA1c : -0.31 [-0.55 , -0.06]) provided similar HbA1c reduction versus long-acting analogs (ΔHbA1c : -0.20 [-0.38 , -0.03]). Pump therapy was associated with increased reports of diabetic ketoacidosis but did not significantly reduce the risk of severe hypoglycemia in comparison to injections. The increased risk of DKA was only significant in trials comparing pumps with 1–2 daily injections but not multiple daily injection regimens. Only two trials compared insulin pumps with multiple daily injections in insulin-naïve participants with type 1 diabetes. There was no relevant effect on HbA1c ($P=0.46$). No meta-analysis could be performed on severe hypoglycemia or DKA because they were only reported in one of the two trials.

Conclusions

Pump therapy seems to produce a small improvement in HbA1c in patients with type 1 diabetes inadequately controlled with MDI. This may be partly attributable to publication bias and the effect is smaller when MDI with short-acting insulin analogs is employed. Outcomes outside of HbA1c, such as quality of life, may be relevant for the choice of pump over multiple daily injections. Additional studies are needed to identify patients likely to benefit from pump therapy.

Comment

We have been comparing injections to pump therapy for over 40 years (10). In this time insulins, dosing regimens, injection and pump technology have all evolved. In this meta-analysis the authors have taken great care to stratify injections in the control arms by dosing regimen and insulin type. Indeed, if we are to be fair, we cannot compare modern insulin pumps and 1–2 daily injection regimens consisting of regular human insulin and NPH insulin. In the current study, more recent trials comparing modern pumps and infusions sets to multiple daily injections show no significant increase in ketoacidosis risk. While there does continue to be a statistically significant HbA1c difference between pump therapy and multiple daily injections with insulin analogs, the long-term clinical significance of these reductions is questionable.

In a world of continuous glucose monitors, it certainly has been argued that HbA1c should not be the gold standard glycemic metric. However, even beyond this, should glucose control always represent our primary outcome measure? For the individual living with diabetes, ease of use and quality of life are more salient and arguably more important, especially once reasonable glycemic control has been achieved. Consistent and reliable measures of these outcomes were not present in the studies utilized for the meta-analysis.

Future studies comparing state-of-the-art insulin pump therapy to modern injection regimens must venture beyond HbA1c. Long-term clinical outcome data is sorely lacking and is difficult to acquire when technology changes so rapidly. The technological breakthrough of automated insulin delivery further incentivizes utilization of pump technology. However, the benefit may be emulated for those on injections with decision support tools. Regardless, having multiple efficacious, affordable options for diabetes care is of great benefit to patients and advances the field of diabetes technology.

Real-world costs of continuous insulin pump therapy and multiple daily injections for type 1 diabetes: a population-based and propensity-matched cohort from the Swedish National Diabetes Register

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Diabetes Care 2019; **42**: 545–552

Background

The objective of this study was to investigate real-world costs of continuous insulin pump therapy compared with multiple daily injection therapy for type 1 diabetes. It is important to understand from a healthcare planning perspective is whether real-world data match earlier model-based predictions for differences in resource use and costs for those on injection and pump.

Methods

Individuals with type 1 diabetes and pump therapy in the Swedish National Diabetes Register (NDR) since 2002 were eligible. Control subjects on MDI were matched 2:1 using time-varying propensity scores. Longitudinal data on healthcare resource use, anti-diabetes treatment, sickness absence, and early retirement were taken from national registers for 2005–2013. Mean annual costs were analyzed using univariate analysis. Regression analyses explored the role of sociodemographic factors. Subgroup and sensitivity analyses were performed.

Results

In all, 14,238 individuals with type 1 diabetes entered in the NDR between 2005 and 2013 were included. There were 4,991 insulin pump users and 9,247 multiple daily injections with switches allowed during the study. Mean age at baseline was 34 years, with 21 years of diabetes duration and a mean HbA1c of 8.1% (65 mmol/mol) with 73,920 person-years of observation with a mean follow-up of 5 years per participant. Mean annual costs were higher for pump therapy than for MDI therapy (\$12,928 vs. \$9,005, respectively; $P < 0.001$; mean difference \$3,923 [95% CI \$3,703–\$4,143]). Healthcare costs, including medications and disposables, accounted for 73% of the costs for pump therapy and 63% of the costs for MDI therapy. The difference in annual medication costs, including disposables, was \$3,600, indicating that they contributed significantly to overall annual cost differences. Medication costs excluding consumables were lower in CSII users and as expected the biggest cost difference was due to consumable cost. Regression analyses showed higher costs for low education, low disposable income, women, and older age.

