Simplified Self-Titration of Basal Insulin Injection in Type 2 Diabetes
การปรับขนาดยาฉีดเบซัลอินซูลินด้วยตนเองอย่างง่ายในผู้ป่วยเบาหวานชนิดที่ 2

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บทคัดย่อ

ผู้ป่วยเบาหวานชนิดที่ 2 ที่รับประทานยาลดน้ำตาลในขนาดสูงแต่ยังไม่สามารถควบคุมระดับน้ำตาลได้ตามเป้าหมาย การเริ่มยาฉีดเบซัลอินซูลิน ร่วมกับการตรวจติดตามระดับน้ำตาลในเลือดด้วยตนเองและผู้ป่วยที่ได้รับการสอนให้ปรับขนาดยาฉีดเบซัลอินซูลินด้วยตนเอง สามารถควบคุมระดับน้ำตาลได้ดีขึ้น

วัตถุประสงค์: เพื่อศึกษาผลของการเริ่มยาฉีดเบซัลอินซูลินร่วมกับการปรับขนาดยาฉีดด้วยตนเองในผู้ป่วยเบาหวานชนิดที่ 2 ที่ไม่สามารถควบคุมระดับน้ำตาลในเลือดโดยการใช้ยารับประทาน

วัสดุและวิธีการ: เป็นการศึกษาแบบย้อนหลัง เก็บข้อมูลจากเวชระเบียนของผู้ป่วยที่มาตรวจที่คลินิกเบาหวาน โรงพยาบาลพระจอมเกล้า จังหวัดเพชรบุรี ตั้งแต่วันที่ 1 กันยายน 2556 จนถึง วันที่ 31 สิงหาคม 2558 และใบบันทึกผลการตรวจระดับน้ำตาลในเลือดด้วยตนเอง ที่โรงพยาบาลส่งเสริมสุขภาพตำบล

ผลการศึกษา: มีผู้ป่วยเบาหวานจำนวน 90 ราย ที่สามารถนำข้อมูลมาวิเคราะห์ผลได้ โดยร้อยละ 70 เป็นเพศหญิง อายุเฉลี่ย 55.2 ± 10.2 ปี ได้รับการวินิจฉัยว่าเป็นเบาหวานก่อนได้รับยาฉีดอินซูลินเฉลี่ย 8.8 ± 4.8 ปี ยาลดระดับน้ำตาลในเลือดที่ผู้ป่วยส่วนใหญ่ได้รับคือ Sulfonylurea ร่วมกับ Metformin (ร้อยละ 46.7) ระดับน้ำตาลสะสม (HbA1c) ลดลงจากร้อยละ 9.2 ± 1.2 เหลือ 8.0 ± 1.2 และ 7.8 ± 1.3 ที่เดือนที่ 3 และ 6 ตามลำดับ เมื่อสิ้นสุดการศึกษามีผู้ป่วยที่มีระดับน้ำตาลสะสมเป้าหมายน้อยกว่าหรือเท่ากับร้อยละ 7 จำนวน 18 คน (ร้อยละ 20) โดยขนาดยาฉีดอินซูลินเพิ่มขึ้นจากขนาดเฉลี่ยเริ่มต้น 7.9 ± 1.6 ยูนิตต่อวัน ไปเป็น 15.2 ยูนิต

ต่อวัน ที่เดือนที่ 6 ในขณะที่น้ำหนักเฉลี่ยเพิ่มขึ้นเล็กน้อยจาก 71.5 ± 15.0 กิโลกรัม เป็น 72.5 ± 10.5 กิโลกรัม ผู้ป่วยให้ความร่วมมือดีในการตรวจระดับน้ำตาลในเลือดจากปลายนิ้ว (ร้อยละ 96.0) ผลการตรวจพบว่าระดับน้ำตาลในเลือดหลังได้รับยาฉีดอินซูลินอยู่ในเกณฑ์ที่กำหนดถึง 1,222 ครั้ง (ร้อยละ 61.5) ผลข้างเคียงที่พบคือ ภาวะน้ำตาลในเลือดต่ำชนิดที่เป็นเพียงเล็กน้อยมีรายงานเพียง 61 ครั้ง และไม่พบรายงานภาวะน้ำตาลในเลือดต่ำชนิดรุนแรง

