

CLINICAL UTILITY OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN PATIENTS WITH TYPE 1 DIABETES: A MACEDONIAN REPORT

Goran Petrovski, Cedomir Dimitrovski, Tatjana Milenković

Key words: continuous subcutaneous insulin infusion, type 1 diabetes, metabolic control, Macedonia

satisfactory metabolic control. Efforts should be invested by healthcare providers to promote this promising alternative treatment in type 1 diabetes.

SUMMARY

The aim of this study was to analyze and evaluate the efficacy and safety of continuous subcutaneous insulin infusion (CSII) in all patients with type 1 diabetes on pump therapy in Macedonia. The study was performed at University Department of Endocrinology in Skopje from January 2004 until December 2006. CSII was initiated in diabetics with poor metabolic control. HbA_{1c}, severe hypoglycemia and diabetic ketoacidosis in the year before CSII were compared with the respective values during one-year pump treatment. Fourteen patients (6 male and 8 female) aged 18.9±6.4 years with type 1 diabetes were included in the study. The mean HbA_{1c} of 9.4±1.1% in one year pre-pump period decreased to 7.3±0.8% one year after CSII. The rate of severe hypoglycemia and diabetic ketoacidosis was reduced upon switch to pump treatment in the next year. CSII is effective and safe treatment in patients with type 1 diabetes to achieve

INTRODUCTION

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy was introduced in the late 1970s, but its use increased significantly in the last several years as an alternative treatment option in type 1 diabetics (1,2), where multiple daily injections (MDI) could not achieve satisfactory metabolic control. New technologies introduced in daily practice and especially in the field of medicine have enhanced the development of ever more convenient insulin pumps (smaller size, precise control, better interface, etc.).

The advantages of CSII include improved metabolic control, less daily fluctuation of blood glucose, decreased risk of hypoglycemia, managing the dawn phenomenon, precise baseline insulin delivery at a specific time, better insulin matching to carbohydrate intake, increased flexibility in daily living, and improved coping with diabetes (3,4).

The disadvantages of CSII include high cost, inconvenience of wearing a mechanical device, the risk for subcutaneous infection at the infusion site, and possible diabetic ketoacidosis (DKA).

Corresponding author: Goran Petrovski, MD, MS, Bihacka 3-2-41, MK-1000 Skopje, Macedonia
E-mail: goranp@endocrinology.org.mk

Meta-analyses of trials on CSII *versus* MDI have demonstrated significant improvement in glycemic control and lower hypoglycemic episodes with the use of insulin pumps (5,6). Adolescents have also reported improved ability to cope with diabetes when using insulin pump therapy as compared with standard multiple daily injection therapy (7). Achieving satisfactory metabolic control is difficult in young adults and adolescents, as a result of wide diurnal fluctuations in physical activity, unpredictable eating habits, different lifestyles, and difficulties in measuring and administering very small doses of rapid, intermediate and long acting insulin. CSII can be an appropriate therapeutic option and alternative choice to MDI to overcome many of these barriers and to achieve better metabolic control.

Our study is the first report on insulin pump therapy utilization in Macedonia, describing the beneficial effect of CSII on HbA_{1c}, hypoglycemia and DKA, where our team convinced the authorities in Health Care Fund and Ministry of Health to support this new optional therapy in type 1 diabetics to achieve and maintain satisfactory metabolic control.

The aims of our study were:

- to implement and explain the importance of CSII in type 1 diabetics,
- to evaluate the efficacy and safety of CSII, and
- to evaluate the metabolic control in patients with CSII.

MATERIALS AND METHODS

Patient selection. The study was performed at University Department of Endocrinology, Medical Faculty in Skopje, from January 2004 until December 2006. All patients with type 1 diabetes who were initiated on insulin pump therapy were analyzed. The requirements for the introduction of pump therapy included frequent monitoring of blood glucose with transcription into a written or computer log, patient motivation, stable psychological family profile, and ability to understand and implement pump treatment. Patients and their families underwent a 5-day education course, where they learned how to use pump therapy along with daily activities. Attention had to be

especially paid to advanced carbohydrate counting, baseline and bolus rate, personal patterns, infusion sets and security. Frequent telephone contact was maintained between visits. The visits were appointed at routine 2-month intervals, as during standard MDI therapy. No patient was taken off insulin pump therapy during the study period.

