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A Comparative Study of Continuous Subcutaneous Insulin Infusion Therapy (CSII) and Multiple Daily Insulin Therapy (MDI) in Children and Adolescents with Type 1 Diabetes Mellitus, A Single Center Experience

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Abstract:

Background: Treatment of type 1 diabetes mellitus has always posed a challenge to balance hyperglycemia control with hypoglycemia episodes. This study aimed to compare the glycemic and metabolic control and quality of life in type 1 diabetic Egyptian children on continuous subcutaneous insulin infusion therapy (CSII) versus multiple daily insulin therapy (MDI).

Patients and Methods: This is a prospective analysis of Seventeen patients with type 1 diabetes mellitus on continuous subcutaneous insulin infusion therapy (CSII) (group A) together with fifty patients with type 1 diabetes mellitus on multiple daily insulin therapy (MDI) (group B), age and sex- matched, coming for regular follow-up at the outpatient endocrinology clinic of Galaa military medical complex from the period of May 2018 to October 2018.

Results and Conclusion: Our study showed that PedQL 3 and PedQL 4 scores were significantly higher in the CSII group than in the MDI group (p=0.024 and p=0.021) and PedQL 4 was higher in females than in males (p=0.029), with no sex-difference in PedQL3. Also, HbA1c was found to be significantly lower in CSII users than in those on MDI.

Keywords: Type 1 Diabetes Mellitus, Continuous Subcutaneous Insulin Infusion Therapy (CSII), Multiple Daily Insulin Therapy (MDI), Quality of Life

1. Introduction

It is well-known that glycemic control tends to be poorer in children and adolescents compared to adults. This may be attributed to multiple physiologic, behavioral and psychosocial factors including hormonal changes, insulin sensitivity and increasing self-management over time [2].

Diabetes mellitus is one of the diseases that impacts individuals' quality of life the most, since therapy requires a radical change in their lifestyle and that of their family, due the need to maintain metabolic control in the ideal parameters. Thus, they must change their diet, physical activity, daily insulin injections and consultations with the endocrinologist to adjust the doses. This routine causes sadness, anxiety and frustration [3].

Continuous subcutaneous insulin infusion therapy (CSII) has been used in the treatment of type 1 DM (T1DM) since the 1970's and is increasingly used as an alternative to multiple daily insulin therapy (MDI), as pumps have become more widely available. Its effectiveness has been confirmed by meta-analyses of various observational and randomized controlled studies and in childhood and adolescence studies [4].

CSII therapy is the most physiological insulin therapy currently available, more closely mimicking daily insulin release and is also reported to improve patients' quality of life [5].

In Egypt, few studies were published assessing the metabolic control in children using CSII in comparison with MDI, due to its high costs [7]. Further studies are needed to reach a conclusion about the efficacy of CSII.

Patients and Methods

Population of the study & disease condition:

This is a case control prospective study. Seventeen patients with type 1 diabetes mellitus on continuous subcutaneous insulin infusion therapy (CSII) (group A) using MINIMED PARADIGM 515/715 INSULIN PUMP together with fifty patients with type 1 diabetes mellitus on multiple daily insulin therapy (MDI) (group B), age and sex- matched, coming for regular follow-up at the outpatient endocrinology clinic of Galaa Military Medical Complex from the period of May 2018 to October 2018.

Inclusion criteria:

1. Onset of type 1 DM before 16 years.
2. Diabetes duration for at least 6 months.

Exclusion criteria:

1. Associated autoimmune disorder.
2. Associated acute or chronic complications.

Interventions:

Consent obtained from patients/their parents for participation in the study.

All patients included were subjected to: full history taking including demographic data (age, sex, parents' consanguinity, family history of diabetes mellitus), age at diagnosis, disease duration. Full clinical examination including anthropometry (height, weight, body mass index), blood pressure measurement, systemic examination, presence of associated conditions e.g., goitre and presence of complications. Review of glycemic control and pump data including random blood glucose readings done at the outpatient clinic every week, insulin/carbohydrate ratio and insulin sensitivity factor, number of hypoglycemic attacks/week and frequency of extra dose of insulin. Laboratory investigations done at time of study including HbA1C, thyroid profile, lipid profile, urinary albumin/creatinine ratio, mean fasting, post prandial and random blood glucose. Quality of life assessed using PedsQL TM version 3 and PedsQL version 4 questionnaires [8, 9].

