The Safety and Efficacy of Insulin Glargine in the Management of Type 1 Diabetes in Muslim Patients during Ramadan in Saudi Arabia

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OBJECTIVE
To determine the safety and efficacy of glargine insulin in patients with type 1 diabetes performing religious fast during Ramadan in Saudi Arabia.

METHODS
We studied 21 patients with type 1 diabetes who performed the religious fast during Ramadan in Saudi Arabia. This was an open label, observational (prospective cohort) study. The patients were already on multiple daily injections of insulin with glargine as their basal insulin. The dose of glargine was originally reduced by 10%. We further adjusted this dose during Ramadan to achieve an optimal fasting glucose reading at sunset, while still avoiding daytime hypoglycemia (during the fast). All the patients were observed for hypoglycemic events. HbA1c and fructosamine levels were assessed before Ramadan, at the end of Ramadan, and 3-6 months after Ramadan.

RESULTS
The patients were able to successfully fast for an average of 28 out of 29 attempted days of fast. The number of hypoglycemic events however was higher during Ramadan, both during the fasting and the fed hours, as compared to the post Ramadan period.

CONCLUSION
Adult patients with type 1 diabetes on multiple daily injections of insulin, with glargine as their long-acting analogue, and with stable metabolic control, may be able to fast safely during Ramadan (with the duration of the fast at 13-14 hours). However, this should only be attempted after proper review and approval by their diabetes care provider, and with close supervision.
INTRODUCTION

Ramadan is the month of fast for Moslems worldwide. The fast is between dawn and sunset daily for the whole month. The fasting includes abstaining from food and drinks. It is both a religious and a cultural season and many patients with diabetes insist on fasting even with clear religious rulings allowing them to skip the fast. Many patients also continue to fast even with the physician’s advice to the contrary. Prolonged fasting lasting up to 14 or more hours daily for a whole month carries a number of risks and complications, chief among them is hypoglycemia that may be quite serious with severe hypoglycemia requiring outside assistance.

There have been a number of studies addressing fasting in Ramadan in persons with diabetes. One study was in patients using a regimen with ultralente and regular insulin reported no daytime severe hypoglycemic episode, and there was no change in the glycosylated hemoglobin before and after fasting. There have been a few studies addressing the safety of the fast in Ramadan in children using different regimens. Only the study by Alwan et al used glargine as the basal insulin in a multiple daily injection regimen in a pediatric population, and they did not note any serious hypoglycemia or significant compromise in the diabetes control. In a study done in Minnesota in 2004, 15 persons with type 1 diabetes treated with glargine insulin safely tolerated a non-religious fast of 18 h for one day only (as opposed to a full month in Ramadan).

STUDY RATIONAL

The main purpose of our study was to determine the safety of fasting during Ramadan for persons with type 1 diabetes, without significant compromise of diabetes control, while using glargine as the basal insulin in a multiple daily injection regimen.

STUDY OBJECTIVES

Primary End Point:
The primary endpoint of the study was the number of hypoglycemic events during the month of Ramadan compared to the number of these events during the month following Ramadan.

Secondary End Point:
The percentage of days of successful fast out of the total number of days of attempted fast; and the effect of the fast on the overall diabetes control as determined by the HbA1c and fructosamine levels, pre and post Ramadan.

STUDY PATIENTS

A total of 21 patients were enrolled in this study (See Table 1) after each subject gave written informed consent. Men and women at least 18 years of age, already on a multiple daily injection of insulin regimen with insulin glargine as basal insulin, were recruited from our clinic patients with type 1 diabetes.

<table>
<thead>
<tr>
<th>TABLE 1: BASELINE CHARACTERISTICS</th>
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<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Gender (n[%])</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>DM Duration (years)</strong></td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong></td>
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<tr>
<td><strong>Total daily insulin requirements at baseline (IU/kg)</strong></td>
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</tbody>
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BMI = body mass index, DM = diabetes mellitus, IU = international unit, SD = standard deviation.
The major exclusion criteria for the study included: history of recent or recurrent severe hypoglycemia or otherwise metabolically unstable diabetes; severe and unbalanced diabetic retinopathy; and other clinically relevant major systemic disease.

METHODS
Open-label, prospective study, was carried out at two of the National Guard Health Affairs centers in Saudi Arabia: King Abdulaziz Medical City in the Central (Riyadh), and Eastern Region (Al-Hassa) after appropriate ethics committee approvals.

Data collected included demographics, a detailed history and physical examination, as well as laboratory investigations to rule chronic conditions, including HbA1c as study measurement.

