ORIGINAL ARTICLE

Efficacy of bolus insulin calculation by a mobile-based bolus advisor: An open label clinical trial

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Background: We investigated the efficacy of a mobile-based bolus advisor app in comparison with the usual multiple daily injections (MDIs) in diabetic patients. **Materials and Methods:** In a nonrandomized, controlled clinical trial, 62 diabetic patients were selected to receive a 12-week intensive glycemic control by either a mobile-based bolus advisor (app) or MDI in the usual manner. We compared mean blood glucose (BG) and HbA1c before and just after the treatment program. The data were analyzed using paired sample *t*-test and analysis of variance (ANOVA). **Results:** Fifty-six patients (30 cases and 26 controls) completed the study. The mean [standard deviation (SD)] of BG was 220.57 (43.7) and 231.5 (55) in the app group and control group, respectively. Mean BG decreased 38 mg/dL in the app and 16 mg/dL in the control group ($P = 0.001$ and 0.049 respectively). Changes of mean BG were different between the two groups significantly ($P = 0.039$). HbA1c decreased from 8.4% to 7.6% in the case and from 8.4% to 8% in the control group ($P = 0.001$ and 0.06, respectively). Changes of HbA1c were not different between the two groups ($P = 0.141$). The mean episodes of hypoglycemia were not different between the groups significantly ($P = 0.108$). **Conclusion:** In conclusion, this study revealed that mobile-based bolus advisors can reduce mean BG better in patients who are planned to have a tight glycemic control as a feasible and available method and may improve HbA1c in the long term.

Keywords: Bolus calculator; carbohydrate counting; intensive glycemic control; insulin therapy

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder and the risk of death in diabetic patients could be much more than that of healthy people in the same age group.[1] It is associated with several complications including vascular changes, which result in chronic renal failure, stroke, myocardial infarction, and retinopathy.[2] It is well-established that stringent glycemic control decreases microvascular and probably macrovascular complications in diabetic patients.[3] Treatment of patients to achieve stringent glycemic control needs various strategies including physical activity, nutritional therapy, and medication.[4] In this regard, intensive insulin therapy is effective but it is important that insulin dosage should be adjusted to balance physical activity and diet in order to maintain the blood glucose (BG) within normal limits.[5] On the other hand, adhering to a specific diet is often difficult for most patients because of personal preferences and habits, cultural food choices, and lifestyle schedules.[6]

Carbohydrates can affect postprandial BG regarding the amount (carbohydrate unit) and properties (glycemic index) in it. It means that for proper control of postprandial BG, the dose of short or rapid acting insulin should be adjusted based on the carbohydrate unit of the planned food.[7,8] So detecting carbohydrate intake and carbohydrate counting (carbo count) is a key principle and a mandatory step for obtaining stringent glucose control.[4,9] This method uses multiple daily injections (MDIs) of insulin adjusted based on

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carbohydrate intake and exercise, and resembles normal insulin secretion in the body.[10-12] So adequate nutrition with adjustments in insulin injections are combined in this method. Additionally, it allows more adherence and dietary management of patients because the patients have a greater variety of food consumption.[13] Carb count frequently is performed by the insulin-to-carbohydrate ratio (I:CHO) technique. This technique estimates the amount of carbohydrates in each meal by grams and then calculates the needed bolus insulin dose before the meal based on an insulin sensitivity measure.[13,14] In fact, in this method, what the patient wants to eat is defined, and how much insulin he/she should inject to cover what has been eaten. Although carbo count is a flexible strategy, there are some limitations including difficulties in understanding the strategy by patients, the need for intense education of patients about the nutritional facts of foods, specifically their carbohydrate content and the amount of time and effort, which is required for counting the carbohydrate content at each meal.[9,15,16]

To minimize the rate of counting mistakes and facilitating this technique for patients, the calculation of required insulin based on meals carbohydrate facts and premeal BG can be performed by automated programs. Recent studies on automated bolus calculator was conducted by calculator devices and resulted in favorable outcomes in glycemic control and treatment satisfaction.[12,17]

In this study, we used a bolus advisor mobile app, which can be used more easily and nearly in all of situations by patients. We investigated the effect of bolus calculation by mobile-based bolus calculator on glycemic control in adult patients.

MATERIALS AND METHODS

Study design and participants

This study is a nonrandomized, controlled clinical trial with two parallel arms including bolus advisor and usual treatment (estimating the premeal insulin doses and using correction boluses empirically), which was performed in 2013-2014. It has been registered in the Iranian Registry of Clinical Trials (number IRCT201502011181N2). The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the Isfahan University of Medical Sciences. All participants provided written informed consent.

