



# Comparison of two insulin injection methods on control of type 2 diabetes; is the new protocol effective or not?

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## Abstract

**Introduction:** Type 2 diabetes is a progressive disease with a significant risk for developing late complications.

**Objectives:** This study aimed to determine if the proportion of NPH to regular in day of discharge is similar to first day of admission or not. In other words, we aimed to compare two insulin injection methods on the control of type 2 diabetes.

**Patients and Methods:** This cross-sectional study was performed on hospital records of type II diabetic patients admitted for insulin therapy with the conventional protocol from 2008-2013. Treatment was initiated with the following proportions; morning NPH: 44%, morning regular dosage: 22%, evening NPH dosage: 17% and evening regular dosage: 17%. Insulin doses of the discharge day in which optimal glycemic control has been achieved were recorded and based on their mean, a protocol was made. Finally, two groups were categorized. Group 1 consisted of patients whose discharge insulin dose was in the range of the mean data of the study ( $\pm 2$  IU/mL) and patients whose discharge insulin dose was in accordance with the conventional protocol ( $\pm 2$  IU/mL) participated in group 2.

**Results:** At discharge day, the mean morning NPH dose was  $34.2 \pm 6.69$ , morning regular:  $23.8 \pm 6.36$ , evening NPH:  $21.26 \pm 6.75$  and evening regular:  $20.74 \pm 5.51$ . The discharge insulin ratios of the conventional protocol were similar to that of the admission ratios in only 17.7% of the patients. Only 34.5% of the patients could include in the new protocol and 50% of them did not fit any protocol.

**Conclusion:** It is suggested to inject one-third of the total daily insulin need as NPH in the morning and divide the remained two-thirds between morning regular, evening NPH and evening regular equally. This may decrease the length of hospital stay and decrease the time to reach the desired glycemic control.

**Keywords:** Type 2 diabetes; Regular insulin; Conventional protocol.

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## Introduction

Diabetes mellitus is a chronic disease and a major global problem, with a global prevalence in adults in 2017 being 8.8% of the world population, with the anticipation of a further increase to 9.9% by 2045 which can cause serious complications (1). Treatment and management of type 2 diabetes is a major challenge (2). Prescribing patterns for diabetic patients show wide variability in different parts of the world (3). Diabetic patients whose blood glucose cannot be controlled with oral medications are treated with insulin. Intensive and conventional insulin therapy are the major insulin regimens used for glycemic control (4).

Insulin dose adjustment should be based on body weight (5). Conventional insulin therapy (1/3-2/3) is one of the most common protocols in which the total daily insulin need of the patient is calculated based on body weight (0.3-0.5 mg/kg). Two-thirds of insulin is injected in the morning, before breakfast (2/3 NPH [neutral protamine Hagedorn] and 1/3 regular) and the remaining portion of the total daily dose is administered in the evening before

dinner ( $\frac{1}{2}$  NPH and  $\frac{1}{2}$  regular), approximately 65-70% of the total dose of insulin is NPH and 30-35% is regular (6). Four daily glucose measurements are used to achieve the glycemic goals obtained by the proposed protocol; pre-breakfast and 2 hours after the first bite of the food at each meal. NPH and the regular ratio are modified to reach glycemic glucose (if FBS is high, evening NPH increases and if 2-hour postprandial (2hpp) is high, mornings regular is increased) (7).

Given the lifelong diabetes course, treatment strategies should take a number of aspects into consideration including medication efficacy, patient satisfaction, and costs of the therapy (8). Health care professionals and policy-makers must assess the increasing burden of diabetes and design appropriate preventive and management strategies (9). For better glycemic control, the usual dose of morning and evening regular are modified. Our experience with admitted patients in hospitals raised the question that: do patients need different doses of the conventional protocol to reach target blood glucose? So, in this study we aimed to know if we achieve glycemic goals

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### ■ Implication for health policy/practice/research/medical education

Diabetes mellitus is a chronic disease and a major global problem. Insulin dose adjustment should be based on body weight. Injecting one-third of the total daily insulin need as NPH in the morning and dividing the remained two-thirds between morning regular, evening NPH and regular equally may decrease the length of hospital stay and decrease the time to reach the desired glycemic control.

