ORIGINAL RESEARCH PAPER

Diabetology

THE METABOLIC CONTROL WITH INSULIN PUMP USE IN POST-TRANSPLANT DIABETICS – AN INDIAN EXPERIENCE

KEY WORDS: NODAT, Insulin pumps, Multiple Subcutaneous Insulin Injections (MSII), Continuous subcutaneous insulin infusion (CSII)

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ABSTRACT

Introduction: There has been an increase in the prevalence of post-transplant diabetics secondary to various organ transplants. The experience with pump use is limited in this subset of diabetics. This study was undertaken to compare the metabolic control in patients with post-transplant Diabetes Mellitus with the use of insulin pumps as compared to conventional insulin therapy.

Materials and Methods: This was an open label pilot study done at a tertiary care hospital in India. A total of 11 patients with New Onset Diabetes Mellitus After Transplant (NODAT), aged between 30 – 65 yr, were included in this study. All patients were started on Multiple Subcutaneous Insulin Injections (MSII) on entry in the study and followed up for six months after which period they were placed on Continuous subcutaneous insulin infusion (CSII) via insulin pump for 6 months with monthly follow up. During the follow up visits, the investigators based on self-monitoring of blood glucose, made insulin dose adjustments, hypoglycemic episodes were enquired and weight was recorded. HbA1c and lipid profile was done every three months during the study period. Insulin dose were assessed at each visit. The Insulin Delivery System Rating Questionnaire (IDSRQ), a validated PRO instrument that assesses treatment preference and satisfaction, was completed at baseline, end of six months and study end. The statistical analysis was done using paired t tests and differences between groups on study end outcome measures were assessed using analysis of covariance (ANCOVA).

Results: The mean (+SEM) HbA1C values at baseline were 8.7 + 0.6% at the beginning, 8.2 + 0.1% after six months of initiation on MSII therapy and 7.2 + 0.3% after another six months of therapy with CSII respectively. The mean (+SEM) weight gain was 0.9 ± 0.3 kg for the MSII group and 0.7 + 0.2 kg for the CSII group. The initial mean (+SEM) basal insulin doses were 54.5 + 1.4 units and 44.4 + 1.1 units for the MSII and CSII groups, respectively. Two patients in the MSII group and no patient in the CSII group reported severe hypoglycemia, three episodes of Hyperglycemic hyperosmolar state (HHS) in the MSII group and two episodes in the CSII group were noted during the study period. The reduction in total cholesterol, LDL cholesterol and triglycerides was significantly more in CSII group compared to baseline after six months. HRQOL and treatment satisfaction levels revealed patient preference for insulin pump therapy.

Conclusion: Better glycemic control with reduced insulin requirement, lesser weight gain, better lipid profile and higher levels of patient satisfaction can be achieved with CSII when compared to MSII therapy without increasing the incidence of severe hypoglycemic episodes.

INTRODUCTION

Dr. Joseph Murray performed the first successful solid organ transplantation when he conducted renal transplantation in Richard Henrick in 1954 and donor kidney was taken from his twin brother.[1] Organ transplantation is complicated by primary graft failure and infection. Almost all organ systems can be affected by transplantation, particularly being the endocrine system.[2] Post transplant diabetes, or New Onset Diabetes After Transplantation (NODAT), is now a well-recognized consequence of organ transplantation. Prevalence of NODAT at 12 months post operation varies from approximately 20–50% for kidney transplants, 9–30% for liver transplants, 28–30% for heart transplants, 6–45% for lung transplants, and approximately 15% for bone marrow transplants.[3] Risk factors for NODAT include family history of diabetes, age, obesity, ethnicity, inactivity, prediabetes status[4] and exposure to immunosuppressive agents, including glucocorticoids and calcineurin inhibitors (tacrolimus and cyclosporine).[5] Also, multiple transplants, infection with diabetogenic viruses like hepatitis C virus (HCV), cytomegalovirus (CMV), preexisting vitamin D deficiency etc. confer increased risk.[6-8] Diagnosis of NODAT is made by same ADA criteria as are used to diagnose diabetes in general population except A1C use for diagnosis is not recommended.[9,10]

The treatment of NODAT include diabetes education, therapy for hyperglycemia, surveillance for microvascular complications, optimization of insulin therapy during episodes of high-dose steroid exposure and evaluation and control of co-morbid conditions.[10,11]

Good glycemic control in NODAT patients becomes even more imperative in view that NODAT being a risk factor for graft rejection, infections, long-term graft failure, and decreased patient survival.[12] The early use of insulin is recommended if target glycemic controls are not met as it is associated with release of proinflammatory cytokines and increased mortality.[13].

