Full Length Research Paper

Safety and Efficacy of Continuous Insulin Delivery via Pumps for Type 1 Diabetics During Ramadan Observance

Waleed I. AlBaker[1], Ammar Khamis[2], Ahmed Abu Al-Hamayal

[1]University of Dammam Consultant of Endocrinology
[2]University of Dammam, Department of Family and Community Medicine, Consultant of Biostatistics and Genetic Epidemiology
[3]MD University of Dammam

The insulin pump has proved to be an effective way to administer insulin in patients with Type 1 Diabetes. However, no data is available to assess its efficacy and safety in fasting diabetics' patients during the fasting time (month of Ramadan) .The purpose of this study was to compare the efficacy and safety of insulin pump in patients with type 1 diabetes mellitus already on the pump, who were fasting during Ramadan, as compared to patients with type 1 diabetes on multiple daily insulin injections and patients on premix insulin. *Methods:* This was a single center non-randomized trial design study. Patients with type 1 diabetes mellitus who were fasting received three types of treatments: patients received insulin through insulin pump (n =10), patients on multiple daily insulin injections (MDII) (n=5) and patients on premix insulin (CI) (n= 5). All patient groups are comparable in patient characteristics (Table 1). The patients were seen once before Ramadan (pre-Ramadan), and once after (post-Ramadan). Weight change, episodes of hypoglycemia, emergency visits, and days of breaking their fast were evaluated. Biochemical, FBS, HbA1c, and lipid profile were also evaluated. *Findings:* Most patients on insulin pump were able to complete their fasting during Ramadan (average 2 fast breaking per patient) with minimal episodes of mild hypoglycemia (2 episodes per patient), no episodes of hypoglycemia requiring assistance and no emergency room (ER) visits . No significant difference was found in biochemical profiles of patients on insulin pump who were fasting during the month of Ramadan as compared to patients on MDII. Both groups had better biochemical profiles than the group of patients managed with premix insulin. *Conclusion:* The insulin pump proved to be effective and safe in patients fasting Ramadan than other insulin regimen.

Keywords: Insulin Pump, Ramadan, Fasting, Type 1 diabetes.

INTRODUCTION

A large number of type 1 diabetic patients are on insulin pump for glycemic control. Although it has been proved to be the most effective way to control blood glucose level with lowest rate of hypoglycemia, little data is available for its safety and efficacy during the month of Ramadan (holy

*Corresponding Author's Email: dr_waleed99@hotmail.com

month of fasting in Muslim religion starting from sunrise to sunset daily for about 29-30 days).

Fasting of patients with diabetes is usually discouraged (Al-Arouj etal., 1902). A large epidemiological study conducted in 13 Islamic countries on 12,243 individuals with diabetes who fasted during Ramadan showed a high rate of acute complications (EPIDAR study) (Salti ET AL., 2001;2004). These risks include hypoglycemia, hyperglycemia, diabetic ketoacidosis and dehydration and thrombosis. The EPIDAR study shows 4.7 fold increase in the incidence of severe hypoglycemia in patients with type 1 diabetes (defined as hospitalization due to hypoglycemia) (Salti ET AL., 2001;2004). The same study also indicated a three-fold increase in episodes of severe hyperglycemia (requiring hospitalization), which might have been due to excessive decrease in their medical dosages to prevent hypoglycemia. The same reason is thought to increase the risk of diabetic ketoacidosis.

According to the Organization of the Islamic Conference in its published recommendations under the head, "Diabetes and fasting in Ramadan: Summary of recommendations of the Organization of Islamic Conference", diabetics can be stratified according to their risk for fasting in Ramadan (Jaleel ET AL., 2011; Hassanein 2010). Categories 1 constitute the very high risk group for fasting in Ramadan. They are generally patients who have brittle diabetes, episodes of hypoglycemic unawareness or hyperglycemic emergencies (Diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic state) in the past 3 months, pregnant ladies, and individuals performing intense physical labor. Category 2 is the high risk group of diabetics for fasting in Ramadan. They are the patients with moderate hyperglycemia (180-300 mg/dL) or HbA1C > 10%, diabetic nephropathy, advance diabetic retinopathy, advance macrovascular complications, aged individuals with ill health, or individuals who live alone. Category 3 are patients with well controlled diabetes with short acting insulin secretagogues and constitute moderate risk for fasting in Ramadan. Category 4 are patients with well controlled diabetes with diet alone, metformin, or thiazolidinediones, and are otherwise healthy. The recommended ruling for patients that fall in categories 1 and 2 is that they are prohibited from fasting to prevent harming themselves. While the ruling for patients that fall in categories 3 and 4 is that they should fast (Jaleel ET AL., 2011; Hassanein 2010). It is essential to avoid hypoglycemia in patients who wish to fast. Thus, some experts recommend keeping the patients on a generally higher plasma glucose concentration. Other recommendations to prevent hypoglycemia includes periodic blood glucose monitoring several times during the day, avoiding of sugary food items, and delaying Suhur, which is the pre-dawn meal during Ramadan (Jaleel ET AL., 2011;Hassanein 2010). Although the effects of short-