(discharge fasting blood sugar [FBS] <150 mg/dL and BS <200 mg/dL) with a new NPH to regular ratio or not.

### Objectives

In this study, we aimed to determine if the proportion of NPH to regular in day of discharge is similar to first day of admission or not. In other words, we aimed to compare two insulin injection methods on the control of type 2 diabetes so that if we need to increase regular dosage for better glycemic control, we adjust the regular insulin with a higher dose from the beginning.

### Patients and Methods

#### Study population and setting

This cross-sectional study was performed on hospital records of type II diabetic patients admitted to Shahid Beheshti and Rohani hospitals of Babol for insulin therapy with the conventional protocol from 2008-2013. The daily need of the patients was calculated according to their weight and two-thirds was injected before breakfast and one-third before dinner. The following insulin protocol was considered: breakfast: 2/3 of NPH and 1/3 of regular; dinner: 1/2 of NPH and 1/2 of regular (6). The person who gathered the data and the analyzer were unaware of the study goals.

Patients with type II diabetes needing insulin therapy who were not pregnant and didn't have renal failure or diabetic foot and their discharge FBS was <150 mg/dL and 2hpp was <200 mg/dL were included in this study. Complications which prolonged the hospital stay duration (myocardial infarction or infection), or more than two insulin injections and those who received oral diabetes medications and renal failure were excluded from the study. Renal failure was defined as creatinine >1 mg/dL in patients older than 60 years and creatinine >1.2 mg/dL in patients younger than 60 years. After evaluating the medical records of 600 diabetic patients for 5 years, finally, 220 patients were eligible to participate in the study.

In all patients, treatment was initiated with the following proportions: Morning NPH: 44%; morning regular: 22%; evening NPH: 17%; and evening regular: 17%. These proportions were in accordance with the conventional protocol's recommendations.

All patients were treated with the conventional protocol

and the insulin dose of the last admission day in which optimal glycemic control has been achieved was recorded. We didn't aim to evaluate the total insulin dose but aimed to study the ratio of NPH insulin and regular insulin and also the ratio of breakfast and dinner insulin. Other variables included age, gender, and duration of diabetes and also hospital stay.

Morning and evening NPH insulin and morning and evening regular insulin doses were calculated separately as a total daily dose and their percentages were obtained. In all 220 patients, optimal glycemic control has been achieved.

The average dose of all four insulin boluses was extracted and based on these means, a protocol was made. Finally, two groups were categorized. Group 1 consisted of patients whose discharge insulin dose was in the range of the mean data of the study ( $\pm 2$  IU/mL) were called "in accordance with the mean" and patients whose discharge insulin dose was in accordance with the conventional protocol ( $\pm 2$  IU/mL) were placed in group 2. The number " $\pm 2$ " was determined based on clinical justification which believes that a 1-2 unit change in insulin dose doesn't have a clinical impact on patients but  $\pm 6$  unit change has many clinical impacts. Therefore, all insulin doses were calculated with  $\pm 2$  and finally, both groups were compared.

If the patient had at least two insulins (of four) in accordance with the protocol, it was defined as "in accordance with the protocol". Finally, the conventional protocol patients were compared with the new protocol (based on the mean) ones. Additionally, the patients were divided into two groups of early and late control (before and after 4 days).

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. Accordingly, written informed consent was obtained from all participants before any intervention. Ethical approval was obtained from the Ethics Committee of Babol University of Medical Sciences (#8930329) and patients' information remained confidential. This study was extracted from MD thesis of Hojatollah Ghorbani at this university (Thesis #2028).

### Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) using t-test or ANOVA for continuous variables, and a chi-squared test for binary/categorical variables and proportions.

