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Safety and Efficacy in Early Insulin Initiation as Comprehensive Therapy for Patients with Type 2 Diabetes in Primary Health Care Centers

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ABSTRAK

Tujuan: *menganalisis efikasi dan keamanan terapi insulin yang diberikan oleh dokter pada penderita diabetes melitus yang tidak terkontrol di pusat layanan kesehatan primer di Surabaya, Jawa Timur, Indonesia.* ***Metode:*** *studi pre-post ini melibatkan 99 pasien DM tipe 2 dengan HbA1c >8% yang belum pernah mendapatkan terapi insulin sebelumnya. Studi dilakukan pada 10 puskesmas di Surabaya antara Oktober 2011 sampai dengan Juni 2012. Terapi insulin diberikan selama 12 minggu. Pemeriksaan laboratorium yang dilakukan pada pasien meliputi glukosa darah puasa (GDP), glukosa darah 2 jam post prandial (GD2JPP) dan HbA1c sebelum dan sesudah terapi. Pemeriksaan gula darah mandiri juga dilakukan untuk menyesuaikan dosis insulin dan mencegah hipoglikemia. Data dianalisis secara statistik dengan uji T-berpasangan.* ***Hasil:*** *GDP awal adalah 209 mg/dL menjadi 152,07 mg/dL pada akhir studi (Δ56,93 mg/dl; p=0,0001) dan GD2JPP juga turun dari 313,00 mg/dl menjadi 220,72 mg/dL (Δ 92,28 mg/dl; p=0,0001). HbA1c turun dari 11,60% pada awal studi menjadi 8,95% pada akhir studi (Δ 2.65%; p=0,0001). Selama penelitian, hipoglikemia didapatkan pada 6 patients (6,06%) dan keseluruhan ringan tanpa membutuhkan perawatan rumah sakit.* ***Kesimpulan:*** *dokter umum pada layanan kesehatan primer dapat melakukan inisiasi terapi insulin dengan penurunan HbA1c yang signifikan dan efek samping hipoglikemia yang rendah.*

Kata kunci: *insulin, dokter umum, pusat layanan kesehatan.*

ABSTRACT

Aim: *to analyze the safety and efficacy of early insulin initiation therapy for patients with type 2 diabetes mellitus (T2DM) in primary health care provided by general practitioners (GPs) in Surabaya, East Java, Indonesia.* ***Methods:*** *pre-post study of ninety nine diabetic patients without previous insulin treatment with HbA1c levels >8% were involved in this study. The study was conducted in 10 primary health care centers in Surabaya between October 2011 to June 2012. Each patient received insulin therapy for 12 weeks. Laboratory examination was performed for each patient including fasting plasma glucose (FPG), 2 hours post-prandial plasma glucose (2hPPG) and HbA1c examination before and after the study. Self monitoring blood glucose (SMBG) examination was conducted in order to adjust the insulin dose and prevent the incidence of hypoglycemia. Data was statistically analyzed using paired-T test.* ***Results:*** *FPG level was decreased from baseline data (209 mg/dL) to 152.07 mg/dL at the end of the study (Δ56.93 mg/dl; p=0.0001). The average of 2hPPG level was also decreased from 313.00 mg/dl to 220.72 mg/dL (Δ 92.28 mg/dL; p=0.0001). HbA1c was reduced from 11.60% at baseline to 8.95% at the end of study (Δ 2.65%; p=0.0001). Hypoglycemia was found in 6 patients (6.06%) in this study, but all events were mild and did*

not need to be admitted to hospital. ***Conclusion:*** *the safety of insulin therapy iniatiation might be provided by GPs at primary health centers with significant efficacy and minimal side effects.*

Key words: *insulin, general practioner, primary health center.*

INTRODUCTION

Type 2 Diabetes Mellitus is a chronic metabolic disease with in current prevalence a rapid increased. The International Diabetes Federation (IDF) estimated the number of people with diabetes from 387 million in 2014 will increase to 592 million in 2035. Indonesia has 9.1 million people with diabetes in 2014.[1] World Health Organization (WHO) estimated that the number of people with diabetes in Indonesia will rise from 8.4 million in 2000 to 21.3 million in 2030. Central Statistics Agency in 2003 showed the prevalence of DM was 14.7% or about 8.2 million in urban areas and 7.2% or about 5.5 million in rural areas. By assuming the population growth in 2030, it is estimated that DM in urban areas will reach 12 million people and in rural areas 8 million people. The report of Basic Health Research in 2007 by the Ministry of Health showed that the prevalence of DM in Indonesian urban areas for ages above 15 years was 5.7%.[2,3]