term hyperglycemia are not clear, there have been some studies on the matter, with the currently available data it is debatable whether or not we should accept the risks of short-term hyperglycemia in favor for less chance of hypoglycemia, or accept the risk of hypoglycemia in favor to avoid short-term hyperglycemia. One study showed that short-term hyperglycemic dysregulation does not modulate myocardial or hepatic TG content or myocardial function, despite considerable metabolic adaptations (Bin-Abbas 2008). Another study performed on mice showed that short-term hyperglycemia is without any effect on deformability of the RBCs, but with increased vascular permeability (Zuurbier ET AL., 2005). Another study

supports that hyperglycemia accelerates retinal metabolism (Klemp ET AL., 2004), the overall effect of higher metabolism on the retina is not clear. Another study shows evidence that supports the hypothesis that hyperglycemia affects renal function activating the renin-angiotensin system (Miller 1999).

Control of type 1 diabetes via insulin pump is relatively new, and neither its safety nor its efficacy has been established during fasting. It's yet unclear whether diabetics can rely on it to fast. We plan to evaluate the safety and efficacy of the insulin pump.

STUDY DESIGN AND METHODOLOGY

Study Design

Insulin pump was initiated in 10 adults with type 1 diabetes mellitus between 2008 - 2010, that used the Medtronic (Northridge, CA) MiniMed 722 model. All patients were followed in Pump clinic at the King Fahad Hospital of the University in Khobar, Saudi Arabia. These patients showed interest in fasting the month of Ramadan in Hijri year of 1431 (August - September 2010). The were introduced to the study, and appropriate consent was taken. All patient groups were comparable in patient characteristics (Table 1). The patients were trained on insulin pump programming and carbohydrates calculating. The results of blood glucose levels and the rate of hypoglycemic episodes were compared with those in 5 patients with type 1 diabetes who were on premixed insulin therapy (CI), and 5 patients on multiple daily insulin injection therapy (MDII). CI therapy is defined as 2 insulin injections per day; before breakfast and before dinner combining the intermediate-acting insulin (NPH) and the short-acting insulin (regular). The patients on CI therapy were trained on the exchange program for diet therapy and showed also interest in fasting Ramadan. MDI is defined as 1 daily injection of long-acting insulin (glargine) with 2 or more rapid acting insulin injections given before meals. All patients visited the clinic prior to the month of Ramadan to adjust insulin doses, and to minimize

Table 1. Clinical observation and outcome in study patients

Patient Group	FBS (mg/dL)	HbA1c (mg/dL)	LDL	HDL
Insulin Pump	+15 [46-111]	+0.02 [-0.7-+0.7]	5.9 [-12-+25]	1.9 [-10-13]
Multiple Daily Injections	-19 [45-168]	-0.08 [-0.6-+0.3]	4.8	4
On Premix Insulin	-----	+0.4 [-0.1-+0.9]	2.4	-4

confounders, patients were educated in the diabetes education clinic to follow a healthy diet appropriate for diabetic patients, and follow a minimum activity level, one week prior to the initiation of the study, they were also instructed to check blood glucose more frequently especially during the fasting hours.

Outcome Variables

Clinical Variables; days of breaking of fast during Ramadan, emergency room (ER) visits for either hypoglycemia or hyperglycemia episodes. Biochemical profile; fasting blood sugar, Hb_{A1c}, total cholesterol, LDL, HDL, and triglycerides levels. All parameters were taken before and after the month of Ramadan and compared to each other.

Study Subjects and Design

10 patients with poorly controlled type 1 diabetes on multiple insulin injection and switched to insulin pump for better control were entered in the study with consent to be followed during the month of Ramadan with average age of 24 years (range 16 - 37 years), 2 were males and 8 were females. Average weight of 65.5 kg and an average duration of diabetes of 9 years (ranging from 5 to 14 years). 5 other patients on MDII were followed as a control group. Average age was 27 years (range 17 - 38 years). 3 were females and 2 were males with an average weight of 66.3 kg and average duration of diabetes of 8.2 years (ranging from 4 to 12 years). 5 other patients on premix insulin(CI) were also included in the study and had an average age of 27 years (range 18 to 42 years), 4 were males and 1 was a female, with an average duration of diabetes of 10.6 years (range 2 to 20 years) Type 1 diabetics had different indications of insulin pump insertion including hypoglycemia unawareness, blood serum glucose variability, and poorly controlled diabetes with

insulin injections. The patients have been on insulin pump for 1 month to 2 years and received insulin pump education and diabetes education clinic and 9 out of 10 patients were experienced in using the insulin pump. All patient groups were comparable in their characteristics (table 1).

