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Comparison of the efficacy and safety of pre-mixed human insulin (Gensulin M30) versus pre-mixed insulin aspart 30/70 (NovoMix 30) in patients with type 2 diabetes mellitus

Abstract

Background. The aim of the study was to compare the efficacy and safety of pre-mixed human insulin (Gensulin M30) versus pre-mixed insulin aspart 30/70 (NovoMix 30) in patients suffering from type 2 diabetes treated by doctors employed at selected diabetic centres in Poland.
This was a survey study in which no specific treatment regimen was imposed and the subjects were managed at the discretion of their treating physicians.

Materials and methods. A total of 557 consecutive patients with type 2 diabetes mellitus were enrolled in the study, 281 of whom were being managed with Gensulin M30 and 276 with NovoMix 30.

Results. We demonstrated that after at least half a year of treatment with the above-mentioned pre-mixed insulin preparations, the study groups did not differ in terms of fasting and postprandial blood glucose concentration and HbA1c levels. Also, the incidence of hypoglycaemia was not different between the groups.

Conclusions. We conclude that in our group subjects with type 2 diabetes treated with the two pre-mixed insulins (pre-mixed human insulin Gensulin M30 and pre-mixed insulin aspart NovoMix 30) did not differ significantly in terms of efficacy and safety.

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key words: type 2 diabetes mellitus, pre-mixed insulin, Gensulin M30, NovoMix 30

Background

The incidence of diabetes is increasing worldwide. Type 2 diabetes constitutes the majority of cases. It is estimated that in the near future the number of people with diabetes will increase twofold.

Management of a diabetic patient usually starts with lifestyle interventions comprising dietary changes, exercise planning involving increased physical activity and weight reduction, and pharmacotherapy with hypoglycaemic agents. Biguanides are the first line treatment; sulphonylurea and other drugs may be further added. If the patient does not reach the glycaemic target, including adequate HbA1c concentration with oral agents, insulin should be introduced. Intensive insulin therapy in elderly patients is usually not recommended. Pre-mixed insulin preparations are chosen most often containing 30% short acting and 70% NPH insulin [1–4].

The aim of the study was to compare the efficacy and safety of pre-mixed human insulin (Gensulin M30) versus pre-mixed insulin aspart 30/70 (NovoMix 30), as well as quality of life in patients suffering from type 2 diabetes treated by doctors employed at selected diabetic centres in Poland.

In the studied population data concerning pre- and postprandial glycaemia, HbA_{1c} concentration, and incidence of mild and severe hypoglycaemia were analysed. Patient satisfaction with insulin preparations was assessed using a dedicated questionnaire. Our studied group consisted of type 2 diabetic patients 18–62 years old treated with pre-mixed insulin Gensulin M30 or NovoMix 30 for at least 6 months. Written informed consent was obtained from all participants.

Material and methods

In our study we compared two human insulin preparations: 30/70 (Gensulin M30; manufacturer Bioton SA)

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and biphasic insulin aspart 30/70 (NovoMix 30; Novo-Nordisk Pharma sp. z o.o.). The study was performed in the second quartile of 2007 in randomly selected diabetic centres in Poland.

The company PBS DGA chose 2–4 diabetic centres in each country region. In each of the selected centres one diabetologist or internal disease specialist involved in the management of diabetic patients was chosen. Each participating physician introduced 10 consecutive patients 18–70 years old, with type 2 diabetes, treated with Gensulin M30 and 10 patients treated with NovoMix 30 for at least 6 months prior to the beginning of the study. The duration of the study was 3 months. If the physician was unable to include the required number of patients another centre was chosen.

A total of 557 consecutive patients (304 female, 253 male) with type 2 diabetes of at least two years duration participated in the study. The mean age of the patients was 56 ± 0.3 years. Of the study population, 18.5% were younger than 50 years old and 81.5% were 50 years of age or older. Mean diabetes duration was 9.5 ± 0.31 years and mean duration of insulin treatment was 4.5 ± 0.23 years.

