THE EFFECT OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION TREATMENT, INSULIN ANALOG, AND HUMAN INSULIN OF CHILDREN WITH DIABETES

Elina Petkova[1], Valentina Petkova[2], Guenka Petrova[3], Maya Konstantinova[4]

Abstract: The aim of this study was to evaluate the cost-effectiveness of continuous subcutaneous insulin infusion (CSII) to multiple daily insulin injection (MDI) either with analogues or with human insulin, based on the achieved therapeutic results such as changes in glycated hemoglobin level (HbA1c) in the various therapies. The study was performed with children with type-1 diabetes in Bulgaria. The objective of this study was to serve for the Bulgarian National Health Fund (NHIF).

Methods: A combined retrospective and prospective study was performed at the Endocrinology diabetes and genetic diseases clinic. 51 children with type-1 diabetes were observed for 7 months dived into three group: Group 1 – on continuous subcutaneous insulin infusion (CSII), Group 2 – on multiple daily insulin analogues injections (MDI), and Group 3 – on human insulin (HI). Patient demographic data, age, sex, weight, duration of disease, HbA1c – values before the start of the study and after the end of the observation and type of treatment (CSII; MDI or HI) were observed. Cost-effectiveness, sensitivity, and statistical analyses are applied to studied long-term therapeutic results.

Results: The three groups of observed children do not differ statistically in age and gender. Most of the participants in Group 1 and Group 2 have suffered from diabetes from 5.6 years. The duration of diabetes was lower in the group of human insulin. All studied children are treated. By all of them, the results of the treatment improved, but in the Group 1 the improvement of HbA1c is the highest. The average improvement of HbA1c in the Group 1 after the CSII introduction is 1.85, while after the application of analogue insulin is 0.59 and 0.28 respectively in the Group 3 after the treatment on human insulin.The cost of insulin pump, consumables-infusion set and insulin reservoir, blood glucose monitoring system, strips, needles and insulin cost was calculated.The total cost ot the treatment of diabetes with insulin pump for 7 months is 2358.85 Euro; 856.98 Euro in the Group 2 on MDI and 744.24 Euro for 7 months in the Group 3 on human insulin.The differences in costs and therapeutic results permit to conduct cost-effectiveness analysis by comparing of the three alternatives.Our study shows that the CSII pumps allows better diabetes control compared to the treatment with analogue insulin and human insulin. Insulin pumps are also a cost-effectiveness alternative for children with type-1 diabetes.

Introduction

Over the 50 years from 1964 to 2014, outcomes for children with type-1 diabetes have improved significantly because of both technological advancements and changes in management philosophy (Fairchild, 2015). For a child with type-1 diabetes in 2014, intensive management with multiple daily injections or insulin pump therapy and the support of a specialist multidisciplinary team are now a standard care. The main treatment goal is no longer the avoidance of hypoglycaemia but the minimization of hyperglycaemia and glucose variability, thereby reducing the risk of microvascular complications. Continuous subcutaneous insulin infusion (CSII) is an option for patients with type-1 diabetes, who are with unsatisfactorily controlled diabetes. The short-acting analogues insulin, used in insulin pumps, are superior to regular human insulin. There is evidence supporting the advantages of short-acting analogue-based CSII over MDI in diabetes type-1. The reduction of glycated hemoglobin

---
[1] Elina Petkova, Faculty of Pharmacy-Sofia, Medical University of Sofia, Bulgaria, elinapetkova@abv.bg
[2] Valentina Petkova, Faculty of Pharmacy-Sofia, Medical University of Sofia, Bulgaria, petkovav1972@yahoo.com
[3] Guenka Petrova, Faculty of Pharmacy-Sofia, Medical University of Sofia, Bulgaria, guenka.petrova@gmail.com
[4] Maya Konstantinova, Pediatric Endocrinology Clinic-Sofia, Medical University of Sofia, Bulgaria, maiakonstantinova@gmail.com

(HbA1c) level with CSII is evident in many international studies (Monami, Lamanna, Marchionni, & Mannucci, 2010); (Weisberg-Benchell et al, 2003). However, the inherent burden of care and diligence required by patients and families have not changed and may even have increased, if they are to maintain optimal diabetes control. While the long sought-after cure for diabetes remains elusive, artificial pancreas or closed-loop systems hold the most promise for improving the burden of care in the near term for children and adolescents with type-1 diabetes (Russell et al., 2014).

The aim of this study is to evaluate the cost-effectiveness of continuous subcutaneous insulin infusion (CSII) to multiple daily insulin injection (MDI) either with analogues or with human insulin, based on the achieved therapeutic results such as changes in glycated hemoglobin level (HbA1c) in the various therapies. The study was performed with children with type-1 diabetes in Bulgaria. The objective of this study was to serve for the Bulgarian National Health Fund (NHIF).