Study Protocol

Patients presented to the Endocrinology or Insulin Pump clinic before Ramadan and were evaluated. They were assessed for their knowledge and experience in using the insulin pump. Patient's insulin dose was adjusted according to readings prior to Ramadan, to match total calorie ingestion during the day and high carb diet during the night in mind. The dose adjustment was individualized for each patient. It was suggested to all patients that they try to fast for few days before the month of Ramadan to test their adjusted insulin doses and relay their results to us.

In all patients we measured their baseline HbA1c, lipid profile, fasting blood glucose, weight, number of times of breaking their fast, and emergency room (ER) visits during Ramadan. The patients were asked to have a diary documenting their blood glucose level before each meal, and 2 hours post-prandial and 2 times during fasting and as needed. They were given direct contact numbers to the diabetic educators in case of emergency or episodes of hypoglycemia. If the patient found that their glucose reading during fasting was less than 75 mg/dL, the patients were asked to stop and disconnect the insulin pump for 2 hours, and then recheck the readings every 15 minutes until blood glucose level is found to be rising. If the patient found his blood glucose level to be less than 60 mg/dL, they were asked to break the fast right away, stop the pump, and have some carbohydrates to elevate his plasma glucose level, and recheck the readings every 15 minutes until it is found to be rising. Mild hypoglycemia was defined in our study as random blood glucose less than 75 mg /dl. Severe hypoglycemia was defined as random blood

glucose less than 60 mg /dl with need of third party assistance. Reasons of breaking fast are blood glucose level of less than 60 mg/dl or less than 75 mg /dl not responding to insulin pump discontinuation or in case of severe hypoglycemic event . Hyperglycemia was defined as random blood glucose more than 200 mg /dl .

Patients were re-evaluated after the month of Ramadan for clinical and biochemical parameters mentioned, and the results will be compared with their baseline parameters before the month of Ramadan, and also compared to the control group on MDII and the group on premix insulin who also were fasting during the month of Ramadan.

RESULTS

Patients on Insulin Pump

The study showed that patients with type 1 diabetes on insulin pump experienced much less episodes of hypoglycemia with only 3 out of 10 patient needing to breakfast, the first patient needed to break his fast for 1 day, the second for 6 days, and the third for 10 days (average almost 2 days of breaking fast); the last patient had the insulin pump only for 2 weeks and was inexperienced in using it. Reasons for breaking of fasting in these patients were blood glucose level of less than 60 mg/dL, or blood glucose level less than 75 mg/dL who did not improve on disconnecting the pump. Patients on insulin pump also showed much fewer episodes of hypoglycemia with 3 patients having episodes of mild hypoglycemia with 2 of them having mild hypoglycemia for 1 episode, and another for 10 episodes; the last patient had the insulin pump installed less than a month prior to Ramadan and was inexperienced in using it. Two out of 10 patients had episodes of hyperglycemia (serum blood sugar of > 300 mg/dL). No statistics are available because of the small size of sample presented at the time of the study.

Table (1) shows clinical observation and outcome in study patients. Table (2) shows a comparison of lab results in study subjects. Patients on insulin pump had a fasting blood sugar average of 131 mg/dL after Ramadan, making an average difference of +15 mg/dL (ranging from decreasing 46 mg/dL, to increasing 111 mg/dL). Hb_{A1c} results had an average result of 6.99% after Ramadan, with an average difference of +0.02% (ranging from -0.7% to +0.7%). Patients had an average LDL level of 96.7 mg/dL with an average difference of +5.9 mg/dL (ranging from -12 to +25 mg/dL), while HDL showed an average of 51.3 mg/dL with an average difference of +1.9 mg/dL (ranging from -10 to 13 mg/dL). Triglycerides level showed an average level after Ramadan of 56 mg/dL (ranging from 15 mg/dL to 100 mg/dL) with an average difference of - 16 mg/dL (ranging from -39 to +32 mg/dL).

