ORIGINAL ARTICLE

Insulin Pumps

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Introduction

IN THIS YEAR'S REVIEW, we have chosen notable papers on insulin pump therapy that deal with four of the themes that have preoccupied investigators and clinical practitioners for several decades: the comparative effectiveness of continuous subcutaneous insulin infusion (CSII) and insulin injection therapy; the factors that determine the effectiveness of CSII; the role of CSII in type 2 diabetes; and the safety and reliability of pump therapy. In addition, we include papers concerning two emerging technologies that have the potential to further improve glycemic control in CSII: new ultra-fast-acting insulin used in CSII and predictive low-glucose insulin-suspend (PLGS) pumps.

The impact of the psychological profile of patients who are being treated with CSII has been discussed since the earliest days of insulin pump therapy, particularly the need for patients to be willing and motivated to get best results, as well as the need for caution when candidates for CSII have a major psychological illness such as depression. The last issue has been somewhat revised in recent years, now that we realize many depressed patients can have good outcomes with CSII, and this should not now be a barrier to a trial of pump therapy. But the interaction of personality type and clinical outcome in diabetes technology continues to gather an evidence base. Here, locus of control and how much patients believe they can influence events and outcomes (like the quality of diabetes control) is the main issue.

The evidence for CSII being more effective than multiple daily insulin injections (MDI), or not, waxes and wanes over the years, and papers are nearly always difficult to interpret: do the patients have a clinical problem at baseline such as disabling hypoglycemia or elevated hemoglobin A1c (HbA1c), or were such groups excluded from the trial, have patients failed best injection therapy (including structured diabetes education) before switching to CSII; what was the type and quality of MDI; was CSII performed optimally with modern pumps and insulins, with structured training, regular follow up, use of computer downloads and bolus calculators, etc.? The paper included here (the REPOSE Study) will likely be much discussed, as it shows that adding CSII to structured diabetes education in a particular group of MDI-treated patients with type 1 diabetes did not further improve glycemic control, but there are many considerations in its interpretation and the meaning for clinical practice, which we briefly note. On the other hand, we review a paper that indicates the success of pump therapy: switching patients with type 1 diabetes from MDI with continuous glucose monitoring (CGM) to CSII with CGM produces additional glycemic benefit.

If insulin pumps are to be used in the large number of people with type 2 diabetes who have poor control on their present therapy, it will be important to identify those who have the biggest improvement on changing from MDI, and an individual patient data meta-analysis of all recent randomized controlled trials points to the best effect in those with the highest baseline HbA1c and insulin dose.

We discussed the recently introduced PLGS pumps and their potential for reducing hypoglycemia in last year's yearbook; they are now established in clinical practice in several countries, and three papers included in this article confirm the value of such pumps in reducing CGM-measured hypoglycemia, including after exercise. But there

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is still a lack of information on long-term PLGS pump performance in adults and the effects on severe hypoglycemia frequency as opposed to short-term effects on CGM values. The same plea for long-term evaluation applies to testing of ultra-fast-acting insulins when used in pumps—although there are first indications of lower postmeal glucose values and less hypoglycemia from a trial performed over a few weeks, and which is included in this article.

As diabetes technology becomes more technically complex, there is a danger that reliability may be compromised. Here, two papers on pump malfunctions confirm that reliability has not much improved with modern devices and the most sophisticated models may be the most unreliable. This is an issue that needs addressing as highly complex closed-loop systems are introduced into everyday clinical practice.

Key Articles Reviewed for the Article

Influence of health locus of control and fear of hypoglycaemia on glycaemic control and treatment satisfaction in people with type 1 diabetes on insulin pump therapy

Indelicato L, Mariano V, Galasso S, Boscari F, Cipponeri E, Negri C, Frigo A, Avogaro A, Bonora E, Trombetta M, Bruttomesso D

Diabet Med 2017; **34**: 691–697

Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE)

The REPOSE Study Group

BMJ 2017; **356**: j1285

Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial

Beck RW, Riddlesworth TD, Ruedy KJ, Kollman C, Ahmann AJ, Bergenstal RM, Bhargava A, Bode BW, Haller S, Kruger DF, McGill JB, Polonsky W, Price D, Toschi E; for the DIAMOND Study Group

Lancet Diabetes Endocrinol 2017; **5**: 700–708

Improved postprandial glycaemic control with faster-acting insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion

Bode BW, Johnson JA, Hyveled L, Tamer SC, Demissie M

Diabet Technol Ther 2017; **19**: 25–33

Glycemic control during continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: individual patient data meta-analysis and meta-regression of randomized controlled trials