สรุป: การเริ่มยาฉีดเบซัลอินซูลินก่อนนอนในผู้ป่วยเบาหวานชนิดที่ 2 ที่ไม่สามารถควบคุมระดับน้ำตาลได้แม้จะรับประทานยาลดน้ำตาลในขนาดสูง ร่วมกับการกำหนดให้ผู้ป่วยตรวจระดับน้ำตาลปลายนิ้วสัปดาห์ละ 1 ครั้ง และปรับขนาดยาฉีดอินซูลินได้ตามเกณฑ์ที่กำหนด สามารถช่วยให้ลดระดับน้ำตาลในเลือดของผู้ป่วยได้อย่างชัดเจนและไม่ทำให้เกิดภาวะน้ำตาลในเลือดต่ำชนิดรุนแรง

คำสำคัญ: การควบคุมระดับน้ำตาล การปรับยาฉีดด้วยตนเอง เบซัลอินซูลิน เบาหวานชนิดที่ 2

ABSTRACT

Plasma glucose of many patients with type 2 diabetes remains poorly controlled even with high doses of oral hypoglycemic agents. Initiation of basal insulin injection daily and self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) may improve target control of plasma glucose.

Objective: To evaluate the efficacy of initiation of basal insulin therapy with self-titration in addition to oral therapy in type 2 diabetic patients whose plasma glucose remains uncontrolled.

Material and method: This was a retrospective study of chart review of selected case files of outpatients who visited diabetes clinic at Phrachomklao Hospital from 1 September 2013 to 31 August 2015 and SMBG logbooks from District Health Promoting Hospitals (DHPH).

Results: A total of 90 patients with evaluable data were identified. The majority of patients were female (70%) with mean age and time after diagnosis of 55.2 ± 10.2 years and 8.8 ± 4.8 years, respectively. The majority of the oral hypoglycemic agents used were Sulfonylureas in combination with Metformin (46.7%). Initial HbA1c was on average 9.2 ± 1.2% which was reduced to 8.0 ± 1.2% and 7.8 ± 1.3% at 3 and 6 months, respectively. The HbA1c target of 7% or less was reached in 18 subjects (20%) at the end of the study. Insulin dosage was titrated from initial dose of 7.9 ± 1.6 unit/day to 15.2 unit/day after 6 months. Weight increased similarly from 71.5 ± 15.0 kg to 72.5 ± 10.5 kg. Patient adherence to the treatment protocol for fingertip blood glucose test was high (96.0%). Of the total number of capillary blood glucose tests after basal insulin initiation, 1,222 (61.5%) were within defined criteria of proper plasma glucose. A mere 61 episodes of mild hypoglycemia were reported. No severe hypoglycemia was found.

Conclusion: Initiation of basal insulin at bedtime in type 2 diabetic patients whose glucose levels remain uncontrolled despite high doses of oral hypoglycemic agents should be encouraged in

combination with weekly SMBG by fingertip sampling and self-titration of insulin doses. This practice markedly helps improve target control of plasma glucose without severe hypoglycemic episodes.

Keywords: Glycemic control, self-titration, basal insulin, type 2 diabetes

Introduction

To evaluate the efficacy of initiation of basal insulin therapy with self-titration in addition to oral therapy in type 2 diabetic patients. In 2013, there were 4,122 registered patients at diabetes clinic of Phrachomklao Hospital in Phetchaburi. Of these, 59.8% had HbA1c of greater than 7%, and 25% were at maximum recommended doses of oral hypoglycemic agents. The purpose of this present study is to evaluate the efficacy of bedtime basal insulin in addition to oral therapy along with the introduction of weekly SMBG and self-titration of insulin doses for optimal control of blood glucose and decreased risk of hypoglycemia.