Conclusions

Nine years of real-world data on all measurable diabetes-related resource use show robust results for additional costs of insulin pump therapy in adults by subgroup and alternative propensity score specifications. The identification of both tangible and intangible benefits of pump therapy over time continues to be important with respect to support resource allocation decisions.

Comment

A previous study from the Swedish National Diabetes Register by Steineck et al. showed that pump users had a significantly lower hazard ratio for fatal coronary heart disease (0.55 [95% CI 0.36, 0.83]), fatal cardiovascular disease (0.58 [0.40, 0.85]), and all-cause mortality (0.73 [0.58, 0.92]) (11).

However, the current analysis, also from the same database and the same period but in a much larger cohort of pump users ($n=4991$ vs $n=2441$), found higher outpatient and inpatient costs for cardiovascular comorbidities in pump users, which may be seen as a contradictory finding. In addition, there was no difference between pump and injection users in overall mortality in the current analysis and similar rates of cardiovascular disease.

Authors provide some explanations to this apparently contradictory finding. Steineck et al. (11) investigated the relative risks of complications based on time to the first event, whereas the current study summarized costs of all events of complications and regular healthcare use, medications, and production loss, given that all contribute to total annual costs. At baseline, the proportion of previous cardiovascular disease in the study by Steineck et al. was 5% versus 8% of the pump versus multiple daily injection groups, respectively, whereas it was 2.5% in both groups of the current study. The overall incidence rate of first events with cardiovascular disease for this study cohort was 9 per 1,000 person-years, whereas the corresponding figure for the study by Steineck et al. was 12.5 per 1,000 person-years.

Ultimately, the fundamental clinical question is whether pump therapy is associated with a reduction in cardiovascular and overall mortality independent of HbA1c and other factors. At least based on the current study, which included a more substantial cohort of pump users, there appears to be no difference between multiple daily injections and pumps in cardiovascular morbidity and mortality and overall mortality. Further studies are warranted to investigate whether pump therapy is associated with benefits beyond HbA1c and hypoglycemia reduction.

Long-term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: a 10-year retrospective controlled study

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Nutr Metab Cardiovasc Dis 2019; **29**: 1110–1117

Background

Excess weight is a growing concern for those with type 1 diabetes. It is unclear whether body composition varies with the use of insulin pump or multiple daily injections.

Methods

This was a retrospective controlled study comparing long-term body weight trajectories. Adult participants with type 1 diabetes on pump or injection were strictly matched for sex, age, BMI, and diabetes duration. Annual changes in body weight, HbA1c and total daily insulin doses were retrospectively analyzed.

Results

Six to ten years of data (mean follow-up 9.1 ± 1.4 years) from 90 participants on insulin pump and 90 participants on multiple daily injections were analyzed. Body weight increased linearly about 0.5 kg/year throughout the observation period with no significant difference between the treatment groups ($P=0.74$) regardless of BMI. HbA1c over follow-up was lower in the insulin pump group ($P=0.037$). Among pump users, insulin doses were stably about 20% lower than baseline. Among injection users, insulin doses increased about 20% from baseline. Mean annual weight change correlated with total insulin dose ($r=0.191$; $P=0.011$), baseline HbA1c ($r=0.267$; $P=0.001$), HbA1c changes (-0.173 ; $P=0.021$) and baseline age ($r=-0.254$; $P=0.001$).

Conclusions

People with type 1 diabetes had improved glycemic control and decreased insulin doses while on insulin pump. Despite this pump and injections users showed comparable weight gain over a maximum 10-year follow-up.

Comment

As we continue to improve glycemic control, insulin delivery can come with consequences of hypoglycemia and weight gain (12). It is unclear whether pump therapy would have different effects on weight versus injection therapy. Insulin pump therapy is associated with reduction in daily insulin and improved glycemic control with reduced episodes of hypoglycemia. There are complex competing factors in the balance of weight with pump therapy. Increased insulin delivery is universally associated with weight gain. Less hypoglycemia means decreased intake of carbohydrates, and thus calories. However, improved glycemic control may reduce calories lost to glycosuria. For pump users, there are also fewer barriers to bolusing for additional carbohydrates.

The above study examined 180 individuals with type 1 diabetes, 90 used an insulin pump and 90 used multiple daily injections with comparable sex, age, baseline body weight/height/BMI, diabetes duration, HbA1c, and total daily insulin. Weight gain over the follow-up period was consistent between both cohorts, with a mean of 0.5 kg/year. HbA1c and total daily insulin doses decreased significantly the first year after initiating insulin pump therapy and the decrease was maintained over the follow-up period. In the injection cohort, HbA1c levels did not significantly change and daily insulin doses increased. Weight change correlated with total daily insulin, baseline HbA1c, change in HbA1c, and baseline age.