Pickup JC, Reznik Y, Sutton AJ

Diabetes Care 2017; **40**: 715–722

Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial

Battelino T, Nimri R, Dovc K, Phillip M, Bratina N

Diabetes Care 2017; **40**: 764–770

“Let the algorithm do the work”: reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients

Biester T, Kordonouri O, Holder M, Remus K, Kieninger-Baum D, Wadien T, Danne T

Diabet Technol Ther 2017; **19**: 173–182

Effectiveness of a predictive algorithm in the prevention of exercise-induced hypoglycemia in type 1 diabetes

Abraham MB, Davey R, O'Grady MJ, Ly TT, Paramalingam N, Fournier PA, Roy A, Grosman B, Kurtz N, Fairchild JM, King BR, Ambler GR, Cameron F, Jones TW, Davis EA

Diabetes Technol Ther 2016; **18**: 543–550

Insulin pump failures: has there been an improvement? Update of a prospective observational study

Guenego A, Bouzillé G, Breitel S, Esvant A, Poirier J-Y, Bonnet F, Guilhem I

Diabetes Technol Ther 2016; **18**: 820–824

Insulin pump failures in Italian children with type 1 diabetes: retrospective 1-year cohort study

Rabbone I, Minuto N, Bonfanti R, Marigliano M, Cerutti F, Cherubini V, d'Annunzio G, Frongia AP, Iafusco D, Ignaccolo G, Lombardo F, Schiaffini R, Toni S, Tumini S, Zucchini S, Pistorio A, Scaramuzza AE, the Italian Paediatric Pump Failure Study Group

Diabetic Med 2017; **34**: 621–624

DETERMINANTS OF CSII EFFICACY

Influence of health locus of control and fear of hypoglycaemia on glycaemic control and treatment satisfaction in people with type 1 diabetes on insulin pump therapy

Indelicato L¹, Mariano V², Galasso S², Boscari F², Cipponeri E², Negri C³, Frigo A⁴, Avogaro A², Bonora E¹, Trombetta M¹, Bruttomesso D²

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Diabet Med 2017; **34**: 691–697

This manuscript is also discussed in the article on Diabetes Technology and the Human Factor, page S-128.

Background

The effect of psychological factors such as locus of control (LOC) on the level of diabetes control achieved during insulin pump therapy has been poorly studied to date and has yielded conflicting results. The aim of this study therefore was to investigate the impact of LOC and fear of hypoglycemia on HbA1c, hypoglycemia frequency, and treatment satisfaction in adults treated by CSII.

Methods

Type 1 diabetic subjects treated by CSII for at least 1 year (n=214, mean age 43 years, diabetes duration 24 years, and CSII duration 7.5 years) were stratified into those with acceptable control in the previous year (HbA1c ≤7.5% [58 mmol/mol]; n=87) and those with suboptimal control

(HbA1c >7.5% [58 mmol/mol]; n=127). LOC, treatment satisfaction, and fear of hypoglycemia were assessed by standardized questionnaires.

Results

Those with suboptimal glycemic control were more likely to be overweight (body mass index: 25.3 vs. 24.0 kg/m²) and to perform less self-monitored blood glucose (SMBG) tests (5.5 vs. 6.1 per day), and they had fewer mild-to-moderate hypoglycemic episodes in the previous 3 months (12.3 vs. 13.2 episodes). Severe hypoglycemia frequency did not differ between acceptable and suboptimal control groups. Both the mean internal LOC and the treatment satisfaction scores were lower in the sub-optimal control group. Fear of hypoglycemia did not differ between groups. A high internal LOC was negatively correlated with HbA1c ($r = -0.15$, $P < 0.05$) and positively correlated with treatment satisfaction ($r = 0.17$, $P < 0.001$). Fear of hypoglycemia was positively associated with the frequency of severe hypoglycemia and negatively associated with treatment satisfaction.

Conclusions

In adults treated by CSII, a high internal locus of control is an important determinant of good glycemic control and treatment satisfaction.

Comments

The finding here that poor control on CSII is associated with a low internal LOC confirms the results of a previous study that investigated psychological factors and the outcomes of CSII (1). The lack of impact of fear of hypoglycemia on HbA1c has also been noted before (2) and is contrary to the frequently held view that poorly controlled patients tend to resist improvements in therapy because they are concerned that increased hypoglycemia will result.

Internal LOC is a psychological construct that expresses the extent to which we feel success or failure in an endeavor is due to our own efforts and not to luck, chance, or the actions of other people. People with diabetes with a high internal LOC may feel more personally responsible for the management of their diabetes and take a more active role in CSII procedures that give good control, such as adjusting basal insulin rates and meal boluses according to blood glucose tests, adhering to diet and exercise advice, attending the clinic as required, and so on. The good control that results affords a higher degree of treatment satisfaction. Alternatively, of course, those patients who have intrinsically difficult diabetes with highly variable insulin absorption and glycemic control and frequent hypoglycemia may try as hard as others (at least at first) but achieve little success with intensified insulin regimens and therefore conclude that their own efforts have little impact on their diabetes, thus acquiring a low internal LOC.