Statistical analysis:

Microsoft excel 2019 was used for data entry. Results were tabulated and statistical significance was tested using the student t-test for quantitative values and chi square test was used for qualitative values.

Results

Table 1: Age, age at onset of disease and disease duration in both groups included in the study.

Variable	Group A (n=17)	Group B (n=50)	P value
Age (years) (mean ±SD)	12.93 ±2.78	11.89 ±3.09	0.218
Age at diagnosis (years) (mean ±SD)	8.4 ±2.6	7.6 ±3.4	0.405
Disease duration (years) (mean ±SD)	4.2 ±3.2	4 ±2.8	0.842

Table 2: Sex distribution and frequency of positive consanguinity and family history in the studied groups.

		Group A (n=17)		Group B (n=50)		Total		P value
		N	%	N	%	N	%	
Gender	Male	6	35.3%	30	60.0%	36	53.7%	0.078
	Female	11	64.7%	20	40.0%	31	46.3%	
Consanguinity	Positive	5	29.4%	10	20.0%	15	22.4%	0.504
	Negative	12	70.6%	40	80.0%	52	77.6%	
Family History	Positive	2	11.8%	17	34.0%	19	28.4%	0.120
	Negative	15	88.2%	33	66.0%	48	71.6%	

No significant differences between groups A and B regarding age, age at diagnosis, disease duration, gender, consanguinity and family history.

Table 3: Comparison of clinical findings in both groups included in the study:

Physical findings/known conditions	Group A (n=17)		Group B (n=50)		Total (n=67)		P value
	N	%	N	%	N	%	
Normal	12	70.6%	45	90%	57	85%	0.132
Fatty liver	0	0.0%	1	2.0%	1	1.5%	
Hirsutism	0	0.0%	1	2.0%	1	1.5%	
Hypertension	1	5.9%	0	0.0%	1	1.5%	
Epilepsy	1	5.9%	0	0.0%	1	1.5%	
Obese	0	0.0%	1	2.0%	1	1.5%	
Short stature	3	17.6%	1	2.0%	4	6.0%	
Thyroid enlargement	0	0.0%	1	2.0%	1	1.5%	

Table 4: Anthropometric measurements of the studied groups.

	Group A (n=17)			Group B (n=50)			P value
	Median	Percentiles		Median	Percentiles		
		25	75		25	75	
Weight SDS	-.1300	-.9350	.2550	-.1800	-1.2325	.5975	0.719
Height SDS	-.8100	-1.6950	-.0050	-1.1250	-1.8025	-.1300	0.416
BMI SDS	.0500	-.4300	.7900	.5000	-.2025	1.1225	0.152

BMI: body mass index *SDS: standard deviation score*

Table 5: Comparison between metabolic control and other laboratory data in the studied groups.

Variables	Group A (n=17) Mean (±SD)	Group B (n=50) Mean (±SD)	P value
HBA1C (%)	8.3 (±1.6)	9.9 (±1.8)	0.002
TSH (uIU/ ml)	2.91 (±1.89)	2.61 (±1.51)	0.584
Free T4 (ng/dl)	1.15 (±0.19)	1.22 (±0.28)	0.466
TG (mg/dl)	74.4 (±27.8)	108.8 (±124.5)	0.507
Cholesterol (mg/dl)	156.3 (±39.8)	178 (±43.3)	0.093
HDL (mg/dl)	64.5 (±18.3)	57.9 (±13.4)	0.296
LDL (mg/dl)	92.6 (±28.2)	99.4 (±28.9)	0.383
FBG (mg/dl)	130.9 (±35.1)	174.6 (±35.7)	<0.001
PPBG (mg/dl)	174.7 (±37.7)	223.7 (±47.2)	<0.001
RBG (mg/dl)	195.2 (±31.7)	234.1 (±45.2)	0.002
Urinary A/C (mg/ml)	23.6 (±28.3)	30.7 (±30)	0.143