A major limitation of the current study is that insulin doses reflected those prescribed, and data regarding true

insulin delivery was not available. The authors concede that a lack of data on hypoglycemia is another limiting factor of the present study. Despite these concerns, the study is certainly hypothesis generating. It may be that for the insulin pump cohort, decrease in HbA1c particularly from a higher baseline, was more directly associated with weight gain. In the injection cohort younger patients with higher HbA1c at baseline experienced greater weight gain. The findings suggest that mechanism of weight gain may differ between injection and pump therapy.

NOVEL INSULINS IN PUMPS

A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5)

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Diabetes Obes Metab 2019; **21**: 961–967

This manuscript is also discussed in the article on New Insulins, Biosimilars and Insulin Therapy, page S-32.

Background

Faster-acting insulin aspart is aspart insulin formulated with the excipients niacinamide and L-arginine; it has an earlier onset and earlier glucose-lowering effect than insulin aspart and earlier offset of action. This study aimed to evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) versus insulin aspart (IAsp) used in CSII in adults with type 1 diabetes.

Methods

This was a double-blind, treat-to-target, randomized, multicenter (92 sites in nine countries), 16-week trial investigating CSII treatment with faster aspart ($n=236$) or IAsp ($n=236$) for which adults (≥ 18 years) with type 1 diabetes (diagnosed clinically for ≥ 12 months), HbA1c 7.0%–9.0% (53 to 75 mmol/mol) and body mass index ≤ 35 kg/m², were eligible.

At randomization, participants switched from pretrial insulin to faster aspart or IAsp, both double-blind, on a unit-for-unit basis, keeping current pump parameters the same. During the 16-week treatment period, the fasting and preprandial blood glucose (BG) glycemic target was 71–108 mg/dL (4.0–6.0 mmol/L). Basal rates were adjusted to ensure that BG was kept in a stable range (within 35 mg/dL [2 mmol/L]) while in a fasting state. Mealtime insulin (initiated 0–2 minutes before a meal) was titrated based on carbohydrate counting using a bolus dose calculator according to usual practice.

In addition, participants had venous glucose levels assessed before and after a bolus dose of faster aspart or IAsp (0.1 units/kg, calculated by the investigator), which was followed by a standardized liquid meal (Ensure, Abbott Nutrition, Columbus, OH; 78 g carbohydrate consumed within 12 minutes). All participants were provided with a blinded CGM device to wear during three trial periods: (a) before randomization (including during the pretreatment meal test); (b) before the eighth week after randomization; and (c) before the 16th week after randomization (including during the within-treatment meal test).

Results

A total of 472 participants were randomized to CSII treatment with either faster aspart ($n=236$) or IAsp ($n=236$) between July 2016 and July 2017. Faster aspart was non-inferior to IAsp regarding the change from baseline in HbA1c; primary endpoint. The mean HbA1c changed from 7.5% (58.4 mmol/mol) at baseline to 7.4% (57.8 mmol/mol) with faster aspart and to 7.4% (56.8 mmol/mol) with IAsp after 16 weeks' treatment, with an estimated treatment difference (ETD) of 0.09% ([95% CI 0.01, 0.17]; $P<0.001$) or 1.0 mmol/mol (95% CI 0.14, 1.87) for noninferiority (0.4% margin; $P<0.02$ for statistical significance in favor of IAsp). Faster aspart was superior to IAsp in change from baseline in 1-h postprandial glucose (PPG) increment after a meal test (ETD -16.4 mg/dL [$-25.7, -7.0$]; $P=0.001$ or -0.91 mmol/L [$-1.43, -0.39$]), with statistically significant reductions also at 30 min and 2 h. Change from baseline in 1-h interstitial glucose (IG) increment after all meals (ETD -3.77 mg/dL [$-5.53, -2.01$] or -0.21 mmol/L [$-0.31, -0.11$]). At week 16, the percentage of time spent with low IG (70 mg/dL [≤ 3.9 mmol/L]) was 5.5% and 5.8%, and for IG in target range (71–180 mg/dL [4.0, 10.0 mmol/L]) it was 52.4% and 54.5% with faster aspart and IAsp, respectively. The 24-hour IG profiles at week 16 between faster aspart and IAsp were broadly similar, although the median and interquartile range IG values during the night trended higher compared with baseline in the faster aspart group. There was no statistically significant difference in the overall rate of severe or blood glucose-confirmed hypoglycemia (estimated rate ratio of 1.00 [0.85, 1.16]). A higher rate of severe or BG-confirmed hypoglycemic episodes was observed for faster aspart vs IAsp within the first hour after the start of a meal (1.25 vs 0.71 events/PYE; estimated rate ratio 1.78 [1.15, 2.75]), with no statistically significant differences at other intervals during the first 4 h after the start of the meal. A numerical imbalance in severe hypoglycemic episodes between faster aspart and IAsp was seen in the treatment (21 vs 7) and 4-week run-in periods (4 vs 0). The event rate for infusion-site reactions considered possibly or probably related to trial product was