The patients in this study had a low frequency of both mild-to-moderate and severe hypoglycemia. It is possible that the association of LOC with metabolic outcomes may be different in those with a very high rate of severe hypoglycemia on CSII; perhaps there may be an even stronger link.

COMPARATIVE EFFICACY OF CSII AND MDI

Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE)

The REPOSE Study Group

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BMJ 2017; 356: j1285

Background

It may be hypothesized that much of the benefit of CSII in type 1 diabetes is due to the retraining and education in insulin usage that is usually given with this treatment. The aim of this study was therefore to compare glycemic outcomes in patients treated by either CSII or MDI with both receiving equivalent education in flexible insulin treatment.

Methods

Adults with type 1 diabetes at 8 centers in the United Kingdom, who had no preference for CSII or MDI, underwent group training in flexible insulin treatment (Dose Adjustment for Normal Eating) and were randomly allocated in pairs (n=317) to either CSII or MDI for 2 years. Those with a strong desire for pump treatment, those requiring a pump in the opinion of the investigator, or those meeting NICE (National Institute for Health and Care Excellence) criteria for pump treatment were excluded. The primary outcome was change in HbA1c and secondary outcomes included quality of life and treatment satisfaction.

Results

With an intention to treat analysis of n=260, for those with an HbA1c $\geq 7.5\%$ (58.5 mmol/mol) (119 on CSII and 116 on MDI) the mean decline in HbA1c was -0.85% on CSII and -0.42% on MDI, mean difference after adjusting for baseline -0.24% , $P=0.1$. With a per protocol analysis, the mean difference was -0.36% , $P=0.02$, favoring CSII. The percentage of patients achieving an HbA1c $\leq 7.5\%$ at 2 years was similar in the two groups (25.0 vs. 23.3%, CSII vs. MDI). The frequency of severe hypoglycemia did not differ between groups. Pump users had a greater improvement in treatment satisfaction and in some domains of quality of life such as dietary freedom and daily hassle.

Conclusion

Type 1 diabetic patients allocated to CSII or MDI showed improved HbA1c, hypoglycemia, and some psychological measures with both treatments, but few patients on either treatment reached current glycemic targets. The authors conclude that adding pump treatment to structured diabetes education does not enhance glycemic control or (most) psychological outcomes. Therefore, the policy of providing insulin pumps to adults with poor glycemic control is not supported, until the effects of training in intensive self-management have been determined.

Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial

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Lancet Diabetes Endocrinol 2017; 5: 700–708

This manuscript is also discussed in the article on Continuous Glucose Monitoring in 2017, page S-13.

Background

The aim of this study was to test whether CSII offers additional glycemic benefit to patients with type 1 diabetes treated by MDI and CGM.

Methods

Using patients from the extension phase of the DIAMOND study, adult subjects with type 1 diabetes treated by MDI and

continuous glucose monitoring (CGM) ($n=75$) were randomized to continued MDI + CGM (DexCom G4 Platinum System) or to CSII (Insulet Omnipod) + CGM over 28 weeks. The primary outcome was CGM-measured time-in-range for glucose (3.9–10.0 mmol/L, 70–180 mg/dL).

Results

Mean sensor usage for the trial was high at 6.8 days/week. Over the follow-up period, mean time-in-range for glucose increased significantly by 83 min/day (CSII + CGM vs. MDI + CGM, $P=0.01$), with the greatest effect occurring during the day, and in those with highest baseline HbA1c. Final HbA1c, though lower with CSII + CGM was not significantly different between groups (difference -0.2% , $P=0.32$), in spite of a reduction in mean glucose and various measures of hyperglycemia (e.g., values >10.0 mmol/L, 180 mg/dL) with CSII + CGM. Time spent in the hypoglycemic range was greater with CSII + CGM than MDI + CGM at completion, though there was less hypoglycemia on CSII than at baseline.

Conclusions

Glycemic control as measured by time-in-range was improved by switching to CSII in adults with type 1 diabetes treated by MDI and CGM, though biochemical hypoglycemia was also increased in this trial of insulin pump therapy.