HBA1C: Hemoglobin A1C *TSH: Thyroid stimulating hormone*
Free T4: Free thyroxine *TG: Triglycerides*
HDL: High density lipoproteins *LDL: Low density lipoproteins*
FBG: Fasting blood glucose *PPBG: Post prandial blood glucose*
RBG: Random blood glucose *Urinary A/C: Urinary albumin creatinine ratio*

The mean FBG of patients in group A was significantly lower than in those of group B (130.9 ±35.1 SD mg/dl vs 174.6 ±35.7 SD mg/dl respectively, p<0.001). Mean two-hours PPBG in those

of group A was also significantly lower than in those of group B (174.7 ±37.7 SD mg/dl vs 223.7 ±47.2 SD mg/dl respectively, p <0.001). The mean RBG in patients of group A was lower than those of group B (195.2 ±31.7 SD mg/dl vs 234.1 ±45.2 SD mg/dl respectively, p <0.002). The mean HBA1C of group A was significantly lower than group B (8.3 ±1.6 SD % vs 9.9 ±1.8 SD% respectively, p <0.002) (figure 5). No other laboratory data showed significant differences.

Table 6: Comparison of hypoglycemic attacks/week, extra dose of insulin/week, I/C ratio, ISF and total insulin dose/kg/day in both studied groups.

Variables	Group A (n=17) Mean (±SD)	Group B (n=50) Mean (±SD)	P value
Insulin/carbohydrate ratio	15 ±7	16 ±9	0.994
Insulin sensitivity factor	70 ±45	59.2 ±31.8.	0.303
Number of hypoglycemic attacks /week	2.6 ±4.5	1.9 ±1.9	0.289
Frequency of extra dose of insulin	6 ±6.7	5.8 ±5.6	0.895
Total insulin dose per kg	0.69 ±0.17	0.9 ±0.31	0.008

Group A, mean number of hypoglycemic attacks per week was 2.6 ±4.5 SD, mean extra dose of insulin per week was 6 ±6.7 SD, mean insulin/ carbohydrate ratio was 15 ±7 SD, the mean of total insulin dose per kg was 0.69 ±0.17 SD and mean insulin sensitivity factor was 70 ±45 SD. Group B, mean number of hypoglycemic attacks per week was 1.9 ±1.9 SD, mean extra dose of insulin per week was 5.8 ±5.6 SD, mean insulin/ carbohydrate ratio was 16 ±9 SD, the mean of total insulin dose per kg was 0.9 ±0.31 SD and mean insulin sensitivity factor was 59.2 ±31.8 SD. The total insulin dose per kg in group A was significantly lower than in group B (0.69 ±0.17 SD vs 0.9 ±0.31 SD respectively, p<0.008) (table 6).

Table 7: Mean of PedQL3 and PedQL4 scores in the studied groups:

	Group A (n=17)			Group B (n=50)			P value
	Mean ±SD	Percentiles		Mean ±SD	Percentiles		
		25	75		25	75	
PedQL3	70 ±11.6	65.000	76.500	61.4 ±14.8	50.750	72.000	0.024
PedQL4	75.5 ±14.8	68.500	85.500	65.9 ±13.9	54.750	76.000	0.021

The PedsQL TM version 3 mean score was significantly higher in group A, 70 ±11.6 versus 61.4 ±14.8 in group B with P value 0.024, and the median (IQR) in group A was 71.4 (66 - 76) versus 56.5 (51 – 71) in group B. While the mean score of PedsQL version 4 was significantly higher in group A, 75.5 ±14.8 versus 65.9 ±13.9 in group B with P value 0.021 and the median (IQR) in group A was 78 (72 - 85) versus 65 (55 - 76) in group B (table 7).

Table 8: Correlations between PedsQL TM version 3 and PedsQL version 4 scores and demographic data and anthropometric measures of patients.