TREATMENT SCHEDULE
At enrollment in the study, all patients were already on a multiple daily injection of insulin: basal insulin glargine taken at 22:00 hour and aspart insulin taken with the meals. The dose of glargine was initially reduced by 10%, followed by adjustments during Ramadan to achieve optimal fasting glucose levels at sunset. This optimal fasting glucose was defined as higher than 80 mg/dl, to avoid hypoglycemia during the fast. During Ramadan, the patients continued to take their basal insulin glargine at 22:00 hour. The pre-meal insulin in all patients was the short-acting analogue aspart. The dose of aspart was tailored to the new meal schedule during Ramadan, with the biggest dose at sunset, a smaller dose at dawn, and a third dose to cover the 22:00 hour snack or meal if there was any (the practice varies, with some people consuming only 2 meals during the 24 hours, with one meal at sunset and the second before dawn).

RESULTS
The frequency of hypoglycemia was higher during the daytime fast as well as during the nighttime feeding hours in Ramadan. The median number of hypoglycemic events during Ramadan (4, range of 0 – 26) was twice that of the post-Ramadan period (2, range of 0 –9) and the difference was statistically significant (p=0.002) (See Table 2). All the hypoglycemic events reported were simple reactions with no instances of severe hypoglycemia; there were no hypoglycemic events during sleep. While the hypoglycemic events occurred throughout the 29 days of Ramadan, we noted a higher frequency during the first week of Ramadan, and in the early morning hours of the fast as opposed to later in the day. All the patients were able to fast successfully for a median of 28 days out of attempted 29 days (range 19-29 days), a 93% success rate.

One patient had recurrent symptomatic hypoglycemic reactions and was withdrawn from the study. This patient however desired to continue the daily fast and had a final total of 26 hypoglycemic reactions throughout Ramadan. We followed this patient closely with ongoing counseling and adjustment of insulin dose. This patient could fast successfully for 19 out of an attempted 29 days, having to break the fast for 10 days due to hypoglycemia.

Another patient broke the fast for one day because of hyperglycemia and excessive thirst. This patient had significant deterioration of diabetes control during the first week of Ramadan and was withdrawn from the study, but the patient still desired to continue the fast and again close follow-up and ongoing counseling were performed.

<table>
<thead>
<tr>
<th>TABLE 2. HYPOGLYCEMIC EVENTS AND INSULIN DOSING</th>
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<tbody>
<tr>
<td>Number of events (Median [range])</td>
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<tr>
<td>During Ramadan</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Total hypoglycemic events</td>
</tr>
<tr>
<td>Symptomatic non-severe</td>
</tr>
<tr>
<td>hypoglycemic events</td>
</tr>
<tr>
<td>Asymptomatic hypoglycemic</td>
</tr>
<tr>
<td>events</td>
</tr>
<tr>
<td>Breakfast days due to</td>
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TABLE 3. FRUCTOSAMINE AND HBA1C LEVELS WITH RESPECT TO RAMADAN FAST

<table>
<thead>
<tr>
<th></th>
<th>Before Ramadan</th>
<th>During/End of Ramadan</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructosamine</td>
<td>370.0 ± 77.68</td>
<td>402.71 ± 55.92</td>
<td>0.363</td>
</tr>
<tr>
<td>HbA1c</td>
<td>07.92 ± 01.13</td>
<td>08.36 ± 01.13</td>
<td>0.385</td>
</tr>
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The data of both of these patients are included in the final statistical analysis.

There was a small increase in fructosamine and HbA1c levels from pre-Ramadan to the end of Ramadan readings; the difference however was not statistically significant (See Table 3).

DISCUSSION

As expected, there was a significant increase in the frequency of hypoglycemia in our study during Ramadan, both during the fasting and fed hours. However, these were exclusively simple reactions with no instances of severe hypoglycemia. The patients were able to successfully fast for a median of 28 of 29 days attempted. Although hypoglycemia occurred throughout the fasting month, it was more common in the early part in Ramadan. This could be because the participants were still adapting to the fast, together with the ongoing active adjustment of the insulin dose.

One limitation of the study is the small number of the patients followed. Larger studies are needed.

CONCLUSION

Successful fasting during Ramadan was possible in majority of selected patients with type 1 DM on insulin glargine as basal insulin in combination with aspart as prandial insulin in our study. Although the number of hypoglycemic reaction was higher during Ramadan, none of these hypoglycemic events was severe and none required outside assistance. Furthermore there was no significant effect on glycemic control during the period of the study.

Although this study was prospective, it has the limitations of small number of subjects and being observational. To make these findings generalizable, larger studies are needed.

Individualized approach to patients with type 1 diabetes who are planning to fast is a key element of diabetes care in combination with sufficient pre-Ramadan (month of fast) preparation and education.

REFERENCES