numerically higher with faster aspart (5.5% of participants [0.29 events/PYE]) vs IAsp (3.8% of participants [0.18 events/PYE]). The mean number of infusion-set changes per week was similar in the faster aspart and IAsp groups (2.55 vs 2.49, respectively). A similar rate of non-routine infusion-set changes was reported with faster aspart and IAsp (6.97 vs 6.68 events), although a higher proportion of participants reported non-routine changes with faster aspart vs IAsp (71.2% vs 57.2%).

Conclusions

In this study, use of faster aspart during CSII was non-inferior to IAsp. However, the superiority of faster aspart over IAsp in the change in HbA1c was not confirmed, with a small but statistically significant difference in favor of IAsp. Faster aspart significantly improved PPG increment vs IAsp at 30 min, 1 h, and 2 h after a standardized liquid meal test, and CGM IG postprandial increments supported this difference.

Comment

During this large, well-conducted study, the use of faster aspart led to superior postprandial glucose control compared to IAsp. This was seen during liquid meal tests as well as real-life sensor glucose profiles. However, these lower postprandial glucose excursions did not translate to a superior HbA1c reduction compared to IAsp. In fact, IAsp led to statistically superior HbA1c reduction, which is in contrast to the onset 1 study where the use of faster aspart led to superior HbA1c reduction compared to IAsp in those using multiple daily injection therapy (13).

What are the possible explanations for this apparently contradictory result? Analysis of sensor glucose profiles (these were only done for short periods) has shown a tendency for higher nocturnal and premeal levels of IG for participants receiving faster aspart. This may have countered the expected overall glycemic benefit of improved PPG control. While the reasons underlying this rise in IG are unclear, it may be that the use of faster aspart in pumps requires further optimizations taking into account different action profile of faster aspart. Due to the double-blind nature of this study, equal dose adjustments were applied in both arms, but this may have inadvertently disadvantaged Fiasp group.

In clinical practice, we have noted the need for more frequent use of dual-wave/extended bolus for the particular types of meals, especially the evening meal with more slowly absorbing foods such as pasta, rice, or combined high fat/protein meals where absorption is delayed. Not using dual-wave bolus for such meals could increase the risk of immediate postprandial hypoglycemia as seen in this study followed by late postprandial hyperglycemia and nocturnal hyperglycemia in the case of the evening meal. In addition, due to the early offset of faster aspart, glucose levels may start to rise before the next meal unless basal insulin is adjusted during this period. Specific recommendations for the use of faster aspart in CSII may include a different distribution of

insulin doses between basal and bolus, undertaking specific basal tests to identify correct basal requirements at different times of the day and more frequent use of dual-wave or other extended bolus functions (14).

The occurrence of a burning or stinging sensation around the infusion site and/or need for more frequent set-change due to unexpected glucose excursions have been reported in some individuals using faster aspart in clinical practice. During the onset 5 study, event rate for infusion-site reactions considered possibly or probably related to the trial, the product was numerically higher with faster aspart, and a higher proportion of participants reported nonroutine changes with faster aspart vs IAsp (71.2% vs 57.2%). Whether this is a chance finding or there is a genuine difference between these two insulins in terms of tolerability remains to be seen.

In conclusion, use of Fiasp might be a useful strategy to reduce postprandial glucose excursions in some individuals treated with CSII. Particular attention needs to be paid to avoid early postprandial hypos by judicious use of dual-wave bolus as well as focusing on accurate carb counting. Additional basal checks may be required during overnight and premeal periods as bolus action of faster aspart tend to wear off more quickly than IAsp, and previous basal rates may not necessarily be adequate.

BioChaperone lispro versus faster aspart and insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion: a randomized euglycemic clamp study

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Diabetes Obes Metab 2019; **21**: 1066–1070

Background

BioChaperone insulin lispro (BCLIS) is an investigational ultra-rapid-acting insulin lispro formulation that contains the BioChaperone BC222, a novel oligomeric excipient derived from natural molecules, and citrate, both acting in the subcutaneous tissue to further promote (a) insulin lispro hexamer dissociation and (b) monomer absorption from the subcutaneous tissue to the bloodstream. Faster insulin aspart (FIA) achieves faster absorption through the addition of niacinamide and L-arginine as absorption modifiers. This study aimed to investigate the pharmacodynamics and pharmacokinetics of BioChaperone insulin Lispro (BCLIS), FIA, and insulin aspart (ASP) in patients with type 1 diabetes using an insulin pump.

