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CONTINUOUS SUBCUTANEOUS INSULIN INFUSION VERSUS MULTIPLE DAILY INJECTIONS FOR CHILDREN TREATMENT – PHARMACOECONOMIC ANALYSIS

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SUMMARY

There are no enough studies comparing the effect of continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI). Most of the available literature is restricted to small scale before and after studies. The aim of this study is to evaluate the cost-effectiveness of continuous subcutaneous insulin infusion (CSII) to analogue multiple daily insulin injections (MDI), based on the achieved short term therapeutic results as insulin dosage per kg and average daily blood glucose level. This is the prospective, observational, comparative, controlled real life study performed at the Endocrinology Clinic with 26 children separated in two groups – active on SCII and passive on MDI. Cost-minimization, cost-effectiveness, sensitivity and statistical analyses are applied to studied short-term therapeutic results.

The average dose of insulin per kg is slightly lower at 0.7323 IU/kg (SD 0.307 IU/kg) in the active group than in the control group at 0.8953 IU/kg (SD 0.165 IU/kg). The blood glucose level is decreasing significantly in active group to 6.59 mmol/l.

No matter the literature evidences that MDI is more effective for short period of application, the statistical processing of our data shows that 46.15% from the active group (CSII) has statistically significant improvement in comparison with the control group (MDI). Based on this fact we can assume that CSII group better insulin management in comparison with the control group. We found that the CSII is cost-effective alternative when the decrease in blood glucose level is considered.

Our study shows that the CSII pumps allows better diabetes control when even short come results are considered, as is the insulin dose per kg, and blood glucose level. They are also and cost-effective alternative for children with type 1 diabetes.

KEYWORDS: continuous subcutaneous insulin infusion, diabetes mellitus, multiple daily injections, children, cost-effectiveness.

INTRODUCTION

The prevalence of diabetes is increasing worldwide. There are many factors that are stimulating this escalation such as aging, urbanization, increasing prevalence of improper diet and physical inactivity. According to WHO, in 2014 the global prevalence of diabetes was estimated to be 9% among adults aged 18+ years. In 2012, an estimated 1.5 million deaths were directly caused by diabetes. More than 80% of diabetes deaths occur in low- and middle-income countries. WHO projects that diabetes will be the 7th leading cause of death in 2030.[1]

Diabetes is one of the most common chronic diseases in children. According to the statistics about 208,000 young people in the US under age 20 had diabetes in 2012. Type 1 diabetes accounts for approximately 5 percent of all diagnosed cases of diabetes, but it is the leading cause of diabetes in children of all ages. Type 1 diabetes accounts for almost all diabetes in children less than 10 years of age.[2] The same is the situation in Europe. Wide variation in incidence of type 1 diabetes in children younger than 15 years has been well characterized by registry reports from the EURODIAB study group within Europe.[3]

Doses of insulin as the only one therapy for type 1 diabetes in childhood are varying in great intervals due to variety of factors as patients' age, nutrition regime, weigh etc.[4] Treatment plans for type 1 diabetes are based on every child's needs and the suggestions of the diabetes health care team. Treatment approaches differ in the types of insulin given and the schedules for giving insulin each day. The advantages and disadvantages of a plan should be considered for every child. Treatment goals for kids with diabetes are to control the condition in a way that minimizes symptoms, prevents short- and long-term health problems and complications, and helps them to have normal physical, mental, emotional, and social growth and development. Unless they're using an insulin pump, children require two or more injections every day to keep blood sugar levels under control. There is no-one-size-fits-all insulin schedule — the type of insulin applied and number of daily injections a child needs depends on the diabetes management plan.