Gensulin M30 was used to treat 281 patients. Their mean age was 56.3 ± 0.42 years, and the mean duration of treatment for diabetes was 9.3 ± 0.38 years. The group treated with Gensulin M30 consisted of 153 female and 128 male participants. 17.1% of patients in this group were younger than 50 years old and 82.9% were 50 or more years old. The mean duration of insulin treatment was 4.2 ± 0.23 years, and the mean duration of treatment with Gensulin M30 was 2.3 ± 0.13 years.

The remaining 276 participants were treated with insulin aspart 30/70 (NovoMix 30). The mean age in this group was 55.7 ± 0.42 years, and the mean duration of diabetes treatment was 9.7 ± 0.5 years. The group treated with NovoMix consisted of 151 women and 125 men. Among the participants, 19.9% were less than 50 years old and 80.1% were 50 years old or above. The mean duration of insulin treatment in this group was 4.8 ± 0.4 years, and the mean duration of treatment with NovoMix 30 was 1.6 ± 0.7 years.

Of the patients, 86.8% were treated with Gensulin M30 twice daily, 3.3% more than twice daily, and 8.2% only once daily. In the group receiving NovoMix 30 therapy 81.9% of participants were given insulin twice daily, 10.1% once daily, and 3.6% more than twice daily.

Table 1 presents the mean age of study participants and percentage of patients older than 50 years as well as the proportion of male and female subjects in the study.

After obtaining written informed consent from each patient, the physician filled in the study questionnaire concerning past treatment and patient's satisfaction with the current insulin therapy. There were two sections to the study questionnaire.

First section covered issues concerning diabetes such as: diagnosis, complications (assessment based on history and case notes), episodes of mild and severe (blood glucose < 40 mg/dl or patient requiring third-party assistance) hypoglycaemia, the highest and mean fasting and postprandial (2 hours) blood glucose values over the last 4 weeks, HbA_{1c} concentration (last 12 weeks), and anthropometric data which allowed the calculation of body mass index (BMI) and waist to hip ratio (WHR). The second section of the questionnaire consisted of questions concerning satisfaction with the patient's current insulin therapy.

Fasting and postprandial blood glucose levels were measured with various glucometers. HbA_{1c} concentration was measured by HPLC method.

Statistical analysis

As in most patients the HbA_{1c} level was measured only once during the preceding 12 weeks, only the last result was included in the analysis.

Fasting and two-hour postprandial blood glucose values were analysed as follows: the highest and the lowest values of analysed parameters from the last 4 weeks (i.e. mean of minimal and maximal blood glucose concentration –fasting and postprandial) constituted the variables.

Additionally, in order to assess if the treatment with each studied insulin preparation resulted in a similar reduction of HbA_{1c} as well as fasting and postprandial blood glucose level results of the last HbA_{1c} concentration were compared between patients treated with each insulin preparation for 6 months. The highest and the lowest results of fasting and postprandial blood glucose levels over the last year for patients treated with each insulin preparation were compared.

In order to obtain more detailed information on treatment results with Gensulin M30 and NovoMix 30, we assessed whether duration of therapy with these preparations influenced HbA_{1c} levels as well as fasting and postprandial blood glucose concentrations.

Distribution of variables such as satisfaction with the used insulin preparation, its effectiveness, and onset of action as well as its shortcomings were used to determine which patient group was more satisfied with the insulin preparation and treatment effects.

Data were processed with SPSS version 15.0 software.