The subjects were selected from diabetic patients who were referred to the endocrinology clinic of Noor (Khorshid) Hospital, Isfahan, Isfahan Province, Iran. The diagnosis of diabetes was made based on the American Diabetes Association's criteria for diagnosis of type 1 and type 2 diabetes mellitus.[18]

All subjects met the following inclusion criteria:

1. Age 18-65 years;
2. More than 1 year duration of type 1 or type 2 diabetes;
3. Treatment with MDI technique, using rapid- and long-acting insulin analogs;
4. Willing and able to comply with study procedures; and
5. Willing and able to provide written informed consent.

Unmet criteria were as follows:

1. Any serious medical condition that might interfere with safe study participation;
2. Current lactation, pregnancy, or inadequate contraception;
3. Gastroparesis or celiac disease;
4. Using of or former training in carb count;
5. Problems with using mobile programs.

A total of 83 individuals were screened. At the screening visit, after recording demographic data, the subjects underwent physical examination and blood urea nitrogen (BUN), creatinine (Cr), and urine pregnancy tests to ensure that the results did not preclude involvement in the study.

Finally, 62 eligible subjects were allocated to two groups by a simple method based on the above criteria (i.e., those who could not or were not interested to work with the software or whose mobile was not compatible with that were put in the control group). It was planned such that the case group would use our mobile-based bolus advisor and the control group would undergo treatment as usual with the MDI method. Six patients dropped out in the study process because of noncompliance [Figure 1].

Procedures and variables assessment

Before the intervention, the long-acting insulin dose was adjusted based on preprandial and postprandial BG assessments in a 1-week period. All of the participants received a 5-h group teaching, which was delivered by an educated physician. The educational topics were the basic knowledge of diabetes including different types of insulin, measuring and monitoring of BG, general food recommendations, appropriate methods of exercise, symptoms and treatment of hyper- and hypoglycemia, and principles of daily insulin dosage adjustment according to amount of meal and pre-prandial BG.

In the bolus advisor arm, patients also received additional education about the principles of carbo count (theory and practical exercises), working with mobile program, and estimating individual insulin sensitivity factors (ISFs) and

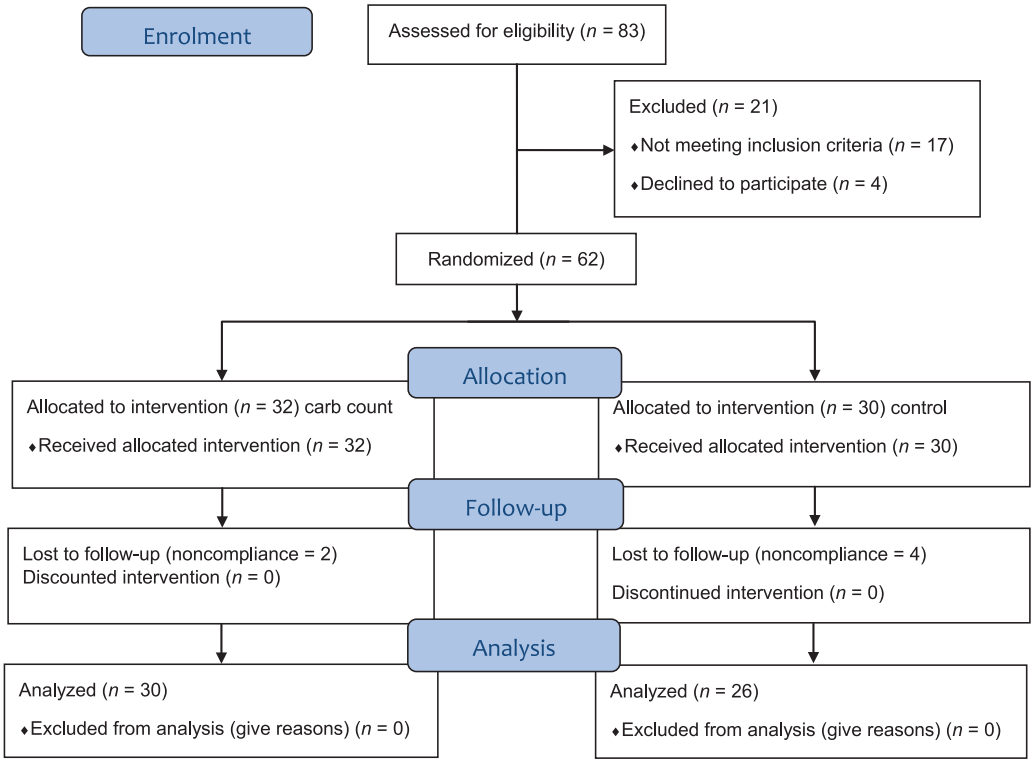

Figure 1: Consort statement

insulin-to-carbohydrate ratios (ICRs) using the rule of 1800 and 500, respectively.[19]

