



Insulin Management of Patients with Inadequately Controlled Type 2 Diabetes Admitted to Hospital: Titration Patterns and Frequency of Hypoglycemia as Results of a Prospective Observational Study (Hospital Study)

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ABSTRACT

Introduction: Despite the continuously growing number of therapeutic options for type 2 diabetes mellitus (T2DM) including insulins, a large percentage of patients fail to achieve HbA1c targets. Several real-world studies focused on patients with T2DM receiving insulin treatment in outpatient settings were conducted, but information about real-world in-hospital insulin management is lacking. The aim of this study was to describe the management of insulin therapy with a focus on basal-bolus and premixed insulin regimens in

patients with T2DM under routine in-hospital medical practice in the Czech Republic.

Methods: This non-interventional prospective study was conducted from June 2014 to December 2017 in 22 centers in the Czech Republic under routine clinical practice conditions. Adult patients admitted to hospital with metabolically uncontrolled T2DM [HbA1c \geq 60 mmol/mol; $>$ 7.6% Diabetes Control and Complications Trial (DCCT)] and there treated with basal-bolus and premixed insulin regimens were documented during hospitalization.

Results: Overall, 369 patients with T2DM (54.7% male, mean age 64.44 ± 13.84 years, BMI 31.10 ± 6.00 kg/m², duration of diabetes 8.11 ± 9.93 years, HbA1c 95.90 ± 24.38 mmol/mol, length of stay was 7.94 ± 4.53 days) were included. The percentage of glucose values under 10 mmol/l at time of randomization (the group with basal-bolus insulin regimen vs. the premix insulin regimen group) was 24.2% vs. 33.5% ($p = 0.053$), at time of first insulin dose adjustment it was 43.1% vs. 50.0% ($p = 0.330$), and 1 day before hospital discharge it was 61.7% vs. 61.4% ($p = 0.107$). A hypoglycemic event occurred in a total of 15 patients in the basal-bolus regimen group, and no hypoglycemic event occurred in the premixed insulin regimen group.

Conclusion: In-hospital insulin management regarding basal-bolus and premixed insulin

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regimens is safe and in concordance with current international recommendations.

Keywords: Basal-bolus regimen; HbA1c; Hospital insulin management; Hypoglycemia; Insulin titration; Premixed insulin regimen; Type 2 diabetes

Key Summary Points

The mean HbA1c level at admission was 95.90 ± 24.38 mmol/mol.

The percentage of glucose values under 10 mmol/l at time of randomization (the group with basal-bolus insulin regimen vs. the premix insulin regimen group) was 24.2% vs. 33.5%.

The percentage of glucose values under 10 mmol/l at 1 day before hospital discharge was 61.7% vs. 61.4%.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14573328>.

INTRODUCTION

Despite the new types of antidiabetic drugs, many patients with type 2 diabetes mellitus (T2DM) do not achieve the recommended HbA1c levels [< 53 mmol/mol; 7% Diabetes Control and Complications Trial (DCCT)] [1, 2] even with insulin therapy. A Czech cross-sectional study focused on patients with T2DM regardless of the type of treatment they were receiving showed that 34.2% reached $A1c < 7%$ [53 mmol/mol] [3]. A further Czech-Slovak cross-sectional observational study focused on insulin treatment found the portion of patients

with well-controlled T2DM ($A1c < 7%$ [53 mmol/mol]) to be 33.4% [4].

Several real-world studies focused on patients with T2DM receiving insulin treatment in outpatient settings were conducted [5], but information about real-world in-hospital insulin management is lacking.

This study was conducted with the aim of describing the management of insulin therapy with a focus on basal-bolus and premixed insulin regimens in patients with T2DM under routine in-hospital medical practice in the Czech Republic.