### Results

In this study, 220 patients were evaluated which 53 (24.1%) with the mean age of  $54.91 \pm 13.95$  years were male and 167 (76.9%) ones with the mean age of  $55.34 \pm 11.77$  years were female. One hundred and seven (48.6%) were admitted to Rohani hospital and 113 (51.4%) patients were admitted

to Shahid Beheshti hospital. The mean insulin doses were as follows: Morning NPH:  $34.2\% \pm 6.69$ ; morning regular:  $23.8 \pm 6.36$ ; evening NPH:  $21.26 \pm 6.75$ ; evening regular:  $20.74 \pm 5.51$ .

Eighteen (8.2%) patients had morning NPH between 42-46% while 65 ones (29.5%) had regular insulin between 20-24%. Fifty-two (23.6%) patients had evening NPH between 15-19% and evening regular 15-17% was observed in 51(23.2%) cases. Morning NPH between 32-36% was seen in 57 ones (25.9%) and 64 ones (29.2%) had morning regular insulin dose between 21-25%. Evening NPH and regular insulin between 19-23% were observed in 56 (25.5%) and 72 cases (32.7%), respectively.

Table 1 shows the percentages of insulin separately. Conformity has been defined if two of four insulins were in accordance with one protocol, the patient was assigned to participate in the non-conforming group.

Of 220 patients who started insulin therapy, only 39 patients (17.7%) had at least two insulin doses conforming to the conventional protocol and 76 ones (34.5%) had at least two insulin doses conforming to the mean protocol at discharge day (Table 2) and their difference was not statistically significant ( $P=0.006$ ).

The mean age of the patients in both groups was not statistically different ( $P=0.08$ ). Diabetes duration in conventional and the mean group were  $11.44 \pm 7.44$  and  $9.32 \pm 6.75$  years, respectively ( $P=0.051$ ). The duration of hospitalization was between 2-13 days ( $5.25 \pm 1.7$  days) and 79 patients (36.1%) needed less than 4 days (early control group) while 140 patients (63.9%) needed more than 4 days to control their blood glucose (late control group). Age and diabetes duration were not significantly different in these two groups ( $P=0.89$  and  $P=0.94$ , respectively). Also, they were not associated with both protocols.

### Discussion

Diabetes mellitus is emerging as a major health problem, with rising prevalence and complications (10). The economic burden of diabetes is enormous and it is a

costly disease due to its chronic nature, the severity of its complications, and the therapeutic approaches to control them (9). Consequently, patients need hospital inpatient care to initiate insulin therapy and finding a way to decrease its duration is economically important. In this study, we aimed to determine if the discharge NPH and regular doses in which optimal glycemic control can be achieved, are similar to those at the initiation of protocol or not. We found that the required dose of regular is higher than the conventional protocol's prediction (44% versus 39%). In addition, the need to evening insulin increased in comparison with the conventional protocol (42% vs. 34%) which might be due to the difference in our diet and our physiological differences with the western community. Previous studies showed that higher slow-acting insulin-containing regimens control the patients better (11-13). The difference in insulin percentage between the two groups was a 10% reduction in morning NPH which was added to evening insulin. It may be due to the low-calorie breakfast and high-calorie dinner of the patients.

We found that the initiation of insulin therapy with the conventional method causes 17.7% control of the patients and 82% of the patients are controlled with different proportions of this protocol. These findings raised the question that can we define an insulin therapy protocol for type II diabetic patients based on the data mean? Based on the results, the insulin ratio of 34.5% of the patients who had glycemic control was within a range. This protocol can be used as a guideline for insulin therapy initiation and the physiological difference of the patients will change these ratios based on their blood glucose level. So, we made a new protocol. Maybe other studies confirm the impact of this protocol on faster glycemic control and reduce the hospitalization duration. It is recommended in conventional therapy to inject one-third of the patient's insulin requirement in the morning as NPH and divide the remained two-third between morning regular and evening NPH and regular (6).