Comments

Both these studies concern the relative effectiveness of CSII and MDI, with or without CGM, and the place of these treatments in clinical practice. The results of the REPOSE Study may be misinterpreted as evidence that CSII is generally no more effective than MDI in type 1 diabetes, though the paper itself only concludes that pumps should not be used in poorly controlled patients with type 1 diabetes “until the effects of training in intensive self-management have been determined,” which is exactly according to many current guidelines, such as those issued by NICE. Actually, in a subgroup analysis in the REPOSE trial of those with an HbA1c at baseline of $\geq 8.5\%$ (69 mmol/mol) (the NICE-recommended level for a trial of CSII), the mean HbA1c difference was significant at -0.4% (-0.8 to -0.1). Nevertheless, a recent BMJ opinion piece (3) commented, ““You might like to send this paper to your local diabetes center the next time they prescribe a pump to one of your patients. You might also like to find out if they receive money from a manufacturer of these pumps.” This suggests that there is a belief among some healthcare professionals that insulin pumps are being widely used inappropriately or, worse, unnecessarily, and the REPOSE trial supports this notion. This is a concern.

There are several issues to be considered with the REPOSE trial. First, in the large group of patients with an HbA1c $\geq 7.5\%$ (59 mmol/mol), the final mean HbA1c on CSII was about 8.75% (72 mmol/mol), for a baseline HbA1c of 9.5% (80 mmol/mol). This level of pump effectiveness is much worse than in most previous studies of pump usage—note, for example, that the mean

HbA1c of all (well and poorly controlled) CSII-treated patients in the study of Indelicato et al. mentioned above was 7.75% (61 mmol/mol). Most clinic surveys of adults with type 1 diabetes treated by CSII show a final mean HbA1c $<8.0\%$ (64 mmol/mol). This raises the question of whether the performance of pump therapy and its procedures in the REPOSE Study may have been suboptimal or whether the patients included in the study were especially resistant to CSII, or both.

The relatively high final HbA1c on CSII in REPOSE was not associated with any increase in insulin dose over the 2-year follow up, suggesting that investigators and patients did not take the opportunity to increase basal and meal insulin in response to suboptimal control. Interestingly, there was a wide variation in the difference in HbA1c between CSII and MDI recorded at different centers, not necessarily related to previous CSII experience: one center, with the largest number of participants, achieved a mean HbA1c difference of -0.78% (95% confidence interval -1.46% to -0.09%), compared with the overall difference of -0.24% for all centers (see the full report on the trial [4]).

It is important also to note that patients normally considered for insulin pump therapy—those desiring pump therapy, those meeting NICE criteria, or those considered in need of a CSII trial by their healthcare professional—were excluded from the REPOSE trial. And there was a very small number of patients with a high frequency of severe hypoglycemia at recruitment, arguably the most common reason for trialing insulin pump therapy. It could be argued that both patients and investigators were less than fully motivated to get the best out of CSII.

Two recent trials, the DIAMOND (5) and GOLD (6) studies, have shown that CGM used with MDI can achieve lower HbA1c levels and less hypoglycemia than MDI used with SMBG. However, the DIAMOND Study had an extension phase, which is the focus of the Beck et al. report, and here it was tested whether switching patients in the MDI + CGM arm of the DIAMOND Study to CSII + CGM produces additionally improved glycemic control. One concern was the increase in biochemical (but not severe) hypoglycemia with CSII during the trial. This may possibly be because insulin pump training, and with it measures to reduce the risk of hypoglycemia, was not standardized between the centers. One may also argue that insulin pump therapy with an automatic low-glucose insulin suspend facility (see below) may have avoided the increase in hypoglycemia seen with the standard sensor-augmented pump therapy used by Beck et al.

FASTER-ACTING INSULIN FOR INSULIN PUMP THERAPY

Improved postprandial glycemic control with faster-acting insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion

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Diabet Technol Ther 2017; **19**: 25–33

This manuscript is also discussed in the article on New Insulins, Biosimilars, and Insulin Therapy, page S-55.

Background

Faster aspart is a new formulation of aspart insulin designed to have a faster onset and offset of glucose-lowering effect. It is a formulation of aspart with the excipients niacinamide and L-arginine, which promotes insulin monomer formation after subcutaneous injection, and thus faster absorption into the bloodstream. The aim of this study was to compare faster aspart with aspart insulin when delivered through CSII in type 1 diabetes.

Methods

In this randomized, double-blind crossover trial, adults with type 1 diabetes (n=43) previously treated by CSII were allocated to a 3 week treatment period of CSII with bolus calculator use and either aspart or faster aspart insulin in the pump reservoir. At day 14 of the treatment, a standardized 600 kcal liquid test meal was given and postprandial glucose responses studied. Masked CGM was performed throughout.