Methods

This was a randomized, single-center, double-blind, three-treatment, three-period, crossover, phase 1 trial in 43 participants with type 1 diabetes. Male and female patients 18–64 years old with type 1 diabetes for at least 12 months with

HbA1c less than 9.0% and BMI between 18.5 and 28.5 kg/m² who were on a stable insulin regimen using an insulin pump or multiple daily injections for at least 2 months prior to inclusion were enrolled. Participants received BCLIS, FIA, or ASP in one of six possible sequences as determined through randomization. The cannula was inserted subcutaneously in the lower abdominal wall at the beginning of each dosing visit, using a different location at each dosing visit. At approximately 9:00 a.m., participants received an initial priming dose of 0.04 units/kg of BCLIS, FIA or ASP, followed by a basal rate of 0.01 units/kg-hour for 15 hours. Approximately 5 hours after initiation of the priming dose, a single bolus dose of 0.15 units/kg of BCLIS, FIA, or ASP was given in addition to basal infusion. A euglycemic clamp procedure was initiated 30 minutes before the priming dose and continued for 15 hours.

Results

With BCLIS, the area under the curve for glucose infusion rate, 0–60 minutes (primary endpoint), was improved compared with ASP (the least square means ratio, 1.63 [95% CI 1.44–1.88]; $P < 0.0001$) and was similar compared with FIA (least-square means ratio, 1.06 [95% CI 0.94–1.18]; $P = 0.4609$). BCLIS showed faster onset of action than ASP and faster offset of action than both FIA and ASP. With BCLIS, time to reach 50% of maximum action (maximum GIR) was 13 minutes earlier, and time to maximum action (maximum GIR) was 23 minutes earlier compared to ASP. The offset of action (assessed by time to reduce maximum GIR by 50%) was 23 minutes earlier with BCLIS than with ASP and 19 minutes earlier than with FIA.

Conclusions

This clamp study demonstrated earlier insulin absorption and earlier onset of action with BCLIS compared to ASP when administered via CSII. The onset of action was similar to BCLIS and FIA, but offset appeared to be faster with BCLIS. No safety concerns emerged with BCLIS.

Comment

Results from this study show faster onset and faster offset of action of BCLIS compared to ASP, which should, in theory, help to reduce early postprandial hyperglycemia and late postprandial hypoglycemia. As with faster aspart studies (15), there is a potential risk of early (<1 hour) hypoglycemia with BCLIS. Further studies are required to assess the effectiveness, compatibility, and stability of BCLIS in insulin pumps under typical day to conditions. Also, as shown in the onset 5 study (16), having a faster-acting insulin per se may not necessarily improve overall glucose control in CSII users. We also need to think about faster offset of action, which may affect how basal rate settings and bolus action may finish before full absorption of food has taken place. There is a need for more studies to better understand the optimal use of these newer ultra-fast insulins during CSII. Future use in closed-loop systems is also of great interest.

SPECIFIC DEVICE PERFORMANCE

Insulin bolus administration in insulin pump therapy: effect of bolus delivery speed on insulin absorption from subcutaneous tissue

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Diabetes Technol Ther 2019; **21**: 44–50

Background

Pumps deliver insulin boluses at different speeds. Subcutaneous absorption kinetics of rapid-acting insulin bolused at different speeds have not previously been measured.

Methods

Twenty individuals with type 1 diabetes and no detectable C-peptides were studied on two occasions, separated by at least 7 days, using the euglycemic clamp. Subjects were bolused Lispro 15 units with either an Animas IR2020 pump (max speed on fast bolus delivery 1 unit every 2 seconds) or Medtronic Paradigm 512 (slow bolus delivery speed 1 unit every 40 seconds). After an overnight fast, subjects were randomized to receive the bolus over 30 seconds from the Animas pump (fast bolus delivery) or over 10 minutes using the Medtronic pump.

Results

From the pharmacodynamics studies fast bolus delivery resulted in significantly ($P < 0.002$) earlier glucose infusion (21.0 ± 2.5 minutes) as compared to slow bolus delivery (34.3 ± 2.7 minutes). Furthermore, time to reach maximum glucose infusion was 98 ± 11 minutes for fast bolus and 125 ± 16 minutes for slow bolus delivery ($P < 0.005$). From the pharmacokinetic studies time to reach 10% max insulin concentration ($P = 0.003$) and time to reach 50% max insulin concentration ($P = 0.046$) were lower in the fast bolus group. Area under the plasma insulin curve from 0 to 60 minutes was greater with the fast bolus ($P = 0.027$).