Variables	PedsQL3		PedsQL4	
	r	P value	r	P value
Age (years)	-.293	.016	-.101	.418

Age at diagnosis (years)	-.240	.050	-.011	.931
Disease duration (years)	-.048	.698	-.129	.297
Hypoglycemic attacks/week	-.225	.067	-.137	.268
Extra insulin dose/week	.110	.374	.051	.681
Weight (SD)	-.075	.549	-.016	.897
Height (SD)	-.061	.624	.110	.377
BMI (SD)	-.140	.259	-.054	.667
IC ratio	.303	.013	.225	.067
ISF	.341	.005	.231	.060
Insulin dose (units/kg/day)	-.239	.051	-.218	.076

There is a negative correlation between PedsQL3 and age of patients (r=-.293, p=.016), age at diagnosis (r=-.240, p=.050), height (r=-.318, p=.009), insulin dose per kg (r=-.239, p=.051). There is a positive correlation between PedsQL3 and IC ratio (r=.303, p=.013) and ISF (r=.341, p=.005) **(table 8).**

Table 9: Correlation between PedsQL TM version 3 and PedsQL version 4 scores and laboratory data of patients.

Variables	**PedsQL3**		**PedsQL4**	
	r	**P value**	**r**	**P value**
Mean FBG (mg/dl)	-.056	.653	-.171	.167
Mean PPBG (mg/dl)	-.031	.806	-.120	.335
Mean RBG (mg/dl)	.036	.774	-.073	.558
TG (mg/dl)	-.056	.654	-.066	.596
Cholesterol (mg/dl)	-.256	.036	-.175	.156
HDL (mg/dl)	.005	.966	-.053	.673
LDL (mg/dl)	-.159	.199	-.087	.485
HBA1C (%)	-.071	.568	-.091	.465
TSH (uIU/ ml)	-.069	.581	-.133	.258
FreeT4 (ng/dl)	.025	.844	-.028	.824
Urinary AC (mg/ml)	-.145	.251	-.240	.056

HBA1C: Hemoglobin A1C *TSH: Thyroid stimulating hormone*
Free T4: Free thyroxine *TG: Triglycerides*
HDL: High density lipoproteins *LDL: Low density lipoproteins*
FBG: Fasting blood glucose *PPBG: Post prandial blood glucose*
RBG: Random blood glucose *Urinary A/C: Urinary albumin creatinine ratio*

There was a negative correlation between serum cholesterol and PedsQL3 score (r=-0.256. p=0.036) **(table 9).**

Table 10: Comparison between PedQL3 and PedQL4 scores in male and female patients:

Sex		**PedQL3**	**PedQL4**
Male	N	36	36
	Median	56.500	64.000

Female	N	31	31
	Median	68.000	74.000
P value		0.326	0.029

PedQL4 (but not PedQL3) scores were significantly higher in females than in males (p=0.029) **(table 10).**

Discussion

Therapy in the form of injectable insulin is designed to keep blood glucose as close to normal as possible. This aims to prevent both microvascular complications and to reduce the risk of macrovascular disease **[10].**

A further aim of treatment is to achieve as good a quality of life as possible, particularly since self-management of the condition is challenging, demanding the implementation of complex skills **[11].**

Insulin may be administered through multiple daily doses of insulin injections (MDI) or through continuous subcutaneous insulin injections (CSII).

Due to the high cost of CSII, few studies have been carried out in Egypt to assess metabolic control and quality of life in children using CSII compared to those on MDI **[7].**

The present study was carried out on a convenience sample of 67 age and sex-matched patients with T1D (50 on MDI and 17 on CSII) in the outpatient diabetes clinic in Galaa Military Hospital, Cairo Egypt.