Results

Basic data of the studied population

Table 1 presents the patients' age in the whole study population and in particular subgroups. The age of patients treated with Gensulin M30 and with NovoMix 30 did not differ significantly between the groups. In the

Table 1. Number of patients, age, duration of diabetes, and duration of treatment with specific insulin preparations (X ± SEM)

	All studied patients	Gensulin M30 (A)	NovoMix 30 (B)	Statistical significance (A–B) (p)
Number of studied patients	557	281	276	
Age	56 ± 0.3	56.3 ± 0.42	55.7 ± 0.42	NS
Female age	56 ± 0.43	55.8 ± 0.65	56.3 ± 0.55	NS
Male age	55 ± 0.4	56.8 ± 0.51	55.0 ± 0.65	0.022
Female < 50 years old	18.5%	17.1%	19.9%	NS
Female ≤ 50 years old	81.5%	82.9%	80.1%	NS
Diabetes duration	9.5 ± 0.31	9.3 ± 0.38	9.7 ± 0.50	0.013
Insulin therapy duration	4.5 ± 0.23	4.2 ± 0.23	4.7 ± 0.40	< 0.004
Duration of therapy with specific Insulin preparation	1.9 ± 0.08	2.3 ± 0.13	1.6 ± 0.07	< 0.001

Table 2. Body mass index (BMI) and waist to hip ratio (WHR) values across the study groups

	All studied patients	Gensulin M30 (A)	NovoMix 30 (B)	Statistical significance (A–B) (p)
BMI [kg/m^2]	29.8 ± 0,2	30.1 ± 0.25	29.5 ± 0.32	NS
BMI — female [kg/m^2]	30.0 ± 0.3	30.2 ± 0.36	29.8 ± 0.46	NS
BMI — male [kg/m^2]	29.6 ± 0.3	30.0 ± 0.35	29.1 ± 0.43	NS
BMI < 20 (%)	0.6	0.4	0.7	NS
BMI 20–25 (%)	13.6	11.3	16.0	NS
BMI 25–30 (%)	42.5	41.8	43.3	NS
BMI > 30 (%)	43.3	46.5	39.9	NS
WHR — female (1/1)	0.88 ± 0.005	0.88 ± 0.007	0.88 ± 0.008	NS
WHR — male (1/1)	0.96 ± 0.006	0.95 ± 0.009	0.96 ± 0.01	NS
WHR > 0.80 — female (%)	82.2	83.9	80.3	NS
WHR ≤ 0.80 — female (%)	17.8	16.1	19.7	NS
WHR > 0.94 — male (%)	55.3	53.8	56.8	NS
WHR ≤ 0.94 — male (%)	44.7	46.2	43.2	NS

group of patients treated with Gensulin M30 there were fewer patients younger than 50 years of age compared with the group treated with NovoMix 30, but the difference was not statistically significant (tab. 1). Patients treated with Gensulin M30 were characterised by shorter duration of diabetes and shorter duration of insulin therapy, but in this group the duration of treatment with a particular insulin preparation was longer than in the NovoMix 30 group (tab. 1).

Table 2 presents data on BMI and WHR. The studied groups did not differ significantly with respect to these parameters.

Fasting, postprandial glucose concentration, and Hba$_{1c}$ in the studied groups

Table 3 presents fasting, postprandial blood glucose values, and HbA1c in the whole study population as well as in both subgroups. The studied subgroups of patients did not differ significantly with respect to these parameters (tab. 3).

Incidence of late diabetic complications

Table 4 presents incidence of late diabetic complications in the whole studied population and in two subgroups. The subgroups did not differ significantly with respect to the incidence of late diabetic complications

Incidence of hypoglycaemia

The incidence of hypoglycaemia in the studied groups is presented in table 5. The groups did not differ significantly with respect to the incidence of hypoglycaemia.

Assessment of treatment quality

During history taking, the patients responded to questions regarding satisfaction and comfort of treatment with specific insulin preparations. Table 6 presents data from the questionnaires filled in by the patients.

