EDITORIAL

Insulin pump therapy, should we consider it more often?

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ABSTRACT

Erratic blood glucose control, hypoglycaemia unawareness and optimisation of glycaemic control during pregnancy are widely recognised indications for commencing diabetic patients on continuous subcutaneous insulin infusion (CSII) using an insulin pump. In patients without such a specific condition, the benefit of CSII over other forms of intensified treatment on glycaemic control and hypoglycaemic rate is generally viewed as too modest to warrant a change of regimen. However, the impact of the treatment regimen on psychosocial parameters is often undervalued, at least in randomised trials. This is unfortunate as quality of life and treatment satisfaction probably determine the patient's preferences more than metabolic parameters. To truly appreciate all potential benefits of either strategy (CSII or injection therapy), these data are urgently required. In the meantime, doctors should keep an open eye for the specific needs of the individual patient to find the best treatment available for that person.

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is thought to be the best way to administer insulin to achieve the criteria of strict metabolic control set out by the Diabetes Control and Complications Trial (DCCT).[1] With CSII, short-acting insulin is infused subcutaneously at a varying rate to match with 24-hour basal insulin demand, whereas boosts of insulin can be administered before meals. Initially, CSII treatment was primarily meant for type 1 diabetic (T1DM) patients with so-called 'brittle' diabetes, but it was later found to also benefit patients with the Dawn phenomenon, gastroparesis, hypoglycaemia unawareness, or during pregnancy. The early pumps had

a number of technological imperfections (e.g. pump failure) and were so large that they were unacceptable for patients without such a specific condition. However, despite advances in the equipment, it is still not routinely offered as an equivalent alternative to multiple daily insulin injection (MDII) therapy in T1DM. Possible reasons for this include a general unfamiliarity with CSII and hesitance to utilise novel technologies on the part of diabetes care providers, psychological resistance against wearing an external device ('being hooked on continuously') and fears of loss of quality of life on the part of patients. The question arises whether it is time to reconsider our position towards CSII. This question can only be answered when it is clear what can be gained by switching to CSII in terms of improvement in glycaemic control and reduction in hypoglycaemic risk, and of quality of life and treatment satisfaction.

Since its introduction in the late 1970s, numerous studies have highlighted the advantages of CSII, yet many of these have methodological flaws, such as lack of control groups, small sample sizes, use of historical controls, and mixing of type 1 and type 2 diabetes and different age groups, which preclude firm conclusions. For example, in a retrospective analysis of 138 Italian T1DM patients who were started on CSII, significant decreases were observed for both HbA_{1c} (from 9.3 to 7.9%) and for hypoglycaemic events (from 0.31 to 0.09 per year) after a mean of seven years of treatment.[2] However, because a control group was lacking, a substantial part of the improvement in glycaemic control might have been the result of a study effect.[3] Furthermore, the insulin injection treatment that preceded the switch to CSII might not have been of optimal DCCT

quality, as it was largely unspecified. Parallel studies in the pre-DCCT era that compared CSII with conventional (i.e. nonoptimised) insulin injection therapy revealed differences in HbA_{1c} ranging from 0.5 to over 4% in favour of CSII, with similar hypoglycaemic risk.[4] Conversely, a recent meta-analysis of 12 randomised controlled trials that compared CSII with optimised injection therapy using MDII reported a modest 0.51% lower HbA_{1c} with CSII, whereas hypoglycaemic risk could not be evaluated because of lack of data.[5] The type of insulin used by the studies evaluated in this meta-analysis was regular insulin, except for one study where insulin lispro was used.[6] Although the results of the lispro study were consistent with the overall results of the meta-analysis, the type of insulin is relevant as fast-acting insulin analogues are currently considered the insulins of choice for pumps. A few randomised trials have been published since, which compare CSII with MDII using fast-acting analogues. In one study using insulin aspart, De Vries *et al.* reported that CSII was more efficacious than MDII in improving glycaemic control (mean HbA_{1c} 0.84% lower with CSII) in poorly controlled T1DM patients, although the number of mild hypoglycaemic events was also higher with CSII.[7] Two other studies using insulin lispro, one in 27 adults, the other in 23 children with type 1 diabetes, reported similar reductions in HbA_{1c} values and a similar rate of hypoglycaemic events with either treatment,[8,9] despite the fact that insulin lispro was not used in the MDII protocol of the latter study. A recently presented paper reported that an MDII regimen consisting of lispro insulin in combination with the long-acting insulin analogue glargine was as good as CSII with lispro to improve glycaemic control in T1DM.[10]