This concept of tight glycemic control though is quite enticing to state but is only achieved in 7-13 % of Type 1 DM[14,15] and a fraction of type 2 DM patients.[16] Use of insulin pump therapy among type 1 DM patient leads to better glycemic control (A1C reduction by 0.3-0.6 %), reduced insulin doses by 10-20 %, lesser hypoglycemic episodes and improved quality of life indices[17,18] and better glycemic control in type 2 DM patients.[19] Therefore it has been suggested to use insulin pump therapy at low threshold to achieve strict glycemic control in NODAT patients who fail to achieve target glucose values.[3]

The experience with pump use in India is limited in view of high cost of therapy and limited availability of pumps. This study was undertaken to compare the metabolic control status achieved in patients with post-transplant Diabetes Mellitus with CSII by pumps as compared to conventional insulin therapy.

AIM

The purpose of this study was to evaluate the glycemic control, safety and efficacy of CSII via insulin pump as compared to that with MSII in post-transplant diabetic patients.

MATERIAL AND METHODS

This was an open label pilot study carried in a tertiary care hospital. A total of 11 patients with New Onset Diabetes Mellitus after transplant (NODAT) (ten Renal and one Liver transplant) recipients, aged between 30 – 65 yrs, were included in this study.

INCLUSION CRITERIA:

1. Not a known Diabetic prior to transplant.
2. On Multiple Subcutaneous Insulin Injections (MSII). Any oral anti-diabetic drugs if being given were stopped.
3. HbA1c between 7.0 to 12.0%.

Exclusion Criteria:
1. Duration of NODAT less than 12 months.
2. HbA1c less than 7.0%

METHODOLOGY

The written informed consent was taken and eligible patients were assigned to Multiple subcutaneous insulin injections (MSII). They were recalled after 7 days for baseline assessments, including A1C, fasting plasma glucose, body weight, and patient-reported outcomes (PRO) measures. They were instructed to record symptoms of hypoglycemia and simultaneous blood glucose values and to immediately report if any episodes of severe hypoglycemia. Minor hypoglycemia was defined as symptoms consistent with hypoglycaemia that resolved either spontaneously or upon self treatment with oral carbohydrate. Severe hypoglycemia referred to symptoms consistent with hypoglycemia during which the patient required the assistance of another individual and was associated with a documented blood glucose concentration of less than 65 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon.

The patients returned for reassessment monthly for next six months and insulin dose adjustments were made based on self monitoring of blood glucose, hypoglycaemic episodes were enquired and weight was recorded. HbA1c was done every three months during the study period.

The Pump therapy was initiated at the end of six months of MSII, with one daily basal rate and insulin boluses at each major meal. The recommended initial total daily insulin dose was 0.5 U/kg of body weight, with 50% distributed throughout the day as one hourly basal rate and the remaining 50% distributed among daily meals. Investigators were instructed to make every effort to safely achieve fasting and preprandial plasma glucose values between 80 and 130 mg/dL and 2 h postprandial values below 180 mg/dL.

The patients returned to the study site initially weekly for two weeks and then every month till the end of the study period i.e. 12 months. Insulin dose and the number of daily basal rates were assessed at each visit. Two self-monitored seven-point glucose profiles (preprandial, 2 h postprandial, and bedtime) were performed within 3 days preceding each visit. A1C was assessed at every three months (Diabetes Control and Complications Trial referenced, normal range 4.0–6.0%). Patients underwent Continuous Glucose Monitoring for 7 days prior to initiation of pump therapy, during the initial 4 weeks of pump therapy, and during the final week of the study. The Insulin Delivery System Rating Questionnaire (IDSRQ), a validated PRO instrument that assesses treatment preference and satisfaction, was completed at baseline, end of six months and study end.

Outcome measures

The primary outcome was assessment of insulin dose and insulin dosing patterns at end of six and 12 months. This included the total daily insulin dose and basal and bolus insulin doses.

The secondary outcomes included change from baseline in A1C, fasting glucose, body weight, PRO, and incidence and event rate of severe hypoglycaemia / HHS / DKA.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the data. Differences between groups at baseline and the study end for demographic and outcome measures were determined using t tests. Differences between baseline and study end values for each group were analyzed using paired t tests. Differences between groups on study end outcome measures were assessed using analysis of covariance (ANCOVA) with respective baseline values as a covariate. Where assumptions of ANCOVA were violated, t tests on change scores were performed to determine differences between groups. Differences in proportions experiencing severe hypoglycaemic episodes were determined using x2 analyses. Excel ® (Microsoft) 2000 was used for data entry, and analysis was done using SPSS version 10.0.