METHODS

Study Design

This is a non-interventional prospective study describing habits associated with certain types of insulin therapy in patients with T2DM admitted to hospital because of insufficiently controlled diabetes in the Czech Republic. The study was conducted from June 2014 to December 2017 and enrolled patients from 22 study centers in the Czech Republic across all regions in the Czech Republic to ensure the highest possible representativeness of the sample. Patients were enrolled onto the study consecutively, with the maximum number of patients per center set at 15, minimum 5.

Study Population

The inclusion criteria were T2DM, patient age of over 18 years with insufficient control of diabetes ($HbA1c \geq 60$ mmol/mol; $> 7.6%$ DCCT), who were admitted to the hospital in noncritical conditions and there treated with basal-bolus or premixed insulin regimen therapy which was continued after discharge from hospital. These two types of insulin regimen determined the two study groups.

The exclusion criteria were types of diabetes other than T2DM, hyperglycemia without a previous diagnosis of diabetes, acute hyperglycemic emergencies, or severe hyperglycemia treated with intravenous insulin infusion on

hospital admission, corticosteroid therapy, and pregnancy, and patients expected to require intensive care unit (ICU) or a hospital stay of shorter than 3 days. In addition, we excluded patients who received parenteral nutrition during the hospitalization.

Insulins Involved in the Study

None of the insulins available in the Czech Republic during the study period were excluded. The basal insulins included an intermediate-acting insulin (neutral protamine Hagedorn, NPH) and long-acting insulin analogues (glargine 100 U/ml, detemir, and in the Slovak Republic also degludec). The short-acting insulin was recombinant human insulin, and fast-acting insulins included insulin analogues (aspart, glulisin, and lispro). Premixed insulin preparations were the proportionate mixtures of a short- or fast-acting insulin and intermediate-acting insulins (in proportions of 25/75, 30/70 and 50/50) produced commercially by Eli Lilly, Novo Nordisk, or Sanofi.

Outcomes

The primary objective of the study was to determine the proportion of patients with basal-bolus and premix insulin regimen used in hospitals and the level of glycemia reached at time of discharge.

The secondary objectives were to determine the efficacy of insulin titration (mean change of plasma glucose level) and its comparison between these two insulin regimens, as well as the proportion of patients experiencing hypoglycemic events during hospitalization.

Data Collection

Data were collected at the inclusion visit (visit 1, day after the admission) and at routine follow-up visits, visit 2 (day of the first insulin dose change) and visit 3 (day before hospital discharge), respectively. Study diabetologists documented data about each patient on a case report form (CRF). During the first visit (V1), insulin therapy was initiated or adjusted, basic

anamnesic data was recorded, and physical examination and blood sampling were performed to analyze basic patient parameters including HbA1c.

During the second visit (V2), the dose of insulin currently used by the patient was recorded and, if necessary, adjusted according to the glycemia records. The third visit (V3) followed the same procedure as V2.

Glucose Monitoring

Glucose monitoring was performed by health staff according to the routine practice of the clinic. Various glucometers were used according to the local customs but all glucometers met the ISO 15197:2013 standards.

Statistical Methods

Statistical methods commonly used for analysis of epidemiological data were used. All collected information was summarized by descriptive statistics (mean \pm standard deviation/relative frequency). The differences between regimens were tested by the Mann–Whitney–Wilcoxon test in the case of continuous variables and by the Fisher's exact test for discrete variables.

The trend of glycemic profile between 3 days of hospitalization was evaluated with the use of the mixed-effects model based on the method of maximum likelihood estimation. The different days represent the fixed effect, and the particular patient signifies the random effect. The *p* value displayed in the last column comes from the likelihood ratio test.

Study Interventions

The study was non-interventional.

Compliance with Ethics Guidelines

Ethics committee approval was not required for the study as the study was based on collection of anonymous unidentifiable data and did not qualify as a clinical trial of a medicinal product. Under local Czech legislation [6], an ethics committee approval is required only for clinical

trials of medicinal products. For other types of biomedical research, ethics committee approval is optional. The study was conducted in accordance with the Declaration of Helsinki and informed consent to participate was obtained from all study participants.