Results

After 2 weeks' CSII treatment, the area under the curve for plasma glucose for the 2 hours after the test meal was significantly less for faster aspart compared with aspart (3.03 vs. 4.02 mmol/L, 55 vs. 73 mg/dL, $P=0.04$). Plasma glucose at 1 h postmeal was also lower with faster aspart (11.7 vs. 12.9 mmol/L, 181 vs. 211 mg/dL, $P=0.006$). CGM results over the treatment period, monitoring all meals, supported these findings, with largest differences in postprandial increments for faster aspart vs. aspart at breakfast. The duration of low CGM values (≤ 3.9 mmol/L, 70 mg/dL) was also lower with faster aspart (2.03 vs. 2.45 hours, $P=0.008$). Insulin doses were similar with the two insulins.

Conclusions

There is a greater glucose-lowering effect after a meal associated with faster aspart vs. aspart insulin when delivered as CSII, with less time spent with low glucose values.

Comments

Excessive meal-related glycemic increases caused by slow absorption of short-acting analog insulins like aspart, lispro, and glulisine are a major contributor to suboptimal and elevated HbA1c levels during CSII. Delayed insulin absorption also leads to the risk of late, postmeal hypoglycemia. Activating the meal bolus some 20 min before the meal start allows insulin absorption to more closely match meal glycemia, but it can be inconvenient. Ultra-fast-acting insulins like the faster aspart studied here have great potential to improve glycemic control and treatment satisfaction with both insulin injection therapy and CSII.

This was a relatively short-term trial over a few weeks, so the impact on HbA1c could not be measured—fructosamine was lower with faster aspart but did not reach significance. Equally, the finding that less time was spent in hypoglycemia with faster aspart hints of the potential to reduce moderate and perhaps severe hypoglycemia in the long term. No safety issues were uncovered and catheter occlusions were similar with the two insulins, but the stability of the new formulation needs to be studied in the longer term.

There are some intriguing suggestions from other short-term studies that the glucose lowering effect of faster aspart at meal times is greater with CSII (i.e., as a bolus on top of a basal infusion) than when given by injection alone (7). Extended trials of faster aspart with CSII will therefore be of great interest.

Although the main reason for introducing ultra-fast-acting insulins and the focus of this study was the improved management of postprandial glycemia, it is also possible that the (un)predictability of subcutaneous insulin absorption is less with faster aspart, and with it the variability of blood glucose levels. Although within- and between-day blood glucose variability is normally significantly improved with CSII, frustrating unpredictability can remain in many patients. The comparative variability of absorption and resultant glycemic control with faster aspart vs. aspart during CSII needs further study, and differences may be revealed especially in those patients with intrinsically unpredictable control.

CSII IN TYPE 2 DIABETES

Glycemic control during continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: individual patient data meta-analysis and meta-regression of randomized controlled trials

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Diabetes Care 2017; **40**: 715–722

Background

The role of CSII in type 2 diabetes is less well established than for type 1 diabetes because of the variable evidence of efficacy compared with MDI in the limited number of randomized controlled trials (RCTs) published in recent years. A recent large-scale RCT has indicated a favorable effect for CSII, which indicates that a meta-analysis of all trials may now provide a more robust view of the value of pump therapy in type 2 diabetes. The aim of this study was to compare glycemic control in type 2 patients treated by MDI or CSII using an individual patient data meta-analysis and

meta-regression and to thereby identify patient characteristics that determine those best treated by CSII.

Methods

RCTs comparing HbA1c during CSII or MDI in type 2 diabetes were selected where the duration of treatment was at least 2 months. Trials of newly diagnosed diabetes and pregnancy in diabetes were excluded. Patient-level determinants of final HbA1c, insulin dose, body mass index, and weight were sought using Bayesian meta-regression models of individual patient data. Summary meta-analysis was also performed. Hypoglycemia data was not available to study from all trials.

Results

Five eligible trials were identified by literature search and individual patient data obtained from all studies, consisting of 590 participants—287 on MDI and 303 on CSII. Three trials were parallel and two were crossover RCTs. In one trial (Opt2mise), participants underwent a prerandomization run-in period to optimize glycemic control with MDI, and only those who still had poor control (HbA1c 8%–12% [64–108 mmol/mol]) were allocated to CSII or continued MDI. Baseline HbA1c was the best determinant of final HbA1c, MDI/CSII difference (%) = $1.575 - (0.216 \times \text{baseline})$ for all trials, but with largest effect in the trial with prerandomization optimization of control (difference = $5.39 - [0.669 \times \text{baseline}]$). Baseline insulin dose predicted final insulin; overall insulin dose was reduced by -0.25 units/kg (mean 26% reduction on CSII, 24.0 units/day). Overall HbA1c difference in summary meta-analysis was 0.40% (4.4 mmol/mol). Mean weight did not differ between treatments.

Conclusions

HbA1c is significantly lower in poorly controlled type 2 diabetes treated by CSII compared with MDI, with an average 26% reduction in insulin dose and no weight change. The best effect is in those with worst glycemic control and highest insulin dose at baseline.