Methods

Type of the CSII Usage Study

This is a combined retrospective and prospective study performed at the Endocrinology, diabetes and genetic diseases Clinic of Specialized Hospital for Active treatment of child diseases of the Medical University, Sofia. The Ethical committee of the Science medical council of the Medical University in Sofia, Bulgaria reviewed and approved the study.

Patient Screening

51 children with type-1 diabetes were observed, divided into three group: Group 1 - with an active group using CSII pumps and two control group: Group 2 - on multiple daily analogues injections, and Group 3 - on standart treatment with human insulin. Their parents signed the informed consent. The group of CSII included all children from the Clinic, who began using the insulin pumps during the period of 2007-2011 when began the data collection. All children used the same type of pump from the same manufacturer. On a random basis were recruited the control groups according to age, duration of diabetes, entrance BMI. Their parents also signed the informed consent. Partial results were reported separately for children on analogues insulin (Petrova et al., 2013a) and on human insulin (Petkova et al., 2013b). Due to the consequtive recruitment of the children in this study we compared the three patients groups to see the general picture.

Data Collection

Data for the selected children was collected on their age, gender, weight, duration of disease, therapeutic schema (CSII, MDI or HI). As the measures of therapeutic results, we choose the level of HbA1c, measured before the inclusion of the pump program and at the end of the observation. The data for the passive groups were collected from children diaries.

Cost-Effectiveness Analysis

For both groups of children, the health care resources used by them were recorded, namely insulin pumps, consumables for pumps (6 to 10 infusion sets and 6 to 10 insulin reservoirs), glucometers, strips (n=1100 per patient per year), needles, insulin costs, GP and endocrinology visits. 7 months costs of CSII, blood glucose monitoring systems, pumps consumables and stips were calculated by multiplying the number of resources used by multiplying the number of resources used by their prices. Prices of pumps and consumables were collected from the manufacturer's websites (http://www.medtronic-diabetes.bg). To calculate the yearly pump costs, the prices were divided by 4, which is recommended by the manufacturers as the period of use for initial users, then on 12 and multiply by 7 to receive the 7 months cost. All other costs were taken from the Bulgarian NHIF tariff (http://www.nhif.bg). Costs are presented in Euro. As the long-term therapeutic result was observed

the change in HbA1c level before the pump introduction and after 6 months, when the child visited his endocrinologist with results of HbA1c level.

When therapeutic results differ statistically cost-effectiveness ratio (CER) was calculated by dividing the 7 months cost of the health care resources and the changes in the observed therapeutic results. Incremental cost-effectiveness ratio (ICER) was also calculated by dividing the differences in costs between the active and control group with the differences in the observed therapeutic results.

Sensitivity Analysis

To test the robustness of the results, a one-way sensitivity analysis was performed by consecutively varying the changes in the HbA1c level within the standard deviation interval for both groups of patients with 0.05.

Statistical Processing

Descriptive statistics were applied to the patient's characteristic and outcomes. A Student T-test analysis was also performed to test the statistical significance in the outcome changes.

Results

Continuous subcutaneous insulin infusion (CSII) systems are of a limited usage for Bulgarian children. They are not included in the Positive list for reimbursement and are not a standard treatment for type-1 diabetes.

From 2007 to 2013, 51 children with type-1 diabetes were observed (mean age 113.82 months in the group with insulin pumps; 115.06 in the group on analogous insulin, and 112.41 in the group on human insulin). The duration of diabetes was a shorter in the group on human insulin with a pen device (see Table 1).

Table 1: Patient main characteristics					
	Gender	**Age (months)**	**HbA1c starting level**	**HbA1c end level**	**Months with diabetes**
CSII	f = 8 m = 9	113.82	8.79	6.94	66.65
MDI	f = 7 m = 10	115.06	9.56	8.97	75.76
HI	f = 9 m = 8	108.65	10.68	10.40	22.76
Source: Authors					

The average improvement in HbA1c level in the active group after the CSII introduction is 1.85, while after the application of analogue insulin and after the application on human insulin 0.59 and 0.28, respectively (see Table 1).

The price of insulin pump was 4025.64 Euro thus reaching 1006.41 Euro per patient per year and 587.07 Euro for 7 months - Table 2. The transmitter cost was 743.59 Euro, respectively 427.82 Euro for 7 months. The test strips was 610.16 Euro for 7 months. Insulin usage due to the strict control was lower in the Group 1 and therefore their cost of insulin therapy was lower, compared with the Group 2- also on analogue insulin. The total cost of insulin pump's therapy for 7 months was higher maily due to the CSII pump and related consumables (see Table 2).Costs are presented in Euro.