Conclusions

Under euglycemic clamp conditions, fast bolus delivery provided more rapid pharmacokinetics and pharmacodynamics. In theory, this may provide a better control of postprandial glucose excursions.

Comment

Insulin pumps manufacturers offer unique bolus delivery speeds and newer Medtronic variants allow bolus speed selection (17). It is unclear if the differences in delivery speed carry any clinical benefit. As a first step in evaluating the theoretical benefits, Regittnig and colleagues performed a euglycemic clamp study with 15 units insulin Lispro delivered at different speeds.

The pharmacokinetic and pharmacodynamics results exceed the difference in speed of bolus alone (9.5 minutes). The authors suggest that this difference with

fast delivery may be due to increased tissue pressure that facilitates convective flow and volume of distribution that increases capillary surface area for absorption. The authors concede that high delivery speed may have potential consequences such as leakage of insulin back to the skin surface and burning sensation at the cannula insertion site.

The authors conclude that bolus delivery times of 1 minute or less will result in fewer delays in subcutaneous absorption. It will be crucial to perform masked clinical trials to confirm if these pharmacokinetic and pharmacodynamic studies prove beneficial for overall glycemic control.

Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomized controlled trial

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Lancet Diabetes Endocrinol 2019; 7: 462–472

This manuscript is also discussed in the article on Continuous and Intermittent Glucose Monitoring in 2019, page S-3.

Background

Hypoglycemia remains a crucial barrier to achieve near-normal glucose control. This study aimed to assess the safety and efficacy of insulin pump therapy with integrated CGM and a suspend-before-low feature (Medtronic MiniMed 640G with SmartGuard) in hypoglycemia-prone adults with type 1 diabetes in comparison with CSII with self-monitoring of blood glucose.

Methods

The SMILE study was an open-label randomized controlled trial carried out in people aged 24–75 years with type 1 diabetes for 10 years or longer, HbA1c values of 5.8%–10.0% (40–86 mmol/mol), and at high risk of hypoglycemia (recent severe hypoglycemia or hypoglycemia unawareness defined by a Clarke or Gold score ≥ 4). Participants were enrolled from 16 centers in Canada, France, Italy, the Netherlands, and the United Kingdom. After baseline run-in phase (2 weeks), participants were randomly assigned to the MiniMed 640G pump with self-monitoring of blood glucose (control group) or to the MiniMed 640G system with the suspend-before-low feature

enabled (intervention group), for 6 months. Because of the nature of the intervention, participants and treating clinicians could not be masked to group assignment. The primary outcome was the mean number of sensor hypoglycemic events, defined as 55 mg/dL (3.1 mmol/L) or lower for more than 20 minutes consecutively, and was analyzed on an intention-to-treat basis in all randomly assigned participants.

Results

Between December 2016, and March 2018, 153 participants (mean age 48.2 ± 12.4 years) were randomly assigned to the control group ($n=77$; mean age 47.4 ± 12.5 years) and the intervention group ($n=76$; mean age 49.0 ± 12.2 years). During the 6-month study phase, the intervention group used CGM a mean of $90.4 \pm 9.3\%$ [95% CI 88.3–92.5] of the time. The mean number of suspend-before-low events in the intervention group was 2.5 (SD 0.6; median 2.5, IQR 2.1–3.0) per participant per 24-hour period and 1.4 (0.2; median 1.4, IQR 1.2–1.5) per participant per night. After 6 months, the intervention group had significantly fewer hypoglycemic events per participant per week (1.1 [SD 1.2] vs 4.1 [SD 3.4] mean events, model-based treatment effect -2.9 [95% CI -3.5 , -2.3]; $P<0.0001$) and fewer severe hypoglycemic events (instances requiring third-party assistance with carbohydrate or glucagon administration, or other resuscitative actions) overall (3 vs 18; $P=0.0036$). Compared with the control group, the intervention slightly increased the overall TIR of 70–180 mg/dL (57.8% vs 59.9%; $P=0.047$), probably driven by the significantly increased TIR during the night (57.5% vs 62.2%; $P=0.0087$). Although the intervention increased the amount of time spent at a glucose concentration greater than 180 mg/dL during the day ($P=0.030$) compared with the control group, it did not affect the amount of time spent at hyperglycemic ranges (>180 mg/dL to >300 mg/dL) overall or at night. From baseline to the end of the study phase, the mean change in HbA1c was -0.25% (SD 0.64) for the control group and -0.16% (0.80) for the intervention group (between-group difference of 0.09; $P=0.44$). The most common adverse events were hypoglycemia (observed in 10 [13%] of 77 participants in the control group vs 4 [5%] of 76 in the intervention group) and hyperglycemia (observed in seven [9%] of 77 vs seven [9%] of 76). No serious adverse device effects or episodes of diabetic ketoacidosis were reported.