RESULTS

Study Sample

A total of 389 patients with T2DM were enrolled onto the study, the final eligible population consisting of 369 patients (54.7% male). The mean age was 64.44 ± 13.84 years, with a mean duration of diabetes 8.11 ± 9.93 years. The mean length of stay was 7.94 ± 4.53 days. An overview of patient group characteristics is shown in Table 1.

The most common reason for admission was insufficient metabolic control of diabetes which was declared in 81.8% of all patients. Hypoglycemia was a reason for admission in 2.4% of all the study subjects; the reasons for admission of the rest of the patients are unknown.

At admission, 147 of the patients were treated with basal-bolus insulin regimen, 33 patients with premixed insulin regimen (two insulin shots per day), and the remaining 189 were treated with oral antidiabetic drugs.

During hospitalization 331 patients were treated with basal-bolus insulin regimen, and 38 patients were treated with premix insulin regimen.

Bedside Blood Glucose Monitoring

The mean daily number of glucose measurements (before breakfast, lunch, dinner and at bedtime) was 3.8 (with additional mean of 0.6 daily measurements 2 h after breakfast) in the group with basal-bolus insulin regimen and 3.9 (with additional daily mean of 0.4 measurements 2 h after breakfast) in the group with premixed insulin regimen. Only a small number of measurements were performed in post-lunch, post-dinner periods and during nights; these

were not entered into the analysis. The precise distribution of the glucose measurements is shown in Fig. 1.

Glycemic Control

The mean HbA1c among the whole study group was 95.9 ± 24.38 mmol/mol, 96.1 ± 24.58 mmol/mol in the group with basal-bolus insulin regimen, and 94.16 ± 23.44 mmol/mol in the premix insulin regimen group. Glycemia at admission in the whole group was 17.35 ± 8.50 mmol/l, 17.45 ± 8.53 in the group with basal-bolus insulin regimen, and 16.52 ± 8.24 mmol/l in the premix insulin regimen group (Table 1).

Fasting glycemia at V1 in the group with basal-bolus insulin regimen was 12.19 mmol/l and 11.05 mmol/l in the premix insulin regimen group. The analysis of the glycemic difference during insulin titration in V1–3 is shown in Table 2.

The daily average glycemia (SD) at V1 (the group with basal-bolus insulin regimen vs. the premix insulin regimen group) was 13.05 (2.87) vs. 12.18 (3.23) mmol/l ($p = 0.058$); at V2 it was 11.06 (2.37) vs. 10.73 (2.81) mmol/l ($p = 0.171$); and at V3, it was 9.59 (2.13) vs. 9.64 (1.88) mmol/l ($p = 0.695$) (Table 3). The percentage of measurements with glycemia under 10 mmol/l did not differ significantly at any visit (Table 3).

Average Insulin Doses and Weight Change During the Study

The mean daily insulin dose at V1 and V3 (V1/V3) was $0.50 \pm 0.20/0.64 \pm 0.25$ U/kg in the basal-bolus insulin regimen group, and $0.24 \pm 0.15/0.44 \pm 0.18$ U/kg in the premix insulin regimen group.