Thus, based on HbA_{1c} and hypoglycaemic rate, it seems unwarranted to advocate CSII to T1DM patients without a specific condition, such as erratic blood glucose control or hypoglycaemia unawareness that failed on optimised insulin (analogue) injection therapy. However, is it fair to base our judgement regarding CSII on these two parameters alone? When a similar standpoint was recently voiced, the authors were heavily criticised by both patients (or their parents) and physicians for being so narrow-minded to only consider the metabolic data.[5] Indeed, to sincerely appreciate insulin pump therapy, we need to look beyond HbA_{1c} values. In this issue of the Journal, Hoogma and co-workers highlight the importance of quality of life and treatment satisfaction when CSII treatment is considered.[11] From a patient's perspective, these factors are probably more important than a change in HbA_{1c} to determine whether CSII is started and continued or not.[4] Longitudinal studies have shown that CSII patients who were previously unhappy with insulin injection therapy generally report increased quality of life and treatment satisfaction in parallel with reductions in HbA_{1c} and hypoglycaemic rate,[12,13]

but very few data are available from randomised trials. Unfortunately, the study by Hoogma *et al.* is not a randomised trial, but a cross-sectional comparison of quality of life and treatment satisfaction between 49 patients treated with CSII for at least one year and 79 patients treated with MDII. In the CSII group, there was a preponderance of females, patients were slightly younger, had slightly shorter disease duration, and their educational level was slightly lower than that in the MDII group. Hypoglycaemic rate was identical and the HbA_{1c} value was 0.4% lower in CSII patients, a difference that did not reach statistical significance, but no differences were observed between the two groups on any of the parameters concerning quality of life. This led the authors to conclude that CSII treatment should be encouraged more in patients not optimally controlled by MDII. Although the authors should be honoured for their efforts, having so thoroughly assessed quality of life in such a large number of patients, their conclusion is somewhat premature. A (small) decrease in HbA_{1c} is probably not enough to motivate patients to decide to use CSII. For example, in a study comparing CSII with MDII, 11 out of 40 patients (the majority of whom were on CSII before the study) preferred MDII,[6] even though CSII was associated with a 0.35% lower HbA_{1c} (similar to the 0.4% difference reported by Hoogma *et al*). It should be acknowledged that the CSII group is a highly selected group; patients who for whatever reason discontinued CSII were not included, which may have affected the outcome of the questionnaires. The groups are also too different to justify a recommendation for MDII-treated patients to switch to CSII. The main reason for CSII patients to try insulin pump therapy was being unsatisfied with injection therapy in some way. As they continued CSII, I assume at least one of the following factors improved: quality of life, treatment satisfaction, glycaemic control, or rate of hypoglycaemia. Yet, this does not mean that patients who are as satisfied with MDII as the average pump user in this study is with CSII will benefit equally from switching to CSII. In this respect it is unfortunate that the study lacks an assessment of quality of life before patients were switched to CSII. As all MDII patients used regular insulin, it may be easier and cheaper to first try fast-acting analogues to optimise metabolic control before commencing CSII.

In conclusion, the study by Hoogma *et al.* shows that quality of life is as high in a sample of insulin pump users as it is in a sample of patients on MDII, but does not measure how CSII affects this parameter. Does this mean that we should not change our attitude towards CSII? Yes and no. Yes, because it is worthwhile to await the results from studies on all-analogue treatment regimens (i.e. the combination of a fast-acting analogue before meals and a long-acting analogue before bedtime). No, because patients are

entitled to information on all treatment modalities currently available and should be offered a treatment that best corresponds to their specific needs. Following that line, patients who require more flexibility from insulin treatment than MDII can provide may benefit from CSII. In the meantime, randomised trials on CSII *vs* MDII are needed that address quality of life at least as meticulous as is presented here.

REFERENCES

1. The diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.

2. Bruttomesso D, Pianta A, Crazzolara D, et al. Continuous subcutaneous insulin infusion (CSII) in the Veneto region: efficacy, acceptability and quality of life. Diabet Med 2002;19:628-34.

3. Vries JH de, Snoek FJ, Kostense PJ, Heine RJ. Improved glycaemic control in type 1 diabetes patients following participation per se in a clinical trial-mechanisms and implications. Diabetes Metab Res Rev 2003;19:357-62.

4. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care 2003;26:1079-87.

5. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2002;324:705.

6. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. Diabetes Care 2000;23:1232-5.

7. Vries JH de, Snoek FJ, Kostense PJ, Masurel N, Heine RJ. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25:2074-80.

8. Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care 2001;24:1722-7.

9. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. Pediatrics 2003;112:559-64.

10. Bolli GB, Capani F, Kerr D, et al. Comparison of a multiple daily injection regimen with once-daily insuin glargine basal insulin and mealtime lispro, to continuous subcutaneous insulin infusion: a randomized open parallel study. Diabetologia 2004;47(suppl 1):A301.

11. Hoogma RPLM, Doorn-Scheele M van, Doorn TT van, et al. Quality of life and metabolic control in patients with diabetes mellitus type 1 treated by continuous subcutaneous insulin infusion or multiple daily insulin injections. Neth J Med 2004;62:383-7.

12. Linkeschova R, Raoul M, Bott U, Berger M, Spraul M. Less severe hypoglycaemia, better metabolic control, and improved quality of life in Type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) therapy; an observational study of 100 consecutive patients followed for a mean of 2 years. Diabet Med 2002;19:746-51.

13. McMahon SK, Airey FL, Marangou DA et al. Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. Diabet Med 2004;Epub: 1111/j. 1464-5491.2004.01359.x.