The aim of our study was to compare the effectiveness of CSII as opposed to MDI in providing better glycemic control and quality of life in individuals with T1D. The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study proved that the microvascular complications of diabetes can be avoided or delayed if blood glucose levels are maintained as close as possible to the normal range **[13].**

There was no difference in age between our two groups with a mean age of the MDI patients of 11.89 $\pm$3.09 years and a mean age of patients on CSII of 12.93 $\pm$ 2.78 years. There was also no difference in mean age at diagnosis in both groups or in disease duration. We included children with similar T1D duration to exclude differences related to treatment fatigue, a condition which can occur when the burden of a chronic disease undermines adherence to health behaviors.

Similar study was carried out in King Saud bin Abdulaziz University in Saudi Arabia ***Al Shaikh et al.*** **[14]** on 68 patients with mean ages of MDI patients of 12.9 $\pm$ 2.8 years and 14.6 $\pm$ 2.5 years in CSII.

There was a positive family history for T1D in 11.4% and 34% of children in the CSI and MDI groups of our study with no significant difference between the two groups. On clinical examination, there was no difference in the findings between the two groups as regards to anthropometric measurements (height SDS, weight SDS or BMI SDS). Thus, we could not link either methods of insulin therapy to either obesity or poor growth.

One of the concerns related to CSII is obesity. This is thought to result from more flexibility in meal times and unrestrained eating behavior which is not ideal for optimal weight or glycemic control.

In our study group, median BMI was 20 (BMI SD=0.05) in CSII compared to 19 (BMI SD=0.5) in MDI. When we compared our study group with others we found the following: BMI (±SD) was 0.39 ±0.95 SD in the CSII group and 0.39 ±0.85 SD in the MDI group in Turkish children [16], BMI Z-score of MDI patients in the Saudi study ***Al Shaikh et al.*** [14] was 0.708 ±0.837 and 0.802 ±0.624 in the CSII patients, in the Chinese children [17], BMI+SD in the CSII group was 17.98 ±3.01, while in the MDI group, it was 18.03 ±2.97 and finally in the Kuwaiti study [18], the mean BMI (kg/m2) of the CSII patients was 18.6±3.9 and 18.7±4.0 in the MDI patients.

Although there was no significant difference in median levels of albumin/creatinine between CSII (10mg/ml) versus MDI patients (13.45 mg/ml), the 75th percentile was lower (30.5mg/ml) compared to 55mg/ml in MDI group. This finding needs longer follow up to provide clear evidence for a positive effect of CSII in preventing diabetic nephropathy. Microalbuminuria is an established risk marker for the presence of cardiovascular disease in T1D and predicts progression of nephropathy when it increases to frank microalbuminuria>300 mg/d [19]. Similarly, to our finding, ***Lepore et al.*** [20] found that CSII seemed to be protective in preventing progression to microalbuminuria.

In some individuals, CSII is able to provide individuals with better self-management of their diabetes due to increased motivation [15]. This is reflected as better HbA1c levels as noted in our study, where HbA1c levels were significantly lower in pump users (mean=8.3%, median=7.7% versus 9.9% ND 9.7%, p=0.002). HbA1c is a better reflection of long-term blood glucose control than fasting and 2-hour postprandial levels which were also significantly lower in CSII patients (p<0.001) on lower total daily dose of insulin (p=0.008). When we compared our findings with those of others, we found the following results for HbA1c: In the study by ***Hu et al.*** [17] on Chinese children mean HBA1C in MDI patients was 12.97 ±2.81% compared to 12.68 ±3.03%, in CSII. In the Saudi study of ***Al Shaikh et al.*** [14] median HBA1C was 9.6% (IQR 2.3) in MDI versus 8.5% (IQR 2.4) in CSII. Meanwhile in the Kuwaiti study by ***Abdul Rasoul et al.*** [18], mean HbA1c (%) was 8.8±1.4 in MDI patients compared to 8.9±1.4 in CSII patients and finally in the Turkish study of ***Korkmaz et al.*** [16] mean HbA1c in MDI patients was 8.3 ±1.6 % and in CSII patients, it was 7.3 ±1.0 %. HbA1c was also found by ***Lepore et al.*** [20] to be significantly lower in CSII users than in those on MDI.