Data at the Dr. Soetomo Hospital in 2007 showed that the prevalence of DM who underwent hospitalization reached 16.4% with a range of complications and mortality reached 28.8%.[4] As the prevalence of DM is increasing, it is very important to improve glycemic control to delay microangiopathy, neuropathy and other complications of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and other studies have shown that intensive glycemic control in type 2 diabetes significantly reduces the risk of microvascular complications and can improve cardiovascular outcomes.[5,6]

Problems due to poor blood glucose control in Indonesia were the reluctance of most of patients to start insulin although their blood glucose have not been well controlled by oral anti-diabetic drugs and reluctance of the physicians to provide insulin therapy due to lack of knowledge, experience and confidence.[7-9] In addition, insulin was not well-distributed among primary health care services. Patients with diabetes who have been poorly controlled with oral antidiabetic drugs for years and patients with special conditions requiring insulin therapy have to go to referral hospital for insulin therapy. This policy had lead to the difficulty of patients and health care providers in receiving insulin. Constraints that arise from GPs at primary health center is lack of knowledge about providing insulin include indication, dosage, insulin regimen selection, SMBG and hypoglycemia side-effects treatment. The impact of increasing blood glucose is more complications arise. This will eventually make the cost higher for treatment of DM and its complications.

Another problem is that patients with diabetes in secondary and tertiary hospitals are stuck due to referrals made by primary health care physicians. This will eventually overwhelm doctors who work in secondary and tertiary health services because of the high ratio of patients per doctor. This could be a warning sign to start early intensive management of diabetes therapy at primary care level. Health care strategy for patients with diabetes should be integrated into primary health care and hence, the role of GPs is crucial. Simple diabetic cases without complications can be managed completely by a GP, especially if blood glucose levels are well controlled. These reasons prompted us to conduct a research on the efficacy and safety of insulin initiation therapy provided by GPs in patients with uncontrolled diabetes mellitus in primary health care centers in Indonesia. Results of this study will be used to recommend the insulin use at the level of primary health centers in Indonesia.

METHODS

Design

The research was conducted at 10 primary health centers in Surabaya between October 2011 and June 2012. This study was a pre-post

study, in which data were collected before and after insulin therapy. Insulin therapy was performed by GP at related health center who had previously received training on insulin therapy, for three times face-to-face and regular meetings with research assistants every 2 weeks to monitor insulin therapy provided by those general practitioners. Insulin therapy training materials included the using of insulin therapy, techniques of insulin injection, side effects of insulin therapy, such as hypoglycemia and its management, and Self Monitoring Blood Glucose (SMBG) examination. The inclusion criteria were subjects with Type 2 Diabetes Mellitus (T2DM) who had not received insulin treatment, subjects with HbA1c levels >8%, and subjects who were willing to participate in the study by signing informed consent. The exclusion criteria included subjects who had insurance which requires the concerned to be referred to the hospital, subjects who were hypersensitive to insulin aspart, insulin detemir, biphasic insulin aspart 30 and ingredients of the products, and women in pregnancy, breastfeeding or planning a pregnancy in the next 6 months period.

In this study, data collection included subject's demographic, weight, duration of diabetes, complications and the medication based on interview and medical record. The subjects were also checked Fasting Plasma Glucose (FPG), 2 hours Post Prandial Glucose (2hPPG) and Hemoglobin A1c (HbA1c) examination on baseline and the end of study. Subjects also filled out questionnaires about quality of life before and after therapy. Self monitoring blood glucose (SMBG) examination was conducted in order to adjust the insulin dose and to prevent the incidence of hypoglycemia. SMBG monitoring was done at waking up in the morning, after breakfast, before and after lunch and dinner. Monitoring was done every three days. This research has been granted permission from the ethics committee of the Faculty of Medicine, Airlangga University, no. 049/EC/KEPK/FKUA/2011 dated 2 November 2011.