After the group's educational session, the study was performed in a 12-week period. Patients in the control arm used MDI technique as usual by estimating the premeal insulin doses and using correction boluses empirically. Control patients used insulin according to physician recommendations about meal dose and the dose also was adjusted if the meal size was different from the patient's average meal or the premeal BG was out of optimal range. The adjustment was done by reducing or adding two units of rapid acting insulin accordingly. In the bolus advisor arm too, patients used MDI technique but with aid of an application, which was installed on their mobile phone or tablet for measuring the needed insulin dose for each meal. The application was designed as a bolus calculator on the basis of current BG, target BG, insulin sensitivity factor (ISF), insulin to carbohydrate ratio (ICR), time of day, insulin on board, exercise level, and amount of ingested carbohydrates.

The patients were visited every 2 weeks for readjusting the dosage of long- and rapid-acting insulin according to a 3-day diabetes worksheet and estimating ISFs and ICRs.

All of participants were asked to check three BG tests per day during the study. The mean BG level and mean HbA1c were assessed before and just after the study.

Statistical analysis

The data were analyzed by chi-square test for qualitative and independent *t*-test for quantitative demographic and clinical differences between the two groups. We used paired sample *t*-test for evaluation of changes of variables during the study in each group. Mann-Whitney test was used for evaluation of side effect differences between the two groups. The data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) and a $P < 0.05$ was considered as statistically significant.

RESULTS

Baseline profile

Fifty-six patients, out of which 33 (58.9%) were male participants and 23 (41.1%) female participants completed the study. The mean [standard deviation (SD)] age was 36 (18.7) years, ranging 12-80 years. The mean (SD) of disease duration was 10.16 (2.55) years, ranging 6-17 years. The mean (SD) of BG was 225.64 (49.1) mg/dL and the mean (SD) of HbA1c was 8.38 (1.4)%.

The two groups were similar regarding sex ratio, educational level, body mass index, and diabetes duration but as expected, the age and diabetes type were significantly different between the groups. [Table 1].

As the control of BG and A1c was the main objective in this study and they were exactly the same in type 1 and 2 diabetic participants (A1c 8.38 versus 8.37, $P = 0.991$, mean glucose 225 versus 226, $P = 0.901$) at the baseline, we did not consider diabetes type as a confounding factor.

The mean (SD) of BG were 220.57 (43.7) and 231.5 (55) in the carb count and the control group, respectively, and the difference between the two groups was not significant ($P = 0.411$). Also, the mean (SD) of HbA1c was 8.39 (1.5) and 8.37 (1.33) in the carb count group and the control group, respectively; there was no significant difference between the two groups ($P = 0.965$).

Outcomes

After treatment, in the bolus advisor group, mean BG and HbA1c decreased significantly ($P = 0.001$ and $P = 0.001$, respectively). In the control group, the changes in mean scores was significant for BG ($P = 0.049$) but not significant for HbA1c ($P = 0.06$).

Between group analyses between the groups showed that the mean BG after treatment and the differences between in BG before and after treatment were significantly different between the two groups ($P = 0.003$ and $P = 0.039$, respectively). The mean HbA1c after treatment and the differences in HbA1c between before and after treatment were not significantly different between the two groups ($P = 0.137$ and $P = 0.141$, respectively) [Table 2].

Tolerability and side effects

The mean episodes of hypoglycemia were 2.13 (1.3) and 1.62 (1) in the bolus advisor group and control group, respectively. There was no significant difference between the two groups in episodes of hypoglycemia during the treatment period (Mann-Whitney test, $P = 0.854$).

Table 1: Demographics and baseline characteristics of the subjects ($n = 56$)

Characteristics	Carb count ($n = 30$)	Control ($n = 26$)	*P*
Age (years)	25.3 (9.6)	48.2 (19.4)	<0.0001
Sex, number (%)			
Male	18 (60)	15 (57.7)	0.538
Female	12 (40)	11 (42.3)	
Diabetes type, number (%)			
Type 1	29 (96.7)	8 (57.7)	<0.0001
Type 2	1 (3.3)	18 (42.3)	
Diabetes duration (years)	9.73 (2.3)	10.65 (2.7)	0.181
Educational level (years)	9.87 (3.2)	10.96 (3.6)	0.234
BMI† (kg/m^2)	22.8 (2.5)	24.1 (2.9)	0.083
Mean blood glucose (mg/dL)	220.6 (43.7)	231.5 (55)	0.411
Mean HbA1c, (%)	8.39 (1.5)	8.37 (1.33)	0.965