Table 3. Fasting blood glucose, postprandial blood glucose, and HbA_{1c} values in the studied population and specific subgroups

	All studied patients	Gensulin M30 (A)	NovoMix 30 (B)	Statistical significance (A–B) (p)
Mean of lowest fasting blood glucose concentrations [mg/dl]	109 ± 1.36	110 ± 1.64	108 ± 1.57	NS
Mean of highest fasting blood glucose concentrations [mg/dl]	150 ± 1.49	151 ± 2.03	149 ± 2.18	NS
Mean of lowest postprandial blood glucose concentrations [mg/dl]	131 ± 1.53	132 ± 2.27	130 ± 2.04	NS
Mean of highest postprandial blood glucose concentrations [mg/dl]	187 ± 2.00	189 ± 2.94	185 ± 2.72	NS
HbA_{1c} (%)	7.52 ± 0.05	7.55 ± 0.07	7.54 ± 0.08	NS
HbA_{1c} — female (%)	7.52 ± 0.07	7.55 ± 0.08	7.48 ± 0.10	NS
HbA_{1c} — male (%)	7.58 ± 0.08	7.54 ± 0.1	7.60 ± 0.11	NS
$HbA_{1c} \leq 6.5$ (%)	12.9	10.3	15.6	NS
$HbA_{1c} > 6.5$ (%)	87.1	89.7	84.4	NS
$HbA_{1c} \leq 7.0$ (%)	34.1	32.4	34.1	NS
$HbA_{1c} > 7.0$ (%)	65.9	67.6	65.9	NS

Table 4. The incidence of late diabetic complications in selected patient subgroups

	All studied patients	Gensulin M30 (A)	NovoMix 30 (B)	Statistical significance (A–B) (p)
Diabetic nephropathy (%)	10.6	9.3	12.0	NS
Chronic renal failure (%)	2.0	1.8	2.2	NS
Diabetic retinopathy (%)	26.9	28.8	25.0	NS
Diabetic foot syndrome (%)	4.8	5.0	4.7	NS
Diabetic neuropathy (%)	29.8	33.5	26.1	NS
Stroke (%)	3.4	2.8	4.0	NS

Discussion

In the presented paper we demonstrated that the studied groups did not differ with respect to the anthropomorphic parameters such as BMI and WHR. The mean age of the studied subjects, mean diabetes duration, and duration of insulin therapy were also similar between the groups (table 1).

In the group of type 2 patients treated with Gensulin M30 and in the group treated with NovoMix 30, the mean lowest and highest glucose concentrations measured in a fasting and postprandial state did not differ significantly. The percentage of patients with $HbA_{1c} < 7\%$ and $< 6.5\%$ was also similar in both groups. It is worth noting that the studied groups were similar with respect to HbA_{1c} concentrations in the whole population and in the subgroups of female and male patients.

Further analysis demonstrated that the incidence of late diabetic complications was similar between the groups treated with human and analogue insulins (tab. 4). In Poland, as well as in other countries, insulin therapy is generally commenced too late, at the stage when complications are already present and insulin therapy, although potentially more efficient, cannot change the situation..

The number of people with at least one episode of hypoglycaemia and the number of patients with one episode of severe and mild hypoglycaemia were analysed. No difference between the two studied groups was observed (tab. 5).

Finally, satisfaction with treatment with each insulin preparation was studied. The patients were generally satisfied with their insulin preparations – both in the group using Gensulin M30 and in the group treated with NovoMix 30. In the latter group the patients were not happy with the price of the insulin, which they believed was too high. Therefore, they did not always buy the medication or purchased less insulin than prescribed by their physician (tab. 6).

Our observations are similar to the results of another study of 464 subjects in which human insulin preparation (Gensulin M30) was used in patients with type 2 diabetes and secondary failure of oral hypoglycaemic drugs. The authors of the study found that using human pre-mixed insulin preparation 30/70 led to an improvement in blood glucose control expres-