Comments

There is increasing evidence for the effectiveness of CSII in poorly controlled type 2 diabetes from clinical experience and from several observational studies, but this individual patient data meta-analysis of RCTs is of note because it identifies those with the largest effect and therefore those who would likely be most cost-effectively treated. The patients in the trials studied here used insulin pumps intended for type 1 diabetes with features such as flexible basal rate control and bolus calculators that may not be needed for treatment of most type 2 diabetes patients. Newer patch pumps specifically designed for CSII in type 2 diabetes that are being introduced into clinical practice or under development should be simpler to use, more cost effective, and therefore more appropriate for this patient group.

An important caveat is that the types and intensities of the MDI regimens and educational programs used in the trials studied in this meta-analysis varied considerably,

and some may not have been optimal by modern standards. The trials selected included four that were published 10 or more years ago. Several new agents for the treatment of type 2 diabetes have entered practice in recent years, such as new long-acting insulins (degludec), glucagon-like peptide (GLP)-1 agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, and with more widespread use of structured diabetes education the number of patients with type 2 diabetes who remain poorly controlled and are candidates for a trial of CSII may diminish in the coming years. The relative costs of these new agents and simpler, type 2 diabetes-intended pumps will need to be considered.

PREDICTIVE LOW-GLUCOSE INSULIN-SUSPEND PUMPS

Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial

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Diabetes Care 2017; **40**: 764–770

This manuscript is also discussed in the article on Continuous Glucose Monitoring in 2017, page S-13, and the article on Diabetes Technology and Therapy in the Pediatric Age Group, page S-114.

Background

The PLGS feature of the Medtronic 640G SmartGuard insulin pump allows for automatic basal rate suspension when the sensor glucose is predicted to reach or fall below a preset low glucose threshold within 30 min, and resumes after recovery from hypoglycemia. The aim of this study was to compare hypoglycemia frequency with the PLGS pump vs. sensor augmented pump (SAP) therapy (PLGS turned off).

Methods

Children and adolescents with type 1 diabetes (age 8–18 years, n = 100) who were previously treated by CSII were randomly allocated to PLGS-on or PLGS-off treatment for 2 weeks. The low threshold was set to 3.6 mmol/L (65 mg/dL) for all patients. The primary endpoint was number of sensor glucose values <3.6 mmol/L (65 mg/dL) for a minimum duration of 20 min, separated by a minimum of 30 min.

Results

The mean number of hypoglycemic episodes was reduced on PLGS vs. SAP (4.4 vs. 7.4 per patient, $P = 0.008$). Day and

night hypoglycemia were both reduced on PLGS. The time spent <3.6 mmol/L was also reduced on PLGS. No severe hypoglycemia occurred. The time spent >7.8 mmol/L (140 mg/dL) was increased on PLGS (936 vs. 861 min/day, $P=0.017$), though the sensor glucose was not different on the two treatments. Morning ketones were similar on PLGS or SAP.

Conclusions

The PLGS insulin pump system was safe and associated with a reduction in hypoglycemic episodes compared to SAP, although this was at the expense of time spent in moderate hyperglycemia.

“Let the algorithm do the work”: reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients

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[Diabet Technol Ther 2017; 19: 173–182](#)

This manuscript is also discussed in the article on Continuous Glucose Monitoring in 2017, page S-13.

Background

The aim of this study was to investigate whether the rate and intensity of hypoglycemia is reduced by the SmartGuard PLGS insulin pump system in a pediatric population of type 1 diabetes patients.

Methods

This was a prospective observational study over 2 months of children and adolescents ($n=24$, age 3–17 years) attending three outpatient clinics at pediatric hospitals in Germany, and previously treated by CSII. After a 4 week training and dose-optimization period, patients received SAP for 2 weeks without PLGS, followed by 6 weeks with PLGS turned on. The low threshold was set at 3.9 mmol/L (70 mg/dL).

Results

Comparison of phases was possible for 18 of 24 subjects. During the PLGS phase, there were an average of 3.2 suspends/patient/day, with an average suspend duration of 59 min/day and average cumulative time in hypoglycemia of 155 min/day. The area under the curve per day (AUC/day) for hypoglycemia (<3.9 mmol/L, 70 mg/dL) was reduced from 0.76 to 0.38 mg/dL ($P=0.027$) and the time spent in hypoglycemia from 73 to 31 min ($P=0.003$) for SAP without PLGS vs. SAP with PLGS. The number of episodes with hypoglycemia was reduced from 1.02 to 0.72, $P=0.027$. Hypoglycemia was prevented in 76.8% of instances. No serious hypoglycemia was observed. There was a nonsignificant increase in mean sensor glucose on switching to PLGS: 171 vs. 180 mg/dL, 9.5 vs. 10.0 mmol/L ($P=0.1$). The sensor

glucose 1 hour after resumption of insulin delivery was higher after manual resumption and extra carbohydrate intake than after automatic basal rate resume: 190 vs. 138 mg/dL, 10.6 vs. 7.7 mmol/L ($P<0.001$).