Patients on MDII

In patients with type 1 diabetes on MDII, 3 out of 5 patients needed to break their fast, the first needed to break his fast for 2 days, the second for 4 days, and the last for 10 days (average around 3 days). Reasons to break fasting include episode of severe hypoglycemia, episode of hypoglycemia less than 60 mg/dL. 2 out of 5 patients on MDII had severe hypoglycemia, one patient had 1 episode, and another had 5 episodes (average of 1 episode during Ramadan). While 2 out of 5 patients had episodes of mild hypoglycemia, a patient had it for 2 days, and the other for 5 days (average of almost 2 episodes during Ramadan). The third patient who needed to break his fast needed to do so exclusively for severe hypoglycemia. 4 out of 5 patients on MDII had episodes of hyperglycemia, (Serum glucose > 300mg/dL), with average of 2 episodes of hyperglycemia during Ramadan.

On lab tests, patients on MDI showed an average fasting blood sugar of 107 mg/dL (range from 45 to 168 mg/dL) with an average difference in FBS of -19 mg/dL. Hb_{A1c} showed an average of 7.18% (ranging from 5.9 to 9.5%) with an average difference of -0.08% (ranging from -0.6% to +0.3%).. These patients also exhibited an average LDL level of 88.4 mg/dL after Ramadan with an average difference of +4.8 mg/dL, with an HDL average of 48.6 mg/dL after Ramadan and an average difference of +4 mg/dL and Triglycerides average of 52.2 mg/dL after Ramadan with an average difference of -11.6 mg/dL.

Patients on Premix Insulin

All patients on premix insulin needed to break their fasting (with an average of almost 11 days (ranging from 5 to 19 days). Reasons of breaking fast were similar to that of the MDII group. 3 out of 5 patients having episodes of severe hypoglycemia, with 2 patients having 1 episode, and another having 3 episodes during Ramadan (average of 1 episodes of severe hypoglycemia during Ramadan). 4 out of 5 patients had episodes of hyperglycemia, (blood sugar of > 300 mg/dL) with the first patient having 1 episode, the second having 2 episodes, the third had 3 episodes and the last had 8 episodes during Ramadan (average of 4 episodes).

On lab workup the patients had an average of fasting blood sugar of 184.8 mg/dL. Pre-Ramadan FBS for this group was not taken so an average difference could not be calculated. This group had an average Hb_{A1c} of 9.16% (ranging from 8.5 to 9.8%) with an average difference of +0.4% (ranging from -0.1% to +0.9%). Average LDL level was 58.8 mg/dL after Ramadan with an average difference of +2.4 mg/dL. HDL level averaged 25.4 mg/dL after Ramadan with an average difference of -4 mg/dL.

4

Triglycerides had an average of 60.8 mg/dL after Ramadan with an average difference +11.2 mg/dL.

DISCUSSION

Studies about insulin pump usage during the month of Ramadan are few. In 2005, a study was conducted by Bin-Abbas (Bin-Abbas 2008), and assessing insulin pump therapy during Ramadan fasting in type 1 diabetic adolescents. The study was conducted on 5 Saudi adolescents with type 1 diabetes mellitus who had CSII through insulin pumps. The results of blood glucose levels and the rate of hypoglycemic episodes were compared with those in 4 adolescents with type 1 diabetes who were on conventional insulin therapy. The results showed significant reduction in HbA_{1c} and the frequency of hypoglycemic episodes in comparison to conventional insulin therapy during Ramadan (Bin-Abbas 2008). In their study, the mean HbA_{1C} was 7.8% on insulin pump group compared to 9.1% in group with conventional insulin therapy. Mean blood glucose was 123 mg/dL in insulin pump group in comparison to conventional insulin group which was 192 mg/dL. Mean frequency of mild hypoglycemia (blood glucose concentration < 60 mg/dL) was 16 (up from 11 before Ramadan) episodes per patient per month in the insulin pump treated group, compared to 29 (up from 18 before Ramadan) episodes per patient per month in the group treated by conventional insulin therapy (Bin-Abbas 2008). None of the patients had any episode of severe hypoglycemia (Bin-Abbas 2008). Three of adolescents on CI therapy had to break their fast during Ramadan once or twice because of hypoglycemia. However, none of the insulin pump group broke their fast. All adolescents on insulin pump therapy had to adjust their basal rate insulin infusion to avoid hypoglycemia prior to Ramadan fasting. 10 to 15% of the basal insulin infusion rate was reduced during the hours of fasting (Bin-Abbas 2008).