Conclusions

Compared with the use of continuous subcutaneous insulin infusion without real-time CGM, insulin pump therapy with integrated CGM and a suspend-before-low feature resulted in a fewer occurrences of sensor hypoglycemic and severe hypoglycemic events in hypoglycemia-prone adults. These results suggest that this technology could be beneficial in this high-risk population.

Comment

Two previous randomized studies have evaluated the short-term (2 weeks) (18) and long-term (6 months) (19) impact of suspend-before-low feature in children and adolescents. The current study is the first randomized trial to assess the safety and efficacy of an insulin pump with a

suspend-before-low feature in a large hypoglycemia-prone adult population with type 1 diabetes. In the present study, the inclusion of adults with impaired awareness of hypoglycemia or a documented severe hypoglycemia event who are prone to disabling hypoglycemia is a significant strength. When used for 6 months, this intervention not only significantly reduced all levels of hypoglycemia but also showed a clinically and statistically relevant reduction in the frequency of severe hypoglycemic events without deterioration of overall glucose control. There was a small increase in the time spent in hyperglycemia during the daytime in the intervention group. One criticism of the study is not using real-time sensors in the control group so we cannot identify the incremental value of suspend-before-low technology from real-time sensors alone with alarms.

Accuracy of bolus and basal rate delivery of different insulin pump systems

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Diabetes Technol Ther 2019; **21**: 201–208

Background

Insulin pumps deliver quasi-continuous basal rates and bolus insulin to individuals with diabetes. This is an *in vitro* study of different commercial insulin pumps examining the accuracy of delivery.

Methods

Accuracy of 10 different insulin pump and infusion set combinations were tested. These systems included: (1) Roche Accu-Check Insight with 6mm Teflon (Insight Flex) and 6 mm Steel (Insight Rapid) infusions sets; (2) Roche Accu-Check Spirit Combo with 8mm Teflon (FlexLink) and 6mm Steel (Rapid-D Link inset™ II) infusion sets; (3) Animas Vibe with 6mm Teflon (inset™ II) infusion set; (4) MiniMed 640G with 6mm Teflon (Quick-Set) infusion set; (5) Insulet OmniPod patch pump with 6.5mm Teflon catheter; and (6) Medtronic Paradigm VEO™ with 6mm Teflon (Mio™), 6mm Teflon (Quick-Set), and 6mm Steel (Sure-T) infusion sets. Accuracy was determined by means of weight differences through insulin delivery into a water-filled, oil-covered beaker placed on a balance. The method was modified for the patch pump due to lack of infusion set. Mean bolus accuracy of 25 successive 1-unit boluses and of 12 successive 10-unit boluses was assessed, and delivery time for 10-unit boluses was measured. Basal rate accuracy at 1.0 unit/hour was evaluated for 72 hours and for individual 1-hour periods.

Results

For both the 1-unit and 10-unit boluses, delivery was within 5% of target. Bolus precision was greater with the larger boluses. Delivery speed was in line with manufacturer

specifications. The total deviation for 72 hours was less than 2.6% in all pumps. Basal rate accuracy demonstrated the largest deviation during the first 12 hours (from a mean of 0.1% deviation for the Accu-Check Insight to 9.9% for the MiniMed 640G). For basal delivery assessed in 1-hour windows, the largest variation was seen for the OmniPod.

Conclusions

In general, the compared pumps showed similar accuracy and delivery speed in line with manufacturer specifications. When considering each hour of basal delivery separately the patch pump showed more deviation than tethered pumps.

Comment

Insulin pumps demonstrate greater dose accuracy than injection or insulin pens (20). However, differences in insulin pump delivery accuracy has not been elucidated in detail. In the present study, Freckmann and colleagues perform detailed analysis of various modern insulin pump systems utilizing different infusion sets.

One-unit bolus accuracy was most precise for the Paradigm VEO™ with Sure-T infusion set and Animas Vibe, while there was greatest deviation for OmniPod. The larger 10-unit bolus demonstrated reasonable accuracy for all systems. At standard speed setting, the Animas Vibe offered the most rapid delivery time (20 seconds) while the MiniMed 640G and OmniPod were the slowest (6 minutes 38 seconds and 6 minutes 39 seconds, respectively). The most obvious discrepancy in initial basal delivery was for the Animas Vibe and MiniMed 640G. Basal delivery was most precise for the Accu-Check Spirit Combo with Rapid-D Link inset™ II infusion set. The OmniPod showed the greatest hourly variation in basal delivery.