Incidence of Hypoglycemia During the Study

The frequency of hypoglycemia [number of events/number of measurements (%)] was

Table 1 Patient characteristics at V1

Type of diabetes	Basal-bolus regimen	Premix regimen	All patients	<i>p</i> value
<i>N</i>	331	38	369	
Sex				0.009
Male	189 (57.1%)	13 (34.2)	202 (54.7%)	
Female	142 (42.9%)	25 (65.8%)	167 (45.3%)	
Demography and physical measurements				
Age (years)	62.74 (13.26)	79.32 (9.17)	64.44 (13.84)	< 0.001
Weight (kg)	91.00 (18.76)	80.42 (20.77)	89.92 (19.21)	< 0.001
BMI (kg/m ²)	31.27 (5.90)	29.54 (6.77)	31.10 (6.00)	0.038
Systolic BP (mmHg)	139.31 (20.17)	139.00 (23.29)	139.28 (20.48)	0.413
Diastolic BP (mmHg)	82.22 (10.86)	81.54 (11.57)	82.15 (10.92)	0.809
Diabetic medical history				
Duration of DM (years)	7.62 (9.65)	12.45 (11.33)	8.11 (9.93)	0.003
Laboratory variables				
HbA1c (mmol/mol)	96.10 (24.58)	94.16 (23.44)	95.9 (24.38)	0.441
Glycemia at admission (mmol/l)	17.45 (8.53)	16.52 (8.24)	17.35 (8.50)	0.435
Therapy (percentage of patients)				
Long-acting insulin analogues	96.1			
Insulin NPH	3.9			
Short-acting insulin analogues	95.5			
Short-acting human insulin	4.5			
Premixed insulin analogues		68.4		
Premixed human insulins		31.6		
Insulin dose (U/kg/day)				
Visit 1	0.50 ± 0.20	0.24 ± 0.15		< 0.001
Visit 3	0.64 ± 0.25	0.44 ± 0.18		< 0.001
Length of stay (days)	7.75 ± 4.51	9.51 ± 4.45	7.94 ± 4.53	< 0.001

18/4198 (0.4%) in the basal-bolus regimen group (all of them occurred in a total of 15 patients). Among all cases, 8/977 (0.8%) were found before breakfast, 0/586 (0%) 2 h after breakfast, 1/975 (0.1%) before lunch, 6/959 (0.6%) before dinner, and 3/901 (0.3%) at bedtime. No hypoglycemic event was classified as serious. No hypoglycemic event out of 491

measurements occurred in the premixed insulin regimen group.

DISCUSSION

This is the first observational real-life study comparing the efficacy and safety of a basal-

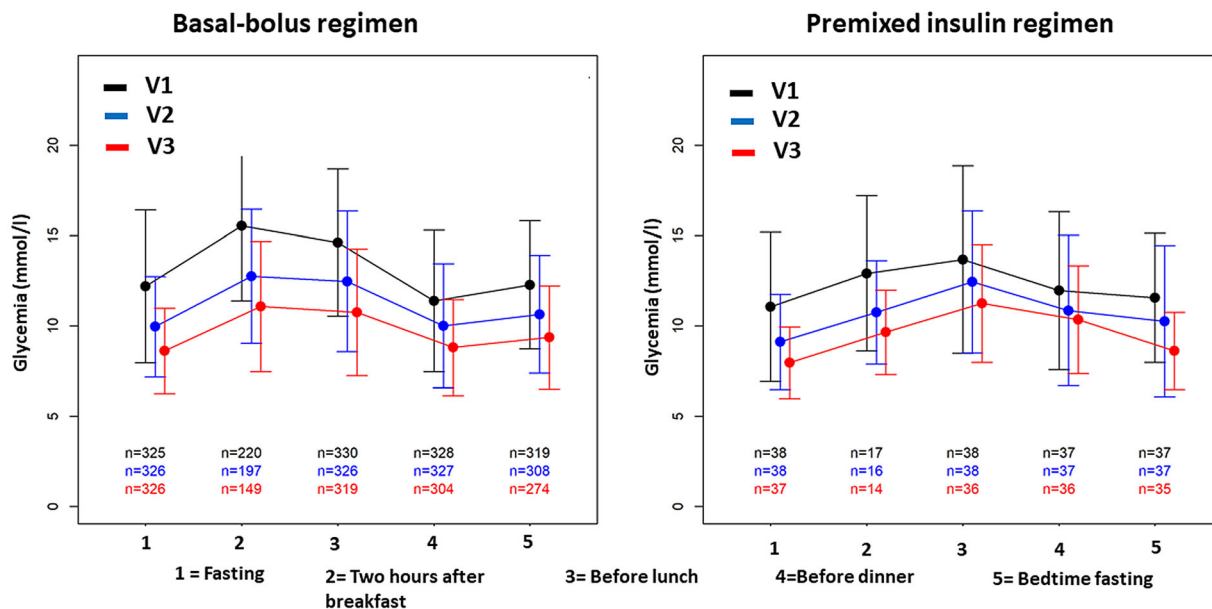


Fig. 1 Mean glycemia levels at different time points (visits 1–3)