Data Collection

This study was a prospective study in which the data were documented in Case Record Forms (CRF) prepared for each patient. Data were obtained through interviews and laboratory tests and other data contained in medical records. Blood samples for HbA1c examination were obtained through blood venous with EDTA 3 ml for all subjects recruited and analyzed using High Performance Liquid Chromatography (HPLC). For patients who have received insulin therapy, SMBG was recorded by GPs, and each week they met the researchers to report on SMBG recording and insulin dose adjustments. Monitoring was scheduled for every two weeks.

Study Population

The study was conducted at 10 primary health centers in Surabaya, such as Pakis, Manukan Kulon, Asem Rowo, Tambak Rejo, Ketabang, Mulyorejo, Pacar Keling, Wonokusumo, Takal and Sawahan. The primary health centers were selected based on geographical distribution and high prevalence of DM. Ninety-nine patients were recruited between December 2011 - February 2012.

Statistical Analysis

Data subject demographic characteristics included age, body mass index, blood pressure, and duration of subjects suffering from diabetes mellitus, HbA1c, FPG and 2hPPG analyzed descriptively by calculating the mean and standard deviation, in addition to calculate the proportion of subjects, including sex, history of medication, side effects, and complications.

To calculate the difference in body mass index (BMI), mean HbA1c levels, FPG and 2hPPG was done before and after insulin therapy. Paired T-test was done preceded by normality test on data distribution of the two groups data using the Kolmogorov-Smirnoff test.

RESULTS

Number of subjects participating in the study was 99 with characteristics shown in **Table 1**. In this study, female subjects were more than male subjects (80 vs 20%). The mean age of the patients was 53.7±9.31 years old, ranging from 33 to 80 years old. The mean weight of the patients was 58±10.39 with BMI of 24.44±4.12kg/m2. Mean duration of diabetes was 6.2±5.3 years. Most of the older patients have been suffering from diabetes for 29 years and there were 7 patients

who have been suffering from diabetes for less than 3 months before the study (**Table 1**).

Diabetes Complications

Sixty four subjects had complications, with neuropathy as the most common single complication. In contrast, cardiovascular disease was rarely found as a single complication. Sixteen subjects suffered from all of three complications and only 35 subjects had no complications. (**Table 1**)

The majority of the subjects (80%) had been previously treated with a combination of metformin and a sulfonylurea. Six subjects received only sulfonylurea, and 7 subjects recieved only metformin. Six subjects were previously not treated with either metformin or sulfonylurea, two subjects used herbal medicines and four subjects did not receive treatment at all. (**Table 1**)

Table 1. Characteristics and patient demographics

Variables	n (%)	Mean ± SD
Total (n)	99 (100%)	
Sex:		
- Male (%)	20 (21%)	
- Female (%)	79 (79%)	
Age (year)		53.7 ± 9.31
Bodyweight (kg)		58 ± 10.39
BMI (kg/m2)		24.44 ± 4.12
Type 2 Diabetes Mellitus Duration (years)		6.2 ± 5.39
HbA1C (%)		11.6 ± 2.03
Fasting Blood Glucose (mg/dL)		209 ± 81.62
2 hour post prandial Blood Glucose (mg/dL)		313 ± 112.32
Complications :		
- No complications	35(35,3%)	
- CVD only	1(1%)	
- Eye only	5 (5%)	
- Neuropathy only	21(21,2%)	
- CVD + Eye	2 (2,1%)	
- CVD + Neuropathy	5 (5%)	
- Eye + Neuropathy	14 (14,2%)	
- All three complications	16 (16,2%)	
Previous therapy history		
- Sulfonylurea only	6 (6%)	
- Metformin only	7 (7%)	
- Sulfonylurea + Metformin	80 (81%)	
- Herbal therapy	2 (2%)	
- No therapy	4 (4%)	