RESULTS

Subject demographics:

There were six women and five men with a mean (±SD) age of 55 ± 13.5 years and mean (±SD) duration of diabetes of 06 ± 4.3 years (Table 1).

Insulin dose:

The total insulin dose was significantly higher in the MSII group, compared with the CSII group at the end of the study ($P < 0.001$, Table 2). The total insulin dose significantly decreased in the CSII group ($P < 0.001$) and it was significantly more than in the MSII group ($P < 0.01$).

The initial mean (±SEM) basal insulin doses were 54.5 ± 1.4 units and 44.4 ± 1.1 units for the MSII and CSII groups, respectively ($P < 0.001$, Table 2). The basal insulin dose decreased significantly with the CSII group ($P < 0.001$); basal insulin dose in MSII group ($P < 0.01$, Table 2) was significantly higher than in CSII group. The mean (±SEM) pre-meal bolus was different at baseline between the two groups ($P < 0.01$, Table 2), although the dose was not different at the end of the study.

HbA1C values:

The mean (±SEM) HbA1C values at baseline were 8.7 ± 0.6% at the beginning, 8.2 ± 0.1% for the MSII group after six months of initiation on MSII therapy and 7.2 ± 0.3% after another six months of therapy with CSII respectively ($P < 0.001$ for both groups when compared with the baseline values). Both groups improved their A1C values similarly (by 1.0% in CSII users and 0.5% in the MSII group, $P < 0.01$), with significant difference in A1C values at the end of study ($P < 0.001$).

Weight:

There was a small but similar weight gain during the study period in both groups ($P < 0.001$). The mean (±SEM) weight gain was 0.7 ± 0.2 kg for the CSII users and 0.9 ± 0.3 kg for the MSII group (Table 2).

Severe hypoglycemic events:

A total of two of 11 patients in the MSII group and no patient in the CSII group reported severe hypoglycemia during the study period.There was a mean (±SEM) of 0.6 ± 0.1 severe hypoglycemic episodes per subject per year in the MSII group. No severe hypoglycemic episodes per subject were noted in the insulin pump group ($P < 0.01$, Table 2).

Diabetic Ketoacidosis / Hyperglycemic hyperosmolar state:

There were three episodes of HHS (Hyperglycemic hyperosmolar state) in the MSII group. There were two subjects who experienced HHS episodes in the insulin pump group during the study period (Table 2). Two of these subjects required hospitalization, increasing the cost of their care. No DKA was seen in any patient.

Dyslipidemia:

The reduction in total cholesterol, LDL cholesterol and triglycerides was significantly more in Insulin pump group compared to baseline after six months of MDI group.

DISCUSSION

This is the first study demonstrating that patients with New Onset Diabetes after Transplant (NODAT) achieve better glycemic control and metabolic profile using an Insulin Pump" (CSII, pump therapy with insulin lispro or insulin aspart) as part of their intensive insulin regimen compared to "Multiple daily sub-cutaneous insulin injections" (MSII) with insulin glargine with premeal insulin lispro or insulin aspart.

There was small but similar weight gain in both the groups (CSII and MSII) during the study period. Mean weight gain in MSII group was slightly more than in CSII group likely due to larger insulin dose requirement in this group.

The mean HbA1c from the baseline was reduced by 0.5% in six months in MSII group and further reduced by 1% in next six months with CSII which was significant in both groups when compared from the baseline. Within the two groups, mean HbA1c reduction was significantly more in CSII cohort (P < 0.001).

The total mean insulin dose was significantly higher in the MSII group compared to the CSII group (P < 0.001). This might be partly due to more weight gain in MSII group and increased doses of immunosuppressant initially in NODAT.

Few episodes of severe hypoglycemia were seen in MSII group and none was seen in CSII group.

Episodes of HHS were similar in both the groups without any statistical significance. Most episodes of HHS in our patient population was secondary to pump failure, to catheter occlusion, or to no insulin left in the syringe. No episode of DKA was seen in any of these patients.

The lipid profile improved significantly more in CSII group with reduction in LDL cholesterol and triglyceride levels, compared to baseline and also six months after MDI therapy as well.

HRQOL and treatment satisfaction levels assessed in patients with IDSRQ revealed patients preference for insulin pump therapy. There were significant differences between treatment strategies on all measures except psychological well-being. Group differences on these measures ranged from 0.3 to 1.4 SD units (median 0.9). The differences were substantial for all items from the treatment preference measure. More MSII users (58.2%) than CSII users (17.2%) expressed desire to switch to another insulin delivery system. More CSII users (93.6%) than MSII users (56.4%) were very or completely satisfied overall with their insulin delivery system. More CSII users (83.6%) than injection users (24.6%) stated that they would definitely recommend their insulin delivery system to others. More CSII users (97.1%) than MSII users (65.7%) reported that their current system was better than their prior treatment strategy (Table 3).