Conclusions

The SmartGuard PLGS insulin pump system reduces the risk of hypoglycemia in pediatric type 1 diabetes. Manual resumption of insulin delivery combined with carbohydrate intake is likely to cause rebound hyperglycemia. Best results are achieved when patients do not interfere with the automatic pump operation.

Effectiveness of a predictive algorithm in the prevention of exercise-induced hypoglycemia in type 1 diabetes

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[Diabetes Technol Ther 2016; 18: 543–550](#)

Background

Exercise has varying effects on glycemic control in diabetes, including hypoglycemia, which is distressing and potentially dangerous and can lead to avoidance of exercise. The recent development of insulin pumps with PLGS algorithms may help to prevent exercise-induced hypoglycemia. The aim of this study, therefore, was to test the efficacy of a PLGS system in preventing hypoglycemia with moderate-intensity exercise performed under in-clinic conditions.

Methods

Subjects with type 1 diabetes ($n=25$, mean age 15.7 years [range 12–25 years]) previously treated by CSII were randomly allocated with crossover to a control day treated by SAP alone or to SAP with PLGS (configured as an investigational device consisting of a Medtronic Veo pump, Enlite glucose sensors, and a smartphone containing the PLGS algorithm). After overnight fasting and when euglycemia was obtained, subjects performed two 30 min periods of moderate-intensity exercise on a bicycle ergometer. The predictive horizon for PLGS was set at 30 min and the threshold at 70 or 80 mg/dL (3.9 or 4.4 mmol/L).

Results

Six subjects were excluded because the predicted hypoglycemia threshold was not reached. In the 19 analyzed, for both thresholds combined, 89% of subjects needed hypoglycemia treatment in the SAP group and 32% in the PLGS group ($P=0.003$). In those with a 2 h suspend on the intervention day, the plasma glucose at pump resumption was 84 or 99 mg/dL (4.7 or 5.5 mmol/L) for the 70 vs. 80 mg/dL threshold.

Conclusions

SAP therapy with PLGS reduced the needed for hypoglycemia treatment after moderate exercise. There was no hyperglycemia associated with PLGS treatment on pump resumption.

Comments

These studies, two randomized and one observational, extend the evidence for the additional effectiveness of PLGS insulin pumps in reducing mild-to-moderate hypoglycemia in type 1 diabetes, over and above that afforded by CSII alone and by SAP without automatic low-glucose insulin suspend. There are several cautions to note in the interpretation of the studies. Both outpatient trials were of short duration, with a period on PLGS pump therapy of 2 or 6 weeks, thus making it impossible to measure changes in the serious acute complications of diabetes—severe hypoglycemia and diabetic ketoacidosis. Both outpatient studies were performed in children and young people who tend to have less hypoglycemia than adults because of a shorter duration of diabetes, though younger children may have more hypoglycemia than older children. The nature of both study populations is rather unclear; it is likely they were not groups who were hypoglycemia prone at baseline, in the sense of suffering previous frequent severe hypoglycemic episodes. Finally, the trials were not blinded, so patients may have altered behaviors such as eating and exercise according to treatment allocation, and this may have significantly influenced the frequency of hypoglycemia and the extent of hyperglycemia.

Similar and other limitations apply to the exercise study of Abrahams et al. The trial was short term (<4 h observation after exercise), so the common problem of exercise-induced late hypoglycemia was not assessed; it was performed in young people who were not hypoglycemia prone (those with a previous history of severe hypoglycemia were excluded); patients were well controlled before exercise started; it was not blinded to the patient, which may have influenced symptom reporting, for example; and results were achieved under supervised and controlled hospital conditions. It remains to be seen how effective PLGS pump therapy is in preventing exercise-induced severe hypoglycemia, as well as mild-to-moderate hypoglycemia, in the poorly controlled, possibly hyperinsulinemic and hypoglycemia-prone patient, studied in the long-term (say >6 months) under everyday life conditions.