Glycemic Control

In this study, 99 subjects of the primary health centers received insulin. 79 subjects received basal insulin (insulin detemir) in combination with the previous oral anti-diabetic drugs, 2 subjects received premixed insulin (Biphasic Insulin Aspart 30), 14 subjects received basal plus insulin (insulin detemir and 1-2x insulin aspart) and 4 subjects received basal bolus insulin (insulin detemir and 3x insulin aspart). FPG were significantly reduced 56.93 mg/dL (p=0.0001) from baseline (209 mg/dL) to 152.07 mg/dL at end of the study in 99 patients. Two hours post prandial glucose also significantly reduced -92.28 mg/dL from 313.00 mg/dL to 220.72 mg/dL (p=0.0001). In this study, we also found a significant decrease of HbA1c from 11.60% at baseline to 8.95% at the end of the study (p=0.0001). Therefore, the mean reduction of HbA1c obtained in patients receiving insulin was 2.65%. (**Table 2**)

Hypoglycemic Complications

In this study, hypoglycemia was found in 6 subjects (6.06%), 4 subjects were receiving therapy with insulin detemir, 1 subject was receiving premixed insulin and 1 subject was receiving basal bolus therapy. Subjects receiving insulin detemir and 1-2 times insulin aspart were not having hypoglycemia. All hypoglycemia event were mild, subjects treated themselves at home, reported to their GP for insulin adjustment doses and did not need hospitalization.

DISCUSSION

Many patients with T2DM are in poor glycemic control leading to an increase in the risk of more severe complications. In this study most of patients with T2DM treated in primary health centers were uncontrolled. The mean HbA1c levels were 11.6%, which was still far from the standard recommended by Perkeni in 2011 which is below 7%.[3] Type 2 diabetes is a disease with progressive natural course, because pancreatic beta cell function and insulin

Tabel 2. Glycemic control in patients before and after insulin therapy

		FPG				2hPPG				HbA1c			
	N	Pre (mg/dL)	Post (mg/dL)	Δ	p	Pre (mg/dL)	Post (mg/dL)	Δ	p	Pre	Post	Δ	p
Total	99	209.00	152.07	56.93	0.0001	313.00	220.72	92.28	0.0001	11.60	8.95	2.65	0.0001
Detemir	79	206.96	147.46	59.50	0.0001	292.80	207.43	85.37	0.0001	11.56	8.75	2.81	0.0001
Basal Plus	14	202.21	148.64	53.57	0.397	345.84	228.06	117.80	0.004	11.52	9.65	9.65	0.011
Basal Plus	4	261.50	213.50	48.00	0.237	237.50	244.50	-7.0	0.469	12.83	11.43	1.47	0.359
Premix	2	125.00	80.50	44.50	0.296	446.50	135.00	311.5	0.303	11.80	7.55	4.25	0.366

physiological response will decrease over time despite good glycemic control management. Thus, many patients still require insulin therapy whether with the increased dose or additional oral diabetic drugs. More than 60% patients with T2DM require insulin therapy within 6-10 years after the initial diagnosis.[8,10] In this study, with an average duration of diabetes of 6.2 years, most of subjects had already required treatment with insulin (**Table 1**).

Insulin is the most effective therapy to achieve glycemic targets. However, there is still a reluctance of both doctors and patients to initiate insulin therapy. Factors related to the patient's reluctance includes fears of insulin injection, insulin addiction, and sometimes skeptical of the success of insulin itself, while GP's reluctance includes the fear of side effects of insulin, such as hypoglycemia and weight gain, limited time for education and training for the patients about the use of insulin. Sometimes GPs have lack of knowledge for using of insulin itself.[11] Another important cause is the availability of insulin in the primary health centers. Insulin distribution did not cover primary health centers in Indonesia.

Poor glycemic control and frequently delayed insulin therapy lead to various complications. The UKPDS showed that the decrease in HbA1c will lower the incidence of complications, both microvascular and neuropathic complications.[5] Similar with the UKPDS, this study showed that 64.5% of patients were having complications with a high baseline of HbA1c (11.6%). One of these complications, cardiovascular disease, retinopathy or neuropathy, was found in 27 T2DM subjects, while 21 subjects suffered from two complications (21.21%) and 16 subjects (16.16%) suffered from 3 complications. It means that 37.37% of patients with T2DM had more than one complications. Similar results were found in a multicenter study in the United Kingdom by Holman et al who conducted study of 708 patients with suboptimal HbA1c levels (between 7.0 to 10.0%). They found 17.2% of the patients had retinopathy, 19.1% with neuropathy, 19.5% with macroangiopathy and 9.6% with nephropathy.[12] This showed that both in modern countries like United Kingdom and developing countries like Indonesia, the complications of diabetes are associated with glycemic control. (**Table 1**)