Syringes and pens are used manually to inject insulin. Applying insulin injections daily is almost painless, thanks to the smaller needles. Insulin pumps, which deliver insulin through a small tube that is placed just under the skin, cut down on the number of injections needed.[5] Pumps are computerized devices programmed to deliver a continuous flow of insulin. There has been approved more than 55 different insulin pumps. A newer type is the "patch" pump, in which the tubing is contained within a pump directly attached to the body with adhesive.[6] There are evidences from the literature that the utilization of continuous subcutaneous insulin infusion via pumps allows better dosing that closer matching the physiological insulin secretion.[7] The pumps devices are expensive and not reimbursed in many countries, which necessitates their cost-effectiveness evaluation in different health care settings.

The aim of this study is to evaluate the cost-effectiveness of continuous subcutaneous insulin infusion (CSII) to analogue multiple daily insulin injections (MDI), based on the achieved short term therapeutic results as insulin dosage per kg and average daily blood glucose level.

METHODOLOGY

This is the prospective, observational, comparative, controlled real life 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 Medical Science Council of the Medical University in Sofia reviewed and approved the study. The observation continue during 2007-2010.

Patients selection

Only 30 children in the country are using CSII pumps. 26 children with type-1diabetes were observed divided into two groups: with an active group using CSII and a control group using analogue insulin therapy with a pen device - multiple daily injections (MDI). With the informed consent of the parents, on a random basis were recruited 13 children from the Clinic and included in the active group. The children were selected during their control visits. From the patients records was formulated the control group on insulin analogues, which matches the active groups as age, gender and weigh of the children. The children were consecutively recruited from the end of 2007 when the first pumps were administered. The active group included all children who began using the CSII pumps during the period 2007–2011 when the data collection began. Also since 2010, all children were transferred to real time insulin pumps; therefore, during the observation, they all used the same type of pump from the same manufacturer.

Therapeutic results measurement

Data for the selected children was collected on their demographics, age, gender, weight, therapeutic schema (CSII or analogue insulin treatment with a pen device - MDI). As the measures of therapeutic results, we choose the mean dose of Insulin per kg weigh (IU/kg), the mean blood glucose level in hour 2, 7, 13, 15, 19 and 22, measured before the meal, for a period of 15 days, as well as the mean daily blood glucose level for the same 15 days. The data for the active group were collected from the electronic records of the pumps and for the passive group from children diaries.

Cost minimization and cost-effectiveness analysis

For both groups of children, the health care resources used by them were recorded, namely insulin, pumps (1 for 4 years), consumables for pumps (6-10 sets and 6-10 reservoirs), strips (n = 1100 per patient per year), glucometers (1 for 5 years including sensor prices), GP and endocrinology visits. Sensors were used from 7 to 10 days. 15 days costs of CSII, blood glucose monitoring systems, insulin therapy, and strips were calculated by multiplying the number of resources used by their prices. Prices of pumps and blood glucose monitoring systems were collected from the manufacturers' websites. 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, and then on 12 and on 2 to receive the 15 days cost.[8] All other costs were taken from the Bulgarian NHIF tariff (9). Costs are presented in Bulgarian leva (BGN). At the time, the exchange rate was 1 Euro: 1.95 BGN.

Cost-minimization analysis was performed for the therapeutic results comparison when no statistically significant differences are observed.

When therapeutic results differ statistically cost effectiveness ratio (CER) was calculated by dividing the 15 days 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 doses of insulin per kg and changes BGN for costs.

Statistical analysis

Descriptive statistics were applied to the patient's characteristic and outcomes. A Student T-test analysis and paired sample statistics were performed to test the statistical significance in the outcome changes. Statistical processing of the information was performed by SPSS and MS Excel 2013.

RESULTS

Results from the therapeutic control measurement

The active and the controlled group do not differ statistically in age and gender (Table 1).