Another study made by Mahmoud Benbaraka et al in 2010[10] conducted on a total of 63 patients were evaluated. Forty-nine patients fasted, and 14 elected not to fast. Those who fasted (24 males, 25 females) were 22 +/-7 years of age (mean +/- SD) and had had diabetes for 9.6 +/- 5.6 years. Patients used the Medtronic (Northridge, CA) MiniMed 722 model and had been using pump therapy for 20 +/- 10 months (Benbaraka et al., 2010). Thirty patients (61.2%) fasted the whole month with no problems, nine (18.4%) fasted 27-28 days, eight (16.3%) fasted 24-25 days, and two (4.1%) fasted 23 days. Nearly half of the patients decreased their basal insulin by 5-50% of their pre-fasting doses. Seventeen patients had hypoglycemia requiring breaking the fast. Fasting was broken on 55 out of 1,450 potential fasting days (3.8%). No severe hypoglycemia was reported by any patient. Unusual hyperglycemia was reported in nine patients (18.4%). Hospital visits were reported for one patient for hyperglycemia (a 16-year-old girl who disconnected her pump).. In this study, p value was not calculated due to small number of patients.

This study was conducted on a total of 20 patients and only 10 of which were on CSII (or insulin pump therapy). A limitation was that the patients did not keep a log of their carbohydrate intake during this month, which would be helpful in analyzing reasons for hypoglycemia or hyperglycemia in some patients. The other limitation of this study is that the daily activities and dietary habits were not documented, however, the patients were instructed to keep a minimum activity level. Also our study is small in size because the of the high cost of insulin pumps, in addition to strict inclusion criteria that we used to assure good follow up of the patient during the study . This pilot result suggested the hypothesis that insulin pump therapy might to be safer than other regimens of controlling type 1 diabetes during fasting in the month of Ramadan. This study's findings are in-line with the results of other studies looking at patients with type 1 diabetes on insulin pump. In terms of both safety of the insulin pump during fasting and its efficacy in effectively managing diabetes during that time.

CONCLUSION

Due to the small sample size of this study, we were unable to use statistical methods with our results, and the study is unable to conclude a definitive superiority of the insulin pump in it's safety or efficacy over other ways to manage insulin during Ramadan. However, the results are promising and are in line with what other authors have found in studying the insulin pump in Ramadan. More research, with larger patient population, needs to be done to conclude an absolute benefit of the insulin pump over other ways to manage diabetes during fasting in Ramadan. We believe individualized insulin dose adjustment according to blood sugar reading before Ramadan, keeping in mind morning and evening readings, and the fact that during daytime in Ramadan patients have no oral intake and during nighttime most patients have high-caloric multiple meals for better glucose control will help better control diabetes during Ramadan.

REFERENCES

Al-Arouj M, Assaad-Khalil S, Buse J, Fahdil I, Fahmy M, Hafez S (1902). Recommendations for Management of Diabetes During Ramadan. Diabetes Care 2010;33(8):1895-1902.

Benbaraka MM, Khalil Ab, Beshyah S, Marjei S, Awad SA (2010). Insulin pump therapy in Moslem patients with type 1 diabetes during ramadan fasting: an observational report. Diab Tech and Therap 2010;12(4): 287-90.

Bin-Abbas B (2008). Insulin Pump Therapy During Ramadan Fasting in Type 1 Diabetic Adolescents. Ann Saudi Med 2008;28(4):305-6.

Hassanein M, Bravis V, Heri E, Devendra D (2009). Ramadan Focused Education and Awareness in type 2 diabetes. Diabetologua 2009:52:367-368.

Hassanein MM (2010). Diabetes and Ramadan- how to achieve a safer fast for muslims with diabetes. Br J Diabetes Vasc Dis 2010;10:246-50.

Jaleel MA, Raza SA, Fathima FN, Jaleel BNF (2011). Ramadan and diabetes: As-Saum (The Fasting). Indian J Endocrinol Metab 2011; 15(4): 268-273.

Klemp K, Larsen M, Sander B, Vaag A, Brockhoff PB, Lund-Anderson H (2004). Effect of short-term hyperglycemia on multifocal electroretinogram in diabetic patients without retinopathy. Invest Ophthalmol Vis Sci 2004;45(10):3812-9.

Miller JA (1999). Impact of hyperglycemia on the renin angiotensin system in early human type 1 diabetes mellitus. J American Society Nephrol. 1999;10: 1778-5.

Salti I, Benard E, Detournay B, Bianchi-Biscay M, LeBrigand C, Voinet C, Jabbar A (2001;2004). EPIDIAR study group. A population- based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004; 27: 2306-11.

Zuurbier CJ, Demirci C, Koeman A, Vink H, Ince C (2005). Short-term hyperglycemia increases endothelial glycocalyx permeability and acutely decreases lineal density of capillaries with flowing red blood cells. J of Appl Physiol. 2005;99: 1471-6.