The study was conducted on T2DM patients with poor glycemic control, characterized by HbA1c levels of >8%, both in subjects treated with and without oral anti-diabetic drugs. Most of the subjects (81%) had been treated with the combination of oral diabetic drugs such as metformin and sulfonylureas available at primary health centers. Those who received single oral drugs only were 13 (13%) subjects, and 6 (6%) subjects had used herbal medicine or never been treated at all. (**Table 1**)

The subjects had significant improvement in glycemic control after being treated with insulin, both in FPG and HbA1c in all groups that received either basal insulin (insulin detemir) alone, premixed insulin, basal plus (combination of insulin detemir + insulin aspart 1-2 times) and basal bolus (insulin detemir combination + 3 times insulin aspart). Overall reduction of HbA1c was 2.65% from 11.60% at baseline to 8.95% at the end of study. The mean FPG decline was

56.93 mg/dL and the mean decline in 2hPPG was 92.28 mg/dL. The highest reduction of HbA1C and 2hPPG was obtained in the premixed insulin group (4.25% and 311.5 mg/dL respectively). However, patients who received premixed insulin were only 2 people. The highest FPG reduction was obtained in the insulin detemir group, which was 59.59 mg/dL. (**Table 2**)

This study showed better results compared to previous studies conducted. Hermansen et al studied 476 patients with HbA1c ranged from 7.5 to 10.0% and he found that additional insulin detemir on oral anti-diabetic drugs therapy for 24 weeks decrease HbA1c from baseline to 1.8%.[13] A study by Rosenstock showed that patients treated with insulin detemir showed decrease of HbA1c from baseline to 1.4% after 52 weeks of insulin therapy and a decline of FPG from 10.8 mmol/L to 7.1 mmol/L.[14] A study by Holman et al revealed a 0.8% reduction of HbA1c with basal insulin alone (insulin detemir), 1.3% with biphasic insulin (premix) and 1.4% with prandial insulin (insulin aspart) alone[12], while the research by Liebl et al.[15] using basal-bolus insulin and biphasic insulin (premix) found a 1.56% and 1.23% decrease of HbA1c.[15] Regarding these facts, this study showed decrease of HbA1c, which was very likely because the baseline HbA1c levels in this study was as high as 11.6% in health centers.

The episode of hypoglycemia was found only in 6 (6.06%) patients, and all were mild episodes, which only required insulin dose adjustment and not requiring hospital treatment. No other side effects were found in this study, such as allergic or local reactions at the site of injection, quite similar with the study by Hollander et al. who reported that hypoglycemia was as high as at 4.7%, and the adverse events (AE) were found in 86.4% of patients (185/214 patients).[16] Holman et al.[12] showed that in patients with insulin detemir alone, three times mealtime insulin aspart and biphasic insulin resulted mean hypoglycemic events per patient per year of 2.3; 12.0 and 5.7.

Considering that the significant decrease of HbA1c level and hypoglycemia episodes that were not much different from other previous studies, it is suggested that GPs in health centers Surabaya were competent to initiate insulin therapy for type 2 diabetes mellitus patients with poor glycemic control.

CONCLUSION

Despite getting oral anti-diabetic drugs therapy for several years, most patients with type 2 diabetes in primary health care centers had poor glycemic control which was shown by their high average of HbA1c and blood glucose level. This study also showed that insulin therapy could significantly control blood glucose levels. It was indicated by decreased level of HbA1c among patients with either basal, biphasic (premixed), or combination of basal and insulin-plus basal-bolus additional insulin therapy. All subjects turned out to have a significant reduction in HbA1c levels. General practitioners at health centers can perform insulin therapy after obtaining training and the provision of sufficient material regarding insulin therapy. General practitioners at health center level are competent to perform insulin therapy indicated by a significant decrease in HbA1c levels and the low rate of hypoglycemic incidence among patients with additional insulin therapy performed by GPs involved in this study.

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