Table 1. Demographical characteristics and daily insulin quantities and doses per kg for the active and control group

Active group (CSII)						Control group (MDI)					
gender	kg	Daily insulin (UI)	SD (UI)	Insulin/ kg (UI/kg)	SD (UI/kg)	gender	kg	Daily insulin (IU)	SD (UI)	Insulin/ kg (UI/kg)	SD (UI/kg)
2	33.5	5.76	0.19	0.17	0.06	2	48.8	28.8	1.42	0.59	0.03
1	35	17.27	1.09	0.49	0.03	1	28.5	24.08	1.75	0.84	0.06
2	31	23.14	1.14	0.75	0.04	2	36	28.66	1.81	0.80	0.05
1	29	15.15	1.58	0.52	0.05	1	22.5	17.83	1.39	0.79	0.06
2	24	16.43	0.84	0.68	0.03	2	21	22.13	1.15	1.05	0.05
1	34	6.96	0.31	0.2	0.001	1	24.7	27.73	1.34	1.12	0.05
2	55	45.71	5.41	0.83	0.09	2	59	57.13	1.77	0.97	0.03
1	24	11.16	1.08	0.46	0.04	1	22	17.13	1.02	0.78	0.04
1	35	21.38	1.22	0.61	0.03	1	45.5	32.2	1.51	0.71	0.03
1	29	31.1	4.83	1.07	0.16	1	24	26.98	0.68	1.12	0.03
2	40	66.65	5.82	1.66	0.14	1	63.3	36.87	2.06	0.58	0.03
2	34	32.01	3.02	0.94	0.09	2	51	39.47	0.72	0.66	0.01
1	53	60.71	6.09	1.14	0.11	1	58.6	27.2	1.04	0.46	0.02

The average age is 10.23±3.166. 53.8% of participants were male. Most participants reported to have suffered from diabetes from 5 to 10 years. The active group weight was 35.12±9.5. while the control group was significantly different – 38.84±16.05. The t-value is 2.393248. The p-value is 0.010248.

The daily quantities of insulin are slightly lower at 27.186 IU (SD 15.422 IU) in the active group than in the control group with 29.708 IU (SD 7.205 IU). The average dose of insulin per kg is slightly lower at 0.7323 IU/kg (SD 0.307 IU/kg) in the active group than in the control group at 0.8953 IU/kg (SD 0.165 IU/kg) – Table 1.

The application of paired sample T-test for the daily quantities of insulin in IU shows that the t-value is 0. -.543. The p-value is 0.597. Comparison between the insulin quantities of the two groups shows that the t-value is -.516. The p-Value is 0.615. This means that the average daily quantities of insulin are not statistically significant between both groups.

The Sig. (2-Tailed) value for the average daily dose of insulin per kg is 0.597. This value is greater than .05. Because of this. we can conclude that there is no statistically significant difference between the mean insulin dose per kg between the control and active group. Thus we can resume that the active and control group are achieving the same therapeutic results when the daily consumption of insulin and mean daily dose per kg is considered as therapeutic control measures.