Material and Method

This was an observational retrospective study of chart review of selected case files of outpatients. The study was approved by the institutional review board of Phrachomklao Hospital (IRB number 09/2015).

Study population

The study included type 2 diabetic patients ages between 30-75 years who had been diagnosed for more than 2 years, received treatment with oral hypoglycemic agents at high doses (defined as more than or equal to a half of maximum recommended dose) for more than 3 months and who had HbA1c levels >7%. Treatment with basal insulin (NPH or Glargine) was administered according to standard clinical practice at Phrachomklao Hospital from 1 September 2013 to 31 August 2015. Evaluable samples included patients who received basal insulin in continuation at diabetes clinic for at least 6 months. Exclusion criteria were current insulin usage, current medication that might have effect on SMBG such as steroid, previous admission because of hypo- or hyperglycemia, eGFR (CKD-EPI) less than 30 ml/min/1.73 m^2, previous stroke, previous ischemic heart disease, active infection including HIV and tuberculosis, pregnancy and anemia.

Study instruments

Basal insulin dose adjustment was based on the previous Treat-to-Target Trial.[1] Morning fasting plasma glucose (FPG) was monitored at least 8 hours after fasting once weekly. A forced titration schedule of basal insulin was used according to daily self-monitored capillary fasting blood glucose. The optimal glucose values were in the 100 - 150 mg/dl range, patient's were required to use the same doses. If glucose values were > 150 mg/dl or < 100 mg/dl, patients were allowed to either increase or decrease insulin dosage of 2 unit/day, respectively.

Before the study, DHPH personnel were trained and all glucose meters were calibrated by the distributors. Patients were also required to bring injection doses and weekly SMBG logbooks to their local DHPHs.

Data collection

Data collection was performed by co-authors no. 2 and 3, and was retrieved from patients' medical and SMBG record forms from DHPHs.

Statistical analysis

All the analyses were performed according to the Statistical Package for Social Science (SPSS 11.5; SPSS Science, Chicago, IL). Descriptive statistics was used for differences in general baseline characteristics. Changes of monitored HbA1c targets at months 0, 3 and 6 were evaluated by analysis of variance (ANOVA). Baseline characteristics and clinical parameters comparison between the achieved (HbA1c 7% or less) and the failed group (HbA1c more than 7%) was performed with the use of the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

Results

A total of 90 patients with evaluable data were identified. The majority of patients were female (70%) with mean age and time after diagnosis of 55.2 ± 10.2 years and 8.8 ± 4.8 years, respectively. Forty percent worked as employee. Subjects with primary school or lower education background comprised about half of all patients. One third of the patients had a low income of less than THB 5,000 per month, and 53.3% also had hypertension and hyperlipidemia in addition to diabetes. The majority of the oral hypoglycemic agents used were Sulfonylurea in combination with Metformin (46.7%). Initial HbA1c was on average 9.2 ± 1.2%. Seventy eight patients (86.7%) received insulin NPH and 12 (13.3%) patients received insulin glargine (Table 1 - 2).

Table 1 Baseline characteristics of patient population prior to initiation of basal insulin

Characteristics	Results (percentage)
Gender (Female : Male)	63 : 27
Age (years)	55.2 ± 10.2
Body weight (kilograms)	71.5 ± 15.0
Duration of diabetes (years)	8.8 ± 4.8
Occupations	
1. Worker	36 (40.0)
2. Business owner	24 (26.7)
3. Agriculturist	14 (15.5)
4. Retired	8 (8.9)
5. Government officer	8 (8.9)

Table 1 Baseline characteristics of patient population prior to initiation of basal insulin (con.)