The reason for and the clinical implications of the small but significant increase in time spent in moderate hyperglycemia with PLGS pumps in the study of

Battelino et al. are unclear. It is reassuring that mean sensor glucose and ketone tests were similar after PLGS on and PLGS off, indicating that there is little evidence of insulin deficiency after the periods of insulin suspension. But again, this was a population of moderately well controlled and well managed patients, who were experienced with CSII, and results may be different in those who are very poorly and unpredictably controlled and ketosis prone, as well as those with frequent severe hypoglycemia. RCTs in these groups—those most likely to be first users of PLGS systems in clinical practice—are still awaited. A nonsignificant increase in mean sensor glucose with PLGS was also seen in the Biester et al. study, where nearly 50% of suspends were accompanied by manual resumption of insulin delivery and frequently also by consumption of extra carbohydrate. This may have contributed to an apparent rebound hyperglycemia after PLGS and the slightly higher overall sensor glucose on this treatment. As Biester et al. say, patients need education not to respond to a PLGS hypoglycemia alert with food intake and to let the pump algorithm “do the work.”

In the Biester et al. study, about 77% of hypoglycemic events were prevented by PLGS pump therapy (i.e., some 23% of sensor values were still <3.9 mmol/L [70 mg/dL]). In the Abrahams et al. study, some 32% on PLGS pump therapy still required treatment for hypoglycemia after exercise. Presumably, complete avoidance of hypoglycemia with PLGS is prevented, at least in part, by the occasions when there is substantial on-board insulin—here basal insulin suspend is insufficient to reduce ongoing insulin-induced blood glucose lowering from a previous large subcutaneous insulin depot.

COMPLICATIONS OF CSII

Insulin pump failures: has there been an improvement? Update of a prospective observational study

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Diabetes Technol Ther 2016; **18**: 820–824

Background

The aim of this study was to update a previous survey of insulin pump failures performed from 2001 to 2007 and to investigate whether there are patient characteristics that are associated with pump problems.

Methods

In a prospective study of 350 new pumps issued to adults with diabetes between 2008 and 2013, type of any pump

defect, model and brand, and patient characteristics such as gender, age, type of diabetes, diabetes duration, and duration of pump treatment were recorded. Infusion set problems were not studied.

Results

The age of subjects at pump start was 25–47 years; 86% had type 1 diabetes, 15% had type 2 diabetes, and 8% secondary or had undetermined etiology. Malfunctions occurred in 68% of patients; 12% had complete failure that rendered the pump immediately unusable, 7% had alarms that required pump replacement, 35% noted mechanical failure (reservoir or battery cracks and display defects) and 44% minor defects. Survival curves did not differ between models or brands. Age <40 years at pump start was associated with higher risk of failure.

Conclusions

Pump malfunctions remain common, though complete failure was less than in a previous survey. This might be because of improved reliability or because of systematic screening and replacement in the event of defects.

Insulin pump failures in Italian children with type 1 diabetes: retrospective 1-year cohort study

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Diabetic Med 2017; **34**: 621–624

Background

The aim of this study was to investigate the rate of insulin pump replacements due to malfunction in a large cohort of Italian children and adolescents with type 1 diabetes receiving CSII during one year (2013).

Methods

A standardized report form was sent to 43 pediatric centers undertaking insulin pump therapy; 40 centers responded (93%). Data included age, gender, pump duration, pump model and manufacturer, infusion set and CGM use, mean HbA1c during pump use, pump replacements and the reason for it, and any associated clinical adverse events.

Results

Data from 1574 CSII users were obtained, mean pump duration 3.1 years, mean HbA1c 7.6% (60 mmol/mol); 28.6% used sensor augmented pump therapy. After excluding replacements due to expiry of warranty, replacements occurred in 16.5% of people (0.165 replacements per patient-year), due to either malfunction (11.8%) or accidental damage (4.7%). Highest rates of replacement occurred with pumps used for sensor augmented pump therapy. Most pump failures (62.3%) were after at least 2 years of pump duration. No relationship was found between replacement and metabolic events (hypoglycemia or diabetic ketoacidosis) or infusion set usage.

Conclusions

Pump failure and subsequent replacement in this large cohort of patients was associated with more sophisticated pump models.

Comments

These studies confirm the results of previous surveys of pump reliability by showing that malfunctions continue to be very common, even with modern technology (8,9): about 70% of the patients had some pump problem at some time in this study reported by Guenego et al. The only patient-related factor in multivariate analysis that was linked to pump defects was age <40 years, and the reason for this association is unclear. Possibly, younger people engage in more sports, work, and leisure activities that could damage the pump, or they could be less likely to immediately replace a pump with a minor defect. In both studies, about 12% of patients experienced a pump malfunction that rendered it unusable and returnable. Most previous studies have not identified a particular pump model as being prone to malfunction, but the survey of Rabbone et al. indicates that the more recently introduced and technically more sophisticated insulin pumps with the capacity for CGM connectivity (even if they were not so used) were the most likely to malfunction.

Author Disclosure Statement

J.C.P. has received speaker and/or consultancy fees from CeQur, Eli Lilly, Medtronic, Novo Nordisk, and Roche.

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