There is a rising trend of overweight and obesity among individuals with type 1 diabetes associated with insulin resistance, increased insulin dose requirements and poor glycemic control [21]. In our two groups of patients, we achieved better HbA1c levels with lower daily doses/kg/day (0.69 ±0.17 U/kg/d in CSII and 0.9 ±0.31 in MDI) than in the Chinese study by ***Hu et al.*** [17] (0.98 ±0.17 U/kg/d in CSII patients and 0.96 ±0.14 in MDI patients), the Saudi study by ***Al Shaikh et***

al. [14] (0.89±0.41U/kg/d versus 1.1±0.23U/kg/d) and the Kuwaiti study of ***Abdul Rasoul et al.*** [18] (0.8±0.2U/kg/d versus 0.8±0.2).

The use of background (basal) insulin as in MDI cannot always meet changing insulin needs, as evidenced in those experiencing the dawn phenomenon or those who have severe hypoglycemic events during the night. In addition, the ability of CSII to deliver tiny amounts of insulin is helpful for those individuals who are extremely sensitive to insulin.

Patients with similar HbA1cs may demonstrate very different blood glucose profiles. Another important consideration besides HbA1c for diabetes management and prevention of long-term complications is what is now being referred to as 'Time in Range' [22]. We did not measure this in our study. This is a CGM-derived metric and is related to the amount of time a person's blood glucose lies between predetermined 'optimal' levels usually of 70-180mg/dL [23].

In our study, Quality of life was assessed using PedsQL TM version 3 and PedsQL version 4 questionnaires [8, 9]. PedQL 3 and PedQL 4 scores were significantly higher in the CSII group than in the MDI group (p=0.024 and p=0.021) and PedQL 4 was higher in females than in males (p=0.029), with no sex-difference in PedQL3. In other studies, on health-related quality of life (hrQOL) in Egyptian children and adolescents with T1D receiving MDI, significantly lower levels were found in females than in males and in those with worse metabolic control [25] or long-term complications [26].

The insulin pump is not a miracle cure for diabetes. Effort still needs to be made, such as keeping food records and blood glucose diaries, calculating insulin/carbohydrate ratios and needing to use bolus insulin. Coping with technology may also be stressful [13]. This necessity for active engagement in diabetes care and achieving optimal glycemic control has the potential to impact negatively on quality of life (QOL). ***Hirose et al.*** [27] cited that improvement to QOL in children was related to the ability to enjoy meals, feel safe in school and to experience positive and supportive relationships. A systematic review carried out by ***Rosner and Roman-Urrestarazu*** [12] showed fewer hypoglycemic but more frequent DKA events in CSII users compared to MDI patients and an overall slight superiority of QOL in pump users over the longer term. In our study, we found no difference in hypoglycemic attacks in MDI and CSII groups (p=0.289), although insulin doses (units/kg/day) were significantly lower in the CSII group (p=0.008).

In our study, a negative correlation was found between PedsQL3 and age of patients (r=-.293, p=.016), age at diagnosis (r=-.240, p=.050), height (r=-.318, p=.009) and total daily insulin dose per kg (r=-.239, p=.051). There is a positive correlation between PedsQL3 and IC ratio (r=.303, p=.013) and ISF (r=.341, p=.005).

While we have demonstrated improved HbA1c levels and QOL in patients on CSII compared to those on MDI, it should be noted that due to the relatively short follow-up times of our and other studies[12] no long-term effects on morbidity and mortality in T1DM patients have been ascertained.

Conclusion

Our study showed that PedQL 3 and PedQL 4 scores were significantly higher in the CSII group than in the MDI group (p=0.024 and p=0.021) and PedQL 4 was higher in females than in males (p=0.029), with no sex-difference in PedQL3. HbA1c was found to be significantly lower in CSII users than in those on MDI. There was no difference in the findings between the two groups with regard to anthropometric measurements (height SDS, weight SDS or BMI SDS). Thus, we could not link either method to either obesity or poor growth. Due to the relatively short follow-up times of our study, no long-term effects on morbidity and mortality in T1DM patients have been ascertained.

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