Table 2. Paired Samples Test

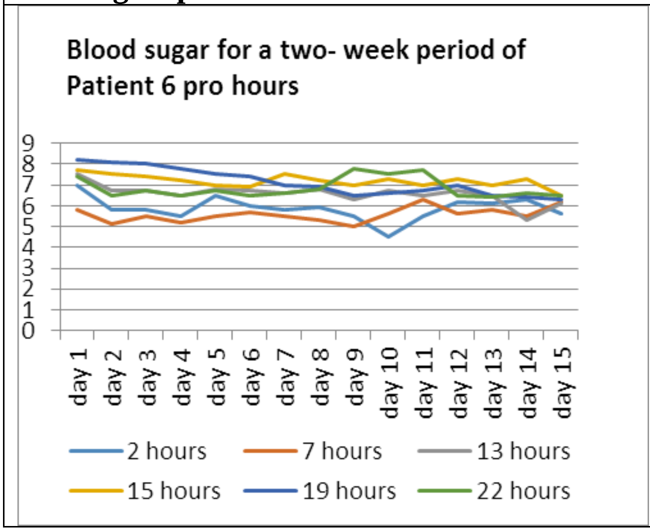
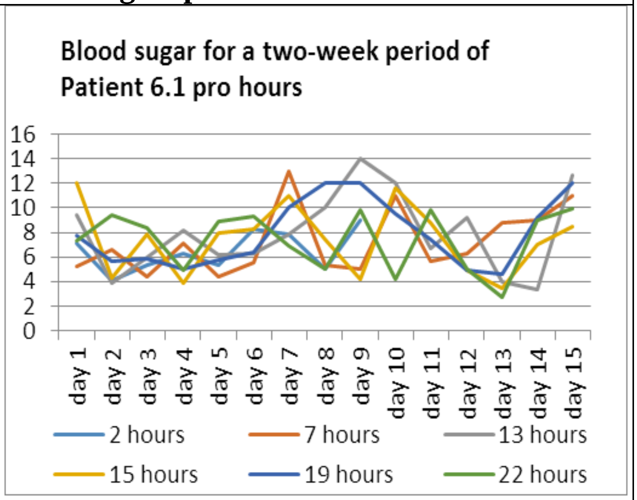
		Paired Differences					T	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	patient1 - patient1_1	-3.47333	.94688	.38656	-4.46703	-2.47964	-8.985	5	.000
Pair 2	patient2 - patient2_1	-.05833	1.45445	.59378	-1.58468	1.46802	-.098	5	.926
Pair 3	patient3 - patient3_1	-3.21667	2.14884	.87726	-5.47173	-.96160	-3.667	5	.014
Pair 4	patient4 - patient4_1	-5.56167	4.30667	1.75819	-10.08124	-1.04209	-3.163	5	.025
Pair 5	patient5 - patient5_1	.49667	.80324	.32792	-.34628	1.33961	1.515	5	.190
Pair 6	patient6 - patient6_1	-1.43333	1.38729	.56636	-2.88921	.02254	-2.531	5	.052
Pair 7	patient7 - patient7_1	.14500	.36768	.15011	-.24086	.53086	.966	5	.378
Pair 8	patient8 - patient8_1	-.33500	.90803	.37070	-1.28791	.61791	-.904	5	.408
Pair 9	patient9 - patient9_1	-.30833	1.40940	.57539	-1.78741	1.17074	-.536	5	.615

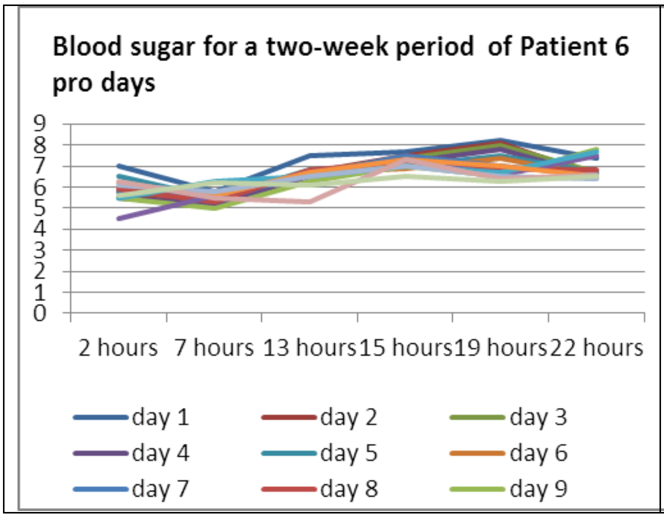
Pair 10	patient10 - patient10_1	-.60333	.85315	.34830	-1.49866	.29199	-1.732	5	.144
Pair 11	patient11 - patient11_1	-3.48667	1.89379	.77314	-5.47407	-1.49926	-4.510	5	.006
Pair 12	patient12 - patient12_1	-2.52500	1.24261	.50729	-3.82904	-1.22096	-4.977	5	.004
Pair 13	patient13 - patient13_1	.16500	1.13160	.46197	-1.02254	1.35254	.357	5	.736

The second short term therapeutic measure that we used in our analysis was the mean blood glucose level at the time of measurement and the mean daily blood glucose level.