Table 5. Incidence of severe and mild hypoglycaemia in the study subjects

	All studied patients	Gensulin M30 (A)	NovoMix 30 (B)	Statistical significance (A–B) (p)
Number of patients with at least 1 episode of hypoglycaemia	20.5% 113/557	18.9% 53/281	22.1% 61/276	NS
Number of patients with more than 1 episode of hypoglycaemia	12% 67/557	11% 31/281	13% 36/276	NS
Number of patients with at least 1 episode of severe hypoglycaemia	3.6% 20/557	2.1% 6/281	5.1% 14/276	NS
Number of patients with more than 1 episode of severe hypoglycaemia	0.9% 5/557	0.4% 1/281	1.4% 4/276	NS
Number of patients with at least 1 episode of mild hypoglycaemia	17.9% 100/557	17.3% 48/281	19.0% 52/276	NS
Number of patients with more than 1 episode of mild hypoglycaemia	10.9% 61/557	10.7% 30/281	11.2% 31/276	NS

Table 6. Satisfaction with the insulins used

		All studied patients		Gensulin M30 (A)		NovoMix 30 (B)		Statistical significance (A–B) (p)
Are you satisfied with your insulin preparation ? (n = 556)	Definitely yes (%)	51.1	284	48.9	137	53.3	147	NS
	Rather yes (%)	42.1	234	44.6	125	39.5	109	NS
	Hard to say (%)	5.4	30	4.6	13	6.2	17	NS
	Rather no (%)	1.3	7	1.8	5	0.7	2	NS
	Definitely no (%)	0.2	1	0.0	0	0.4	1	NS
What are the disadvantages of your insulin?	Inability to achieve good glycemic control	52.9	18	61.5	8	47.6	10	NS
	Plunger jams and/ /or inoperable pen	17.6	6	46.2	6			NS
	High price	44.1	15			71.4	15	NS
	Others	5.9	2	7.7	1	4.8	1	NS
	Note: percentage of patient in each group Respondents: patients unsatisfied with their insulin, n = 15/n = 26							
How fast does your insulin start to work?	Too slow	25.0	11	50	10	4.2	1	0.000
	Fast enough	36.4	16	10	2	58.3	14	0.000
	Hard to say	38.6	17	40	8	37.5	9	0.000
	Respondents: patients unsatisfied with their insulin, n = 20/n = 24							
How long does your insulin work?	Long enough	36.4	16	20	4	50	12	NS
	Too short	13.6	6	20	4	8.3	2	NS
	Hard to say	50	22	60	12	41.7	10	NS
	Respondents: patients unsatisfied with their insulin, n = 20/n = 24							
Did the high price of insulin cause you…	...not to buy your insulin?	2.4	13	0	0	4.8	13	0.0000
	...to purchase reduced amount of insulin?	6.5	36	1.8	5	11.4	31	0.0000
	...to resign from other drugs?	6	33	4	11	8.1	22	0.04
	Respondents: all studied patients							

sed as a reduction in HbA_{1c} concentration and improved 24-hour blood glucose profile, which was similar to the improvement achieved with analogue insulins. The treatment resulted in only a slight increase in body mass and risk of severe hypoglycaemia, but improved the patient's quality of life and reduced the burden of therapy [5].

In yet another study, the timing of human (Gensulin M30) insulin injection in patients with type 2 diabetes was compared. Insulin was injected 5, 15, and 30 minutes before a meal. Blood glucose profiles registered with continuous glucose monitoring system (CGMS) were similar regardless of timing of injection. Thus, in type 2 patients treated with pre-mixed insulin preparation 30/

70, the interval between insulin dosing and meal initiation does not affect the glicemic profile [6] However, it should be mentioned that the patients reported occasional malfunctioning of the pen device (jamming and delayed operation).

On the basis of the presented results and observations from recently published studies, treatment with premixed human insulin preparation Gensulin M30 seems to be effective and safe for patients with type 2 diabetes.

Conclusions

Treatment of the study population, consisting of type 2 diabetic patients, with Gensulin M30 or NovoMix 30 insulins resulted in similar metabolic control. In addition, the safety of treatment with pre-mixed human (Gensulin M30) or analogue (NovoMix 30) insulins was similar.

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