All variables are mean (SD) unless otherwise indicated, *P* = *P* value is extracted from independent samples *t*-test, chi-square test; †MBI = Body mass index

Table 2: Changes of mean blood glucose and mean HbA1c between the two groups after treatment

Characteristics	Carb count ($n = 30$)	Control ($n = 26$)	*P***
Mean blood glucose, (mg/dL)			
Before	220.6 (43.7)	231.5 (55)	0.411
After	182.7 (34.8)	214.5 (42.2)	0.003
Change	-37.9 (32.1)	-17 (41.8)	0.039
*P**	0.001	0.049	
$p^{£}$			0.079
Mean HbA1c			
Before	8.39 (1.5)	8.37 (1.33)	0.965
After	7.6 (0.87)	8 (1.1)	0.137
Change	-0.78 (1.1)	-0.36 (0.95)	0.141
*P**	0.001	0.06	
$p^{£}$			0.51

*Within group significance, *P* = *P* value is extracted from paired sample *t*-test; **Between group significance, *P* = *P* value is extracted from ANOVA; £*P* value after controlling for age as a confounding factor; All variables are mean (SD)

DISCUSSION

Our controlled study showed that the use of bolus advisor by the mobile bolus calculator leads to better control of BG compared with usual MDI treatment. Both groups improved in glycemic control after treatment but the improvement in BG was more prominent in the bolus advisor group.

This results shows that flexible intensive insulin therapy with MDI, either as usual or with bolus advisor software, is an effective method for controlling BG. This is consistent with previous studies, which showed that MDI has similar effects to that of continuous subcutaneous insulin infusion on glycemic control in type 1 and type 2 diabetes mellitus.[20,21] In our study, HbA1c was not significantly different before and after treatment in the control group.

On the other hand, several studies had revealed that monitoring of total ingested carbohydrates by counting of food nutritional facts helps to estimate the dose of rapid acting insulin appropriately. They concluded that carbo count leads to stricter glycemic control.[10,11,22]

Bolus calculation is usually performed manually, which needs considerable time and effort by patients and intense education of them about the nutritional facts of foods.[15,16] So recent studies has used automatic bolus calculators for measuring of rapid acting insulin doses. Schmidt *et al.*, used a bolus calculator device to compare glycemic control in three parallel groups including treatment with MDI as usual, treatment with manual carbo count, and treatment with carbo count and bolus calculation by automated device. They measured the HbA1c differences between the groups and concluded that there was no significant difference between different treatment methods.[12] Our

results with the mobile-based bolus calculator also showed that the difference in HbA1c was not significant but mean BG difference was significant between the two groups. The nonsignificance of HbA1c could be because of the relatively small duration of our study (12 weeks) as well as the study of Schmidt *et al*. (16 weeks). Rabbone *et al*., in an 18-month study on children, revealed that the use of an automated bolus calculator compared with MDI treatment without bolus calculator improves HbA1c significantly after 18 months of treatment but not 6 months.[17] Błazik *et al*., also showed that in a 3-month study, patients who used a bolus calculator had more improvement in 2-h postprandial BG.[23]

The mean episodes of hypoglycemia were not significantly different between the two groups in our study as well as in the study of Błazik *et al*.[23] So this method can be used safely by the patients.

Previous studies used an automated device for bolus calculation, which might not be available in any clinical setting and the patients need to pay for that. But we prepared a mobile-based application which is free, easy to use, and available everywhere because of the widespread use of smartphones in the world. This has been the first mobile-based bolus calculator according to our research.

Considering that strict glycemic control, especially in HbA1c would lead to fewer microvascular and macrovascular complications in diabetes mellitus,[3] long-term use of the bolus calculator method by an available application can improve the well-being and quality of life of diabetic patients.

Limitations

Our study had some limitations. First, it was limited by the relatively short time of follow-up (12 weeks). Second, the control and case groups were not matched in age and type of diabetes.

CONCLUSION

In conclusion, this study revealed that mobile-based bolus advisors can reduce better the mean BG in patients who are planned to have tight glycemic control as a feasible and available method and may improve HbA1c in the long term A larger, long-term study is suggested to evaluate the long-term effects of this method on HbA1c and treatment adherence of patients.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

MS contributed to the conception and design of the work, conduct the study, software design, data analysis, revision of the draft, approval of the final version of the manuscript, and agreed with all aspects of the work. MT contributed to the conception of the work, data acquisition, draft of the work, approval of the final version of the manuscript, and agreed with all aspects of the work. MA contributed to the conception of the work, draft of the work, approval of the final version of the manuscript, and agreed with all aspects of the work.

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