The comparison of the mean glucose level after 15 days treatment shows that 6 patients on CSII have statistically significant lower levels of blood glucose which is an evidence for better management in their therapy. No matter the literature evidences that MDI is more effective for short period of application the statistical processing of our data shows that 46.15% of the patients from the active group (CSII) has statistically significant better control in comparison with the passive group (MDI) -Table 2.

This fact is also graphically evident from the figure 1. The blood glucose excursions are more evident in the control group.

Active group	**Control group**
	



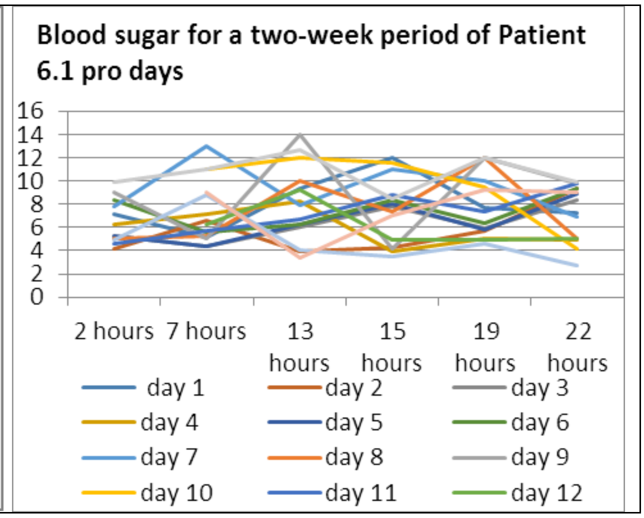


Fig.1. The average blood glucose level for 15 consecutive days in active and control group

Results of the pharmacoeconomic analyses

The CSII price of the blood glucose monitoring system was 7850 BGN (4025.64 Euro) thus reaching 1962.50 BGN (1006.41 Euro) per patient per year and 80.65 BGN for 15 days – Table 3. The transmitter cost was 425 BGN (217.95 Euro), respectively 17.47 for 15 days. The test strips is 9.25 BGN for 15 days.

Insulin usage due to the strict control was lower in the group of children with CSII and therefore their cost of insulin therapy was lower (Table 3). The total cost of therapy in the group of CSII users for 15 days therapy was higher mainly due to the CSII pumps and related consumables.

Table 3. Cost of the therapy for 15 days (BGN)

Patient group	Daly insulin usage (IU)	15 days insulin cost	Pump cost	Transmitter cost	Consumables	Total cost 15 days
MDI	29.708 IU (SD 7.205 IU)	104.28			9.25	113.53
CSII	27.186 IU (SD 15.422 IU)	95.42	80.65	17.47	138.08	331.62

Cost-minimization analysis

Regarding the first therapeutic measure, we found that the average daily dose of insulin was 0.7323 IU/kg (SD 0.307 IU/kg) in the active group and 0.8953 IU/kg (SD 0.165 IU/kg) in the control group. This difference is not statistically significant meaning and we can compare only the cost of therapy. In the active group due to twice-higher prices of consumables, pump and transmitter the cost of therapy is higher. Nevertheless, that the insulin consumption per kg is lower and the cost of insulin is lower in the active group on CSII it could not setoff the twice-higher cost connected with the application of the medical device. Thus from the purposes of the cost-minimization analysis we can consider that the CSII group is more costly in the way of controlling the insulin usage per kg in children with diabetes type 1.

Cost-effectiveness analysis

The average blood glucose level for the active group is 6.586 (mmol/l) and for the control group is 8.13 (mMol/l) – Table 2. Therefore, the cost-effectiveness and cost-effectiveness ratio are 13.96 and 50.35 BGN for every unit of decrease in the blood glucose level, and 141.25 BGN additionally for every additional decrease in the blood glucose level, respectively (Table 4).