bolus insulin regimen with a premixed human insulin regimen in hospitalized patients with type 2 diabetes. Both treatment regimens resulted in a significant improvement in the mean daily blood glucose concentration and in the percentage of glucose readings within the target range of 80 and 180 mg/dl before meals; the mean daily glycemia did not differ between both regimen groups.

The aim of the study was to determine the manner in which insulin therapy was conducted among metabolically uncontrolled patients with T2DM admitted to a hospital in noncritical condition. The majority of patients were referred to a hospital by their diabetologists for insulin initiation or insulin therapy adjustment. At the time of hospital discharge, the majority of patients were treated with basal-bolus insulin regimen and the rest of them with premixed insulin regimen. The most prevalent choice of insulin regimen is concordant with the current recommendation for in-hospital insulin treatment of patients with uncontrolled T2DM under noncritical conditions [7]. Although the premixed insulin regimen is not recommended for in-hospital settings as it was found to be linked to frequent hypoglycemic episodes [8], up to 10% of patients were treated

with this type of insulin management. The majority of them had been treated with a premixed regimen during their pre-hospital period, but 12 patients started with this type of therapy during their hospitalization.

The precise reasons for the therapy regimen choice were not ascertained in the study, but patients treated with a pre-mixed regimen were much older, with an average age of almost 80 years. However, their mean HbA1c level was similar to that in the basal-bolus group. Thus, we may speculate that the regimen choice was caused by the inability of the patients to properly carry out daily multiple insulin dose therapy, or that they required assistance with insulin injections which sometimes was not possible to arrange for nighttime injections at homecare settings, as previously described [9–11]. The length of stay was significantly longer in the pre-mixed regimen group, which might be explained by the longer period of time necessary for insulin dose adjustment.

The bedside glucose monitoring frequency correlated with the recommendations [12] and was performed on average before almost every meal and at bedtime in both groups. Additional tests were quite frequently performed 2 h after breakfast.

Table 2 Differences in glycemia at V1–3 in the basal-bolus a premixed insulin regimen groups

	Basal-bolus regimen (mmol/l)	<i>p</i> value*	Premixed insulin regimen (mmol/l)	<i>p</i> value*
Fasting				
Visit 1	12.19		11.05	
Visit 2	– 2.26		– 1.94	
Visit 3	– 3.58	< 0.001	– 3.11	< 0.001
Two hours after breakfast				
Visit 1	15.54		12.91	
Visit 2	– 2.7		– 2.18	
Visit 3	– 4.69	< 0.001	– 3.31	0.016
Before lunch				
Visit 1	14.61		13.67	
Visit 2	– 2.16		– 1.23	
Visit 3	– 3.88	< 0.001	– 2.5	0.002
Before dinner				
Visit 1	11.38		11.95	
Visit 2	– 1.4		– 1.11	
Visit 3	– 2.63	< 0.001	– 1.67	0.055
Bedtime				
Visit 1	12.28		11.56	
Visit 2	– 1.65		– 1.3	
Visit 3	– 2.98	< 0.001	– 2.96	< 0.001

*Likelihood ratio test

Both treatment regimens resulted in a significant improvement in the pre-meal and post-breakfast glucose concentration (the difference before dinner in the pre-mixed regimen was on the borderline of statistical significance) and in a similar percentage of glucose readings within the target range of below 10.0 mmol (180 mg/dl). Similar results were found in the study by Bellido et al. [8].