This *in vitro* comparison of insulin pumps involved the most systems tested in parallel. There are a few limitations. Because testing procedures varied between OmniPod and tethered pumps, it is uncertain if differences were due to the differences in assay. While differences from insulin infusion sets were not profound, some did exist. Indeed, there was some concern that the performance of the Medtronic 640G pump may have been hampered by the recalled infusion sets utilized during the experiment. It remains to be seen whether the current *in vitro* testing is reflective of *in vivo* performance wherein the infusion set plays a larger role. Most importantly, future head-to-head clinical trials are needed to determine if the differences reported here have any meaningful clinical impact.

Comparative dose accuracy of durable and patch insulin pumps under laboratory conditions

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Diabetes Technol Ther 2019; **21**: 371–378

Background

There is some debate and controversy about the accuracy of different types of insulin pumps. The aim of this study was to measure dose accuracies of the patch pump Insulet OmniPod in comparison with the durable insulin pump MiniMed 640G simulating real-life clinical situations under laboratory conditions.

Methods

Thirty-two OmniPod and 15 MiniMed 640G were tested using insulin aspart at five different boluses (0.5, 1, 5, 10, and 15 units) and three basal rates (0.2, 0.6, and 1.8 units/hour) at different time points during a 70-hour investigation period. Owing to malfunctions, only 22 OmniPod and 11 MiniMed 640G could be analyzed. Dose accuracy was measured by an experimental setting based on IEC 60601-2-24:2012 with determination of weight differences of insulin collection tubes before and after experiments using a precision scale. A maximal tolerance of $\pm 5\%$ for boluses and basal rates was considered adequate according to IEC 60601-2-24:2012.

Results

For the five boluses (0.5, 1, 5, 10, and 15 units), the percentages of measurement results within the $\pm 5\%$ accuracy threshold were as follows: OmniPod (18.6%, 26.5%, 89.0%, 96.0%, and 96.0%); MiniMed 640G (21.7%, 44.1%, 88.1%, 98.3%, and 100.0%). Both pumps were more accurate at higher bolus volumes (5, 10, and 15 units), later bolus periods. The outcomes of individual bolus volumes revealed that OmniPod values displayed a more precise average, but more individual outliers. For the three basal rates 1.8, 0.6, and 0.2 units/hour, the percentages within the $\pm 5\%$ accuracy threshold were as follows: OmniPod (66.7%, 22.7%, and 16.7%); MiniMed 640G (14.3%, 0.0%, and 0.0%) and at $< 10\%$ accuracy threshold OmniPod (85.7%, 54.6%, 25%); and MiniMed 640G (78.6%, 7.1%, 0.0%).

Conclusions

This study demonstrates low accuracy for basal rates and single bolus deliveries at low insulin doses for both pump models. Percentage of correctly delivered basal insulin $\pm 5\%$ and 10%, at all three basal rates, were numerically higher with OmniPod. Clinicians should be aware of this variability when initiating insulin pump therapy, especially in insulin-sensitive patients with low insulin dose requirements.

Comment

This study assessed the accuracy of two well-established pumps, the OmniPod and MiniMed 640G. Although authors were experiencing more frequent acute complications such as hypoglycemia and ketoacidosis with OmniPod pump, results of the study do not support any inferiority of OmniPod pump compared with MiniMed 640G within the confines and testing methods employed in this study. When assessing basal accuracy, authors did not assess single pulse accuracy (rather assessed accuracy over 22 hour periods) but given that subcutaneous insulin is absorbed over a period of time, single pulse

accuracy may not be that critical. In contrast, even single bolus dose accuracy can be clinically relevant, especially in those with high insulin sensitivity. Accuracy of both pumps at low bolus doses was low, and OmniPod had more outliers but more precise average.

Under real-life conditions, many other factors may also affect the accuracy of insulin delivery and absorption after delivery. These include the presence of lipohypertrophy or scarring, local trauma and inflammation around cannula site, and type of cannula (21). These latter factors may be more critical for a given individual than any subtle differences between dosing accuracy between pumps. A previous study has compared different insulin pumps under real-life conditions over extended follow-up periods and found no clinically relevant difference between different pump models in terms of HbA1c reduction (22).

Author Disclosure Statement

R.L. has research support from the NIDDK (1K12DK122550) and Stanford Maternal Child Health Research Institute. Dr. Lal has consulted for GlySens Incorporated and Abbott Diabetes Care. L.L. reports having received speaker honoraria from Animas, Abbott, Insulet, Medtronic, Novo Nordisk, Roche, and Sanofi. Advisory panel for Animas, Abbott, Novo Nordisk, Dexcom, Medtronic, Sanofi, and Roche. Research support from Novo Nordisk and Dexcom.

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