Table 4. Cost- effectiveness and incremental cost-effectiveness ratio for 15 days (BGN)

Patient group	Total cost 15 days	Average blood glucose level (mmol/l)	CER	ICER
MDI	113.53	8.13	13.96	
CSII	331.62	6.586	50.35	141.25

Results from the sensitivity analysis

The starting point in the sensitivity analysis is the ICER in the base case (141=25 BGN). In the active group, the blood glucose level was within the recommended physiological limits and we vary only the blood glucose level in control group by decreasing its value with 0.05 to 7 mmol/l. Improvement in the blood glucose level in the control group let to the increase in ICER to 526.78 BGN. The same is the situation with the decrease in the cost of SCII therapy. Even during the first change with 50 BGN decrease the ICER dropped down to 88 BGN (Figure 2). We can conclude that the ICER is more sensitive to the changes in cost of the therapy.

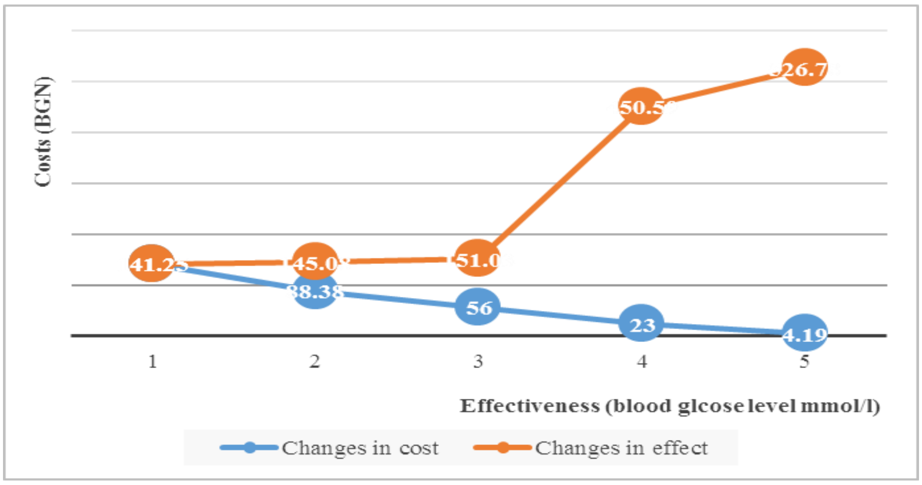


Fig. 2. Sensitivity analysis

DISCUSSION

There are many discussions in the literature for the advantages of the CSII via insulin pumps.[10] Some authors consider that CSII should be recommended for children and widely used to achieve better glycemic control.[11]

Our study confirms that the daily consumption of insulin is lower in the group on CSII and this saves financial resources. Although the difference in the daily consumption is not statistically significant for higher number of children, the effect will be more evident.

Similarly the consumption of insulin per kg is lower. The latter is very important clinical parameter because badly regulated insulin with high doses per kg of child weigh could lead to severe hypoglycemic episodes.

Children are very active and their glucose level is fluctuating in a great extend during the day. Knowing the exact doses allows better control and minimization of the risk for them. That's why for the other short come therapeutic results we choose to measure the blood glucose level. The recommended doses before meal are 4 to 7 mmol/L for people with type 1 diabetes. We found that the observed children have little more higher than recommended level in the control group, but it is almost matching the standard in the active group. The differences are statistically significant among active and control group for half of the patients. Thus, we can conclude that the CSII allows better diabetes control leading to decreased insulin consumption, and low blood glucose level.

We also could consider that the CSII pumps are cost-effective when the short-come results as the decrease in the blood glucose level are considered. Because the CER and ICER are below the GDP per capita that is 4642.93 USD (8474.42 BGN), and respectively below the GDP of USD 190.76 (348.18 BGN) for 15 days.[12] Nevertheless, we found that the SCII are cost effective the sensitivity analysis shows that even the small decrease in the cost of therapy with them influences the ICER in a great extent. If SCII pumps are included in the reimbursement, this will increase their utilization and probably decrease the cost of the therapy that will benefit all children and the society.

CONCLUSIONS

Our study shows that the SCII pumps allows better diabetes control when even short come results are considered, as is the insulin dose per kg, and blood glucose level. They are also and cost-effective alternative for children with type 1 diabetes.

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