Interestingly, a very small amount of hypoglycemia occurred during the treatment, and even more interestingly, all the events were found in the basal-bolus regimen group. This sharply contrasts with the findings of Bellido et al., whose study was stopped early because

the frequency of hypoglycemia was greater than 50% in patients treated with the premixed human insulin regimen, while it was only one-third in the basal-bolus group. We believe that the main reason for such a difference was the glycemic target for every insulin dose in the previously mentioned study. According to protocol, every dose of insulin should be adjusted for a glycemic target of between 7.8 and 10 mmol/l before meals. There was no such target in our study, so insulin dosing changes could be more finely tuned, thereby avoiding the higher frequency of hypoglycemia. Also in our study the glycemic values were higher at the beginning of insulin adjustment, which also

Table 3 Changes in mean daily blood glucose concentration and percentage of measurements with glycemic values < 10 mmol/l

	The mean daily glycemia (mmol/l)			The percentage of measurements with glycemia under 10 mmol/l (%)		
	Basal-bolus regimen (mmol/l)	Premixed insulin regimen (mmol/l)	<i>p</i> value	Basal-bolus regimen (mmol/l)	Premixed insulin regimen (mmol/l)	<i>p</i> value
Visit 1	13.05 (2.87)	12.18 (3.23)	0.058	24.2	33.5	0.053
Visit 2	11.06 (2.37)	10.73 (2.81)	0.171	43.1	50.0	0.330
Visit 3	9.59 (2.13)	9.64 (1.88)	0.695	61.7	61.4	0.107

might contribute to the low frequency of hypoglycemia. Another possible explanation might be that a substantially high proportion of our patients was treated with premixed insulin analogues linked to a lower frequency of hypoglycemia, contrary to the study by Bellido et al. [8] in which only premixed human insulin was used.

There is a significant difference between the mean insulin doses at the time of insulin initiation and at the time of discharge; the insulin dose in the premixed regimen is lower. This could be explained by concomitant oral antidiabetic therapy, but unfortunately such information is not available. Also, it should be noted that patients in the premixed regimen are older with slightly lower glycemia at admission. Both these characteristics might lead physicians to safer insulin dosing at the time of insulin introduction.

We acknowledge several limitations in the study. The patients with basal insulin only regimen were not entered into the study protocol as this type of insulin initiation is usually provided in outpatient units.

The number of patients in the premixed regimen group is relatively small but the relation between both regimen groups reflects usual daily hospital practice. Also it should be mentioned that certain groups of patients, mainly those in critical conditions (see exclusion criteria), were not included in the study. Some

patient information was missing, such as therapy with oral antidiabetic drugs and comorbidities. Unfortunately, we were not able to collect these data in the all patients.

In addition, we lack information on nutritional intake and missed meals, which represents a significant risk factor for hypoglycemia and overall glycemic control in the hospital setting.

Nevertheless, we believe that, our study is the only observational study focused on in-hospital insulin management in patients admitted to the hospital in noncritical conditions and there treated with basal-bolus or premixed insulin regimen therapy which was continued after discharge from hospital and that the presented results show important information about routine clinical practice in the Czech hospitals related to this type of therapy.

CONCLUSIONS

In-hospital insulin management regarding basal-bolus and premixed insulin regimens is safe and in concordance with current international recommendations.

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Disclosures. Jan Brož, Denisa Janíčková Žďárská, Jana Urbanová, Pavlína Pit'hová, Viera

Doničová, Sabina Pálová, Barbora Pelechová, Anna Smržová and Milan Kvapil declare no potential conflicts of interest.

Compliance with Ethics Guidelines. Ethics committee approval was not required for the study as the study was based on collection of anonymous unidentifiable data and did not qualify as a clinical trial of a medicinal product. Under local legislation Czech Pharmaceuticals Act No. 378/2007 Sb., an ethics committee approval is required only for clinical trials of medicinal products. For other types of biomedical research, ethics committee approval is optional. The study was conducted in accordance with the Declaration of Helsinki and informed consent to participate was obtained from all study participants.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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