Table 2: Yearly cost of therapy

	Insulin cost	Pump cost	Consumable	Total costs
CSII	204.00	587.07	1567.78	2358.85
MDI	220.11		636.87	856.98
HI	107.37		636.87	744.24

Source: Authors

The HbA1c level is with lowest at the beginning and at the end of observation, showing considerably better control of diabetes in CSII group (Table 1).

Cost-Effectiveness Analysis

Table 3:Cost-effectiveness and incremental cost-effectiveness ratio for 7 months (Euro).

	Total cost 7 months	Average inprovement in HbA1c level	CER	ICER
CSII	2358.85	1.85	1275.05	1184.18
MDI	856.98	0.59	1452.51	363.68
HI	744.24	0.28	380.52	

Source: Authors

In the reduction of HbA1c analogues insulin are cost- effective compared to human insulin. Insulin pumps are cost- effective therapy compared with both alternatives.

In the entire range of variation of the variable ICER remains below the threshold of profitability, which means that insulin pumps are cost-effective alternative to change its long-term therapeutic results as HbA1c.

Discussion

Continuous subcutaneous insulin infusion (CSII) are of a limited usage for Bulgarian children. They are not included in the Positive list for reimbursement and are not a standard treatment for type-1 diabetes. Only parents with sufficiently high income are able to afford such therapeutic approach. In this sense, evaluation of the cost-effectiveness of insulin pumps usage is influenced by a number of factors, such as health insurance policy, endocrinologist' preferences, income of parents and therapeutic standards. This study shows that the usage of insulin pump with child populations with type-1 diabetes is an efficient therapy, compared with the other two alternatives—on MDI or on human insulin with a pen device. The same results were also achieved by comparing the alternatives separately during the whole observed period (Petkova et al., 2013b)

The study also shows that children using CSII manage to maintain stable and target HbA1c levels, which are preconditions for better diabetes management (UKPDS, DCCT). The studies of the CSII usage in child populations are very limited in terms of long-term results comparison in detail. But, by bearing in mind the evidence for the adult population, it can be predicted that strict and reliable disease control for children will support their long-term treatment.

Maahs, Horton, & Chase (2010) considered that CSII should be recommended for children with type-1 diabetes and in the future to achieve better glycemic control.

The results of this study and the results of our other studies (Petkova et al., 2013a; 2013b) can serve as justification for the Bulgarian NHIF to include CSII in the reimbursement system.

Conslusion

The reduction in HbA1c can guarantee good diabetes management. Also the insulin pumps are characterized with many advantages: nearly physiological release of insulin, reduction in insulin requirements, avoidance of injection-induced pain.

References

Fairchild, J. (2015), Changes in Management and Outcomes for Children and Adolescents with Type-1 Diabetes over the Last 50 Years. *Journal of Paediatrics and Child Health*, 51, 122–125. doi: 10.1111/jpc.12821

Maahs D. M., Horton, L. A., & Chase, H. P. (2010, Jun). The Use of Insulin Pumps in Youth with Type-1 Diabetes. *Diabetes Technology and Therapeutics, 12*(1), 59-65. doi: 10.1089=dia.2009.0161

Monami, M., Lamanna, C., Marchionni, N., & Mannucci, E. (2010). Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Insulin Injections in Type-1 Diabetes: A Meta-Analysis. *Acta Diabetologica*, 47, 77-81.

Petkova, E., Petkova, V., Konstantinova, M., & Petrova, G. (2013a). Economic Evaluation of Continuous Subcutaneous Insulin Infusion for Children with Diabetes - a pilot study: CSII application for children – an economic evaluation. BMC Pediatrics, 13, 155.

Petkova, E., Petkova, V., Konstantinova, M., & Petrova, G. (2013b). Economic Evaluation of Continuous Subcutaneous Insulin Infusion for Children with Diabetes - Part II. *Modern Economy*, 4, 9-13.

Russell, S. J., El-Khatib, F. S., Sinha, M., Magyar, K. L., McKeon, K., Goergen, L. G., Balliro, C., Hillard, M. A., Nathan, D. M., & Damiano, E. R. (2014). Outpatient Glycaemic Control with a Bionic Pancreas in Type-1 Diabetes. *New England Journal of Medicine*, 371, 313-25.

Weisberg-Benchell, J., Antisdel-Lomaglio, J., & Seshadri, R. (2003). Insulin Pump Therapy: A Meta-Analysis. *Diabetes Care*, 26, 1079-1087.