Characteristics	Results (percentage)
Educational status	
Primary level or lower	48 (53.3)
Secondary level	32 (35.6)
Tertiary level	10 (11.1)
Income (Baht per month)	
Lower than 5,000	30 (33.3)
Between 5,001 and 10,000	42 (46.7)
Greater than 10,000	18 (20.0)
Concomitant diseases	
Hypertension and dyslipidemia	48 (53.3)
Dyslipidemia	14 (15.6)
Hypertension	15 (16.7)
Others	13 (14.4)
Medications	
SU + BG	42 (46.7)
SU+BG+TZD	35 (38.9)
SU+BG+TZD+AGI	7 (7.8)
Others	6 (6.6)

SU = Sulfonylurea, BG = Biguanide, TZD = Thiazolidinedione, AGI = α-glucosidase inhibitor

Table 2 Baseline clinical parameters of patient population

Clinical parameters	Mean ± S.D.
Systolic blood pressure (mmHg)	138.8 ± 18.0
Diastolic blood pressure (mmHg)	78.1 ± 12.0
Fasting plasma glucose (mg/dl)	196.0 ± 59.5
Hemoglobin HbA1c (%)	9.2 ± 1.2
Serum creatinine (mg/dl)	0.7 ± 0.3
Estimated glomerular filtration rate (ml/min/1.73 m^2)	100.4 ± 35.5
Total cholesterol (mg/dl)	179.0 ± 54.0
Triglyceride (mg/dl)	150.0 ± 95.5
High density lipoprotein (mg/dl)	49.5 ± 12.0
Low density lipoprotein (mg/dl)	100.8 ± 44.4

Insulin dosage and weight change

Mean daily doses for basal insulin were titrated from initial dose of 7.9 ± 1.6 unit/day to 15.2 unit/day after 6 months. At study exit, mean weight increased similarly from 71.5 ± 15.0 kg to 72.5 ± 10.5 kg (Table 3)

Table 3 Insulin titration schedule for average weight changes at each visit

	Visit No.						
	0	1	2	3	4	5	6
Dose (unit/day)	7.0 ± 1.7	8.8 ± 3.5	9.9 ± 5.7	12.0 ± 7.0	13.8 ± 10.0	15.8 ± 12.8	15.2 ± 10.6
Range (unit/day)	4 - 18	4 - 22	4 - 32	4 - 36	4 - 48	4 – 56	4 - 40
Body weight (kilograms)	71.5 ± 15.0	71.4 ± 15.8	71.9 ± 15.6	72.2 ± 16.0	72.6 ± 18.0	73.0 ± 16.0	72.5 ± 10.5

Glycemic response and treatment success

After 3 and 6 months of insulin initiation, mean HbA1c statistically significantly decreased from 9.2 ± 1.2% at baseline to 8.0 ± 1.2% ($p<0.01$) and 7.8 ± 1.3% ($p=0.01$), respectively. Mean FPG levels also decreased from 196.0 ± 59.5 mg/dl to 138.6 ± 41.4 and 135.8 ± 44.1 mg/dl, respectively. The HbA1c target of 7% or less was additionally reached in 14 (15.6%) and 18 (20.0%) subjects in 3 and 6 months respectively after initiation of insulin therapy (Table 4). There was no significant between-group difference in any of the characteristics listed in table 1 and 2 ($p > 0.05$) except for HbA1c ($p < 0.01$) (Table 5).

Table 4 HbA1c values and number of subjects achieving HbA1c of 7% or less at 0, 3 and 6 months

	Baseline	3rd month	6th month
Mean HbA1c (%) ± standard deviation	9.2 ± 1.2	8.0 ± 1.2	7.8 ± 1.3
Subjects achieving HbA1c 7% or less (%)	0	14 (15.6)	18 (20.0)

Table 5 Baseline HbA1c of the achieved group (7% or less) and the failed group (more than 7%)

Group	Baseline HbA1c	No. of patients
Achieved group	8.3 ± 0.9%	18
Failed group	9.4 ± 1.4%	72
Total	9.2 ± 1.2%	90

Self-monitoring of blood glucose

In this study subjects were asked to test glucose levels once weekly. Among these patients, only 2 (2.2%) patients had a home device for self-monitoring of glucose using fingertip blood samples. The rest of the subjects (N=88) were required to visit nearby DHPHs or diabetes clinic at Phrachomklao Hospital.