Our study showed that adherence to a certain protocol

Table 1. Frequency of the patients based on conventional protocol and the means

Protocol Insulin	Conventional	The mean	Kappa	P value
Morning NPH	18 (8.2%)	57 (26%)	0.14	0.009
Morning regular	65 (29.5%)	64 (29.2%)	0.01	0.58
Evening NPH	52 (23.6%)	56 (25.5%)	0.32	0.001
Evening regular	51 (23.2%)	72 (32.7%)	0.37	0.001

Table 2. Comparison of total conform with two protocols

Conventional protocol	Data mean		
	Non-conforming	Conforming	Total
Non-conforming	111 (61.3%)	70 (38.4%)	181 (82.3%)
Conforming	33 (84.6%)	6 (15.4%)	39 (17.7%)
Total	144 (65.5%)	76 (34.5%)	220 (100%)

and also hospitalization period are not related to age, gender and diabetes duration ( $P > 0.05$ ). Comino et al reported that the association between male gender and the risk of hospitalization was enhanced in people with diabetes (14). In Schneider and colleagues' study, diabetes duration was moderately associated with the risk of hospitalization, but this result was not significant ( $P = 0.102$ ) (15).

We observed that the insulin ratio of the conventional protocol was unchanged in only 17.7% of the patients and these ratios were not found in 82.3% of them. Only 34.5% of the patients could include in the new protocol (about two-fold of the conventional protocol) and 50% of the patients' ratio didn't fit any protocol. It can be justified by the physiological difference of the patients (12,16). It confirms various protocols in different people and our study predicted the probability of these various protocols' existence.

Not only a greater proportion of participants with diabetes admitted were younger than those without diabetes, but also the association between age and hospital admission was attenuated for participants with diabetes. This suggests that diabetes may have an "aging effect" that leads to poorer health outcomes at an earlier age for diabetics compared to those without diabetes. Once adjusted for age and gender, the patterns of socioeconomic factors influencing the relative rate of hospitalization were broadly similar (14).

A frequent complication following glycemic control in diabetics is hypoglycemia which is defined as a blood glucose level  $< 70$  mg/dL (17). In the case of better hyperglycemic control, it is a predictable complication (18) and this protocol may increase the number of patients experiencing hypoglycemia. But using this protocol at beginning of treatment can reduce the time to achieve glycemic goals and hospitalization duration. It is suggested to evaluate this protocol for insulin therapy initiation at home (due to the difference of home regimen with the hospital).

In diabetic patients who were hospitalized for insulin therapy, insulin starts with a dose of two-third in the morning and one-third in the evening and increases based on patient's glucose level. As shown in this study, this ratio is often disturbed when discharging and only 17% of the patients discharged with the initial insulin ratio.

Our study hypothesizes that if the pre-mix insulin dose, which usually starts with 70/30 pre-mix (2/3 in the morning and 1/3 in the evening), starts with 75/25 in the morning and 50/50 pre-mix at night, patients will probably have better glycemic control. RCT studies are required to prove this theory. The insulin proportion that we suggested in this study was 1/2 morning NPH, 1/3 other insulins with equal proportion and 1/3 evening NPH, and morning and evening regular because it is more consistent with the patient's final insulin (43%).

## Conclusion

The discharge insulin ratios of the conventional protocol were similar to that of the admission ratios in only 17.7% of the patients. It is suggested to inject one-third of the total daily insulin need of the patients as NPH in the morning and divide the remained two-third between morning regular, evening NPH and evening regular equally. This may decrease the length of hospital stay and decrease the time to reach the desired glycemia. We also found that 50% of the patients' ratio didn't fit any protocol that shows the physiological difference of the patients and can justify the existence of different protocols for patients.

## Limitations of the study

Limitations of this study must be stated. First, BMI and weight of the patients were not recorded and we were not able to calculate GFR. Second, the patients did not follow any diet. Although most of the patients ate hospital foods, some of them consumed other foods which might confound the study results. Another confounding factor may be the difference in patients' physical activity during the hospitalization period. A sedentary lifestyle is a powerful but modifiable risk factor for diabetes; therefore, moderate exercise is of the utmost benefit in patients with diabetes (19).

## Authors' contribution

MAB: concept, design, manuscript preparation and final revision; HG: performing experiments, data collection and writing proposal; RA: data collection, statistical analysis, provision of the first draft, manuscript editing.

## Conflicts of interest

The authors stated that they have no conflict of interest.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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