Data collection. Body mass index (BMI), total daily dose (TDD) and HbA_{1c} at pump initiation, as well as episodes of severe hypoglycemia (SH) and DKA in the year before pump initiation were compared with the same variables post-pump. SH was defined as an episode that required treatment with parenteral glucagon or dextrose, either by the family or emergency medical personnel, or was associated with seizure and/or loss of consciousness. DKA was defined as the presence of hyperglycemia (>14 mmol/L), metabolic acidosis (pH <7.35) and ketonemia/heavy(3+) ketonuria, that required emergency medical treatment and hospitalization. HbA_{1c} levels were obtained every 3 months (four results in one-year pre-pump period and four results in one-year post-pump period) and measured by high-performance liquid chromatography (normal range 3.8%-5.8%).

Statistical analysis. HbA_{1c} data are reported as mean \pm SD. A mean pre-pump HbA_{1c} was determined for each patient on the basis of the mean of four available HbA_{1c} measurements in one year period before CSII initiation. The mean post-pump HbA_{1c} was determined for each patient on the basis of the mean of four available HbA_{1c} measurements in one year period after CSII initiation. All patients included in the study had a history of diabetes of more than one year. For comparison of HbA_{1c} levels, the mean pre- and post-pump HbA_{1c} levels were analyzed by *t*-test. The evaluation of SH and DKA was also performed as a mean of episodes *per patient per year*.

RESULTS

The study population was composed of 14 patients (six male and eight female) with mean age at pump initiation of 18.9 \pm 6.4. The mean duration of diabetes at CSII initiation was 5.1 \pm 3.3 years (Table 1).

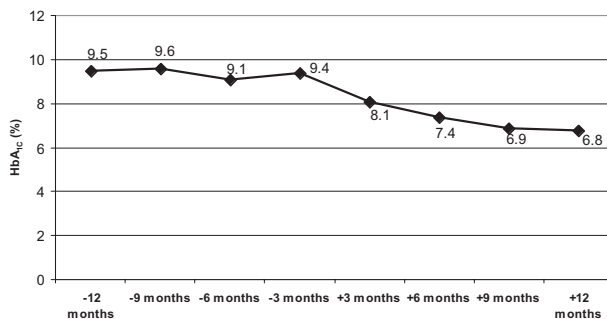
Table 1. Patient demographics

Total patients	16
Sex	Male 6 / Female 8
Age (yrs)	18.9±6.4
Body mass index (kg/m ²)	22.6±2.4
Diabetes duration (yrs)	5.1±3.3 yrs

All patients had normal body mass index (BMI, 22.6±2.4 kg/m²) and poor metabolic control (HbA_{1c} 9.4±1.1%) in a one-year pre-pump period (Fig. 1).

As shown in Figure 1, HbA_{1c} levels started to decrease 3 months after CSII initiation. The *t*-test for dependent samples showed a significant decrease (*p*<0.005) of mean HbA_{1c} from 9.4±1.1% in the pre-pump period to 7.3±0.8% in the post-pump period. There was a decrease by 2.7%, if the first HbA_{1c} of 9.5±1.4 (-12 months before CSII initiation) is compared with the last HbA_{1c} of 6.8±0.6 (12 months after CSII initiation). The levels of HbA_{1c} were stable during the period of 9 and 12 months after CSII initiation.

Figure 1. Metabolic control by HbA_{1c} one year before (pre-pump period -12, -9, -6, -3 months) and one year after (post-pump +12, +9, +6, +3 months) continuous subcutaneous insulin infusion (CSII)



Besides lowering HbA_{1c} levels, insulin pump treatment lowered the TDD by 29%. The rate of SH episodes was also reduced from 3.7 to 1.6 episodes *per* patient. There were four DKA episodes in the pre-pump period. In the post-pump period there was one episode of DKA, which was due to irregular exchange of insulin set. The patient was re-educated in pump

treatment. There was no significant difference in BMI between the pre-pump (22.6±2.4 kg/m²) and post-pump (22.1±1.6 kg/m²) period (Table 2).

Table 2. Total daily dose (TDD), HbA_{1c}, severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) episodes in pre-pump and post pump period

	Pre-pump period	Post-pump period	Significance (p)
TDD (IU)	69.1±12.8	48.8±7.8	0.000016
HbA _{1c} (%)	9.4±1.1	7.3±0.8	0.000000
Total SH (episodes) <i>per</i> patient	3.7±2.2	1.6±0.7	0.001101
Total DKA (episodes)	4	1	/

DISCUSSION

Even without having to learn the technology associated with CSII pumps, dealing with type 1 diabetes is stressful for adolescents and parents (8). Implementing a new therapy model in a country is very difficult, especially in south-east countries like Macedonia due to financial deficit in healthcare funds. In 2002, insulin pump therapy was introduced and described in Macedonia (9). The first four patients on CSII had to buy the pump and necessary insulin sets and reservoirs themselves. Two years elapsed in meetings, negotiations with authorities at Ministry of Health and Health Care Fund on the need and importance of this kind of therapy. As the result of our enthusiasm and motivation, the National Program for Insulin Pump Therapy was implemented in 2004, with insulin sets and reservoirs now covered by the special fund.