CONCLUSION

Form this study it is concluded that slightly better glycemic control with reduced insulin requirement, lesser weight gain and better lipid profile can be achieved with insulin pump when compared to MDI therapy without increasing the incidence of severe hypoglycaemic episodes. Still, increased cost of therapy with insulin pump and insulin pump being more labour intensive (to educate and train patients for insulin pump therapy) favours trial of MSII therapy routinely prior to considering insulin pump therapy.

Table 1: Baseline Demographics And Characteristic

	Basal Cohort (On initial reporting)	MSII cohort (Initial 6 month)	CSII Cohort (6—12 months)
	11	11	11
Age ± SD (yrs)	55 ± 13.5	55 ± 13.5	55 ± 13.5
Gender (Male/female)	5(45.5)/ 6(54.5)	5(45.5)/ 6(54.5)	5(45.5)/ 6(54.5)
Weight (Kg)	68.2 ± 15	70.5 ± 15	69.4 ± 14
BMI (kg/m2)	28 ± 5	29 ± 5	28.3 ± 5
Duration of Diabetes (Yrs)	6 ± 4.3	6 ± 4.3	6 ± 4.3

Data are mean ± SD values, BMI-Body mass index, MSII—multiple subcutaneous insulin injections, CSII—Continuous subcutaneous insulin infusion (Insulin pump therapy)

Table 2: Results showing comparison in 2 groups

		MSII	CSII	p^a value
Total daily insulin dose (units)	Initial	58.5 ± 1.4	54.5 ± 1.2	<0.001
	Final	54.5 ± 1.2	44.4 ± 1.1	<0.001
	p^b value	<0.001	<0.0001	
Basal insulin dose (units)	Initial	29.4±1.3	28.3±1.2	0.2
	Final	28.3±1.2	24.6±1.4	0.1
	p^b value	<0.01	<0.001	
Body weight	Initial	68.2±1.5	70.5±1.5	0.01
	Final	70.5±1.5	69.2±1.3	0.01
	p^b value	<0.001	<0.001	
HbA1c (%)	Initial	8.7 ± 0.6	8.2 ± 0.1	<0.001
	Final	8.2 ± 0.1	7.2 ± 0.3	<0.001
		<0.001	<0.001	
FPG (mg/dl)	Initial	170 ± 42	156 ± 41	<0.01
	Final	156 ± 41	138 ± 45	<0.01
		<0.001	<0.001	
Hypoglycemic episodes/pt/yr		0.6 ± 0.1	0.0	0.01
Total DKA/HHS episodes		3	2	0.6
Total Cholesterol		206 ± 24	154±21	<0.001
LDL Cholesterol		115±13	92±19	<0.001
HDL Cholesterol		36±8	40±11	0.05
Triglyceride		190±21	150±14	<0.001

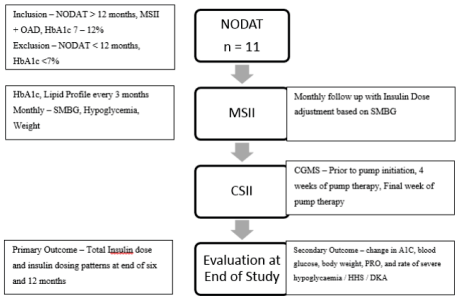
Data are Mean ± SD

Pa values comparing insulin doses between treatment groups were calculated using paired t tests, Pa values comparing severe hypoglycemic & HHS/DKA episodes between treatment groups were calculated using X2 analysis, Pb values comparing initial & final insulin doses, body weight were calculated using ANCOVA.

Table 3: Group Comparison

	CSII	MSII	Significance (F-test)	△ (in SD Units)
Treatment Satisfaction	80.5±15.0	60±16.9	<0.001	1.2
Daily Activity Interference	19.5±14.2	35.5±19.8	<0.001	0.9
Clinical Efficacy	72.2±16.1	55.2±18.5	<0.001	0.9
Diabetes worries	36.4±15.4	53.4±20.2	<0.001	0.7
Psychological well-being	65.2±16.2	48.2±17.4	<0.001	0.7
Social burden	29.8±14.6	38.6±15.8	<0.001	0.6
Overall performance (4/6items)	86.2±14.2	61.4±18.8	<0.001	1.4
Overall Performance (3/6 items)	82.6±15.2	60.8±14.2	<0.001	1.3

Fig 1:



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