Several studies have reported the ability of pump therapy to lower both HbA_{1c} levels and the risk of SH in adolescent patients (10). Other studies report the ability of pump therapy to sustain improvements in HbA_{1c} levels after the first 6 to 12 months of treatment, demonstrating durable improvements in glycemic control (11) and others showing deterioration over time (12). Our study showed it to be possible to reduce HbA_{1c} levels in the first 6 months.

Our study reports on clinical outcomes in all implemented insulin pumps in Macedonia and how new therapy such as CSII may be implemented successfully in patients with type 1 diabetes. The HbA_{1c} levels decreased significantly during the first 12 months of pump treatment. Our group consisted of patients with a mean duration of diabetes of 5.1±3.3 years at the time of pump initiation, and there was no overlapping of the pre-pump period with “honeymoon” period.

Some studies report that the risk of DKA increased in patients with CSII (13). If CSII is used by the protocols, the potential of developing DKA is rare. In our study, there was only one DKA episode in the post-pump period due to irregular exchange of infusion set. Other studies report a DKA rate of 4 to 8 *per* 100 patient-years in patients with established diabetes (14,15).

Improvement in metabolic control does not mean only reduction of HbA_{1c}. The ability of CSII to achieve lower mean blood glucose while simultaneously reducing the rate of SH is the most significant characteristic of insulin pump therapy. Determination and/or confirmation of the bolus dose with a diabetes team through the use of mobile phone, SMS or e-mail

communication before insulin delivery is another popular management to achieve better metabolic control.

The present study may be considered to be limited by its nonrandomized and uncontrolled design. Patients were selected for insulin pump therapy on the basis of poor metabolic control including multiple glucose monitoring tests daily, recording blood glucose values and other important variables in a written or computer log, and clear commitment to insulin pump treatment.

It remains the task of the health care team to select good candidates for insulin pump treatment. However, this report shows that a group of motivated doctors can implement a new therapeutic tool in the treatment of type 1 diabetes. Therefore, efforts should be invested by authorities at Ministry of Health and Health Care Fund to support this and other new treatments.

CONCLUSION

An important lesson learned from this study and also from the literature is that CSII is an effective and safe optional therapy for patients with type 1 diabetes, where MDI cannot achieve satisfactory metabolic control. This is the first experience with CSII in Macedonia, where special efforts should be invested by healthcare providers to promote this promising alternative treatment in type 1 diabetes.

REFERENCES

1. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med* 1979;300:573-578.
2. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *BMJ* 1978;1:204-207.
3. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care* 2002;25:593-598.
4. Schade DS, Valentine V. To pump or not to pump. *Diabetes Care* 2002;25:2100-2102.
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;324:1-6.

6. Weissberg-Benchell J, Antisdell-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care* 2003;26:1079-1087.
7. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion: a "new" way to achieve strict metabolic control, decrease severe hypoglycemia, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999;22:1779-1784.
8. Sullivan-Bolyai S, Deatrick J, Gruppuso P, Tamborlane W, Grey M. Constant vigilance: mothers' work parenting young children with type 1 diabetes. *J Pediatr Nurs* 2003;18:21-29.
9. Petrovski G *et al.* Insulin pump therapy: an overview. *MMP* 2002;3-4:125-128.
10. Doyle EA, Weinzimer SA, Steffen AT *et al.* A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004;27:1554-1558.
11. Ahern JH, Boland EA, Doane R *et al.* Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* 2002;3:10-15.
12. Plotnick LP, Clark LM, Brancati RL, Erlinger T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* 2003;26:1142-1146.
13. Hanas R, Lindblad B, Lindgren F. Predisposing conditions and insulin pump use in a 2-year population study of pediatric ketoacidosis in Sweden. *Diabetes* 2005;54:455.
14. Smith CP, Firth D, Bennett S, Howard C, Chisholm P. Ketoacidosis occurring in newly diagnosed and established diabetic children. *Acta Paediatr* 1998;87:537-541.
15. Rewers A, Chase HP, Mackenzie T *et al.* Predictors of acute complications in children with type 1 diabetes. *JAMA* 2002;287:2511-2518.