Most subjects complied with weekly SMBG schedule. Patient adherence to doctors' order for blood sugar measurements was high 96.0% (1,108 of total 1,987 tests). Of the total number of capillary blood glucose tests after basal insulin initiation, 1,222 (61.5%) were within pre-defined criteria for proper plasma glucose levels, whereas 566 (28.5%) and 199 (10.0%) were higher and lower than reference concentrations, respectively (Table 6).

Patients whose glucose values were higher than 150 mg/dl were allowed to titrate insulin dosage up for another 2 unit/day. There were 566 events of blood glucose measurements that were higher than the threshold, however, records showed that the patients did upward titration in 407 events (71.9%) only. Data analysis indicated that 80.8% of the patients did increase insulin doses in the first three months whereas only 65.9% followed the same instruction in the next three months (Table 7). The reasons for this discrepancy are shown below.

1. Patients continued upward titration for several consecutive weeks but failed to achieve target, and, therefore, believed further titration would result in hypoglycemia.

2. Patients felt that glucose levels were slightly higher than the threshold (151 - 160 mg/dl) and continued the same dosage.

3. Patients previously experienced episodes of hypoglycemia.

Table 6 Patient compliance with SMBG and self-titration guideline

	No. of tests (percentage)
No. of SMBG tests ordered	2,070 (100)
No. of actual tests	1,987 (96.0)
Results of plasma glucose from SMBG	
1. Within proper pre-defined threshold	1,222 (61.5)
2. Higher than pre-defined threshold	566 (28.5)
3. Lower than pre-defined threshold	199 (10.0)

Table 7 Patient compliance with self-titration of insulin dosage when SMGB values were higher than pre-defined threshold

Period (month)	Self-titration/SMBG values higher than pre-defined threshold (times)	Percentage
1^{st} -3^{rd}	185 / 229	80.8
4^{th} -6^{th}	222 / 337	65.9

Treatment-related side effects and management

Hypoglycemia

Since most subjects in this study had no glucose meter in their possession, episodes of hypoglycemia were, therefore, collected and arbitrarily defined by patients' self-report of recovering from symptoms that might be related to hypoglycemia after they had consumed meals, sugared drink or fruits, etc. Thirty six patients (40.0%) had 61 events of daytime hypoglycemia (symptom that occurred after breakfast to bedtime insulin injection) whereas 13 (14.4%) patients had documented 14 nocturnal hypoglycemia (symptom that occurred after bedtime insulin injection to before the next breakfast). These were mostly due to low food intake, but one particular event was due to inadvertent overdose of insulin injection for an extra 2 unit (a 10 unit was filled instead of 8 unit as a result of FPG measurement of 160 mg/dl, patient was originally on 6 unit). No severe hypoglycemia was found in this study.

Two particular subjects were withdrawn from insulin injections at 3 months due to nocturnal hypoglycemia even with low dose (4 unit/day). Insulin dose was discontinued with continued weekly SMBG.

Edema

Thirty five patients were having triple therapy with Sulfonylurea, Metformin, and

Pioglitazone prior to the period of the study. After initiation of insulin therapy, 3 patients developed generalized edema and 4 - 7 kg increase in weight. Pioglitazone was subsequently discontinued.

Discussion

In consistence with previous studies, the presented results indicate that injection of 0.1 unit/kg basal insulin at bedtime added to oral therapy and once weekly fasting glucose test to guide dosage adjustment of basal insulin can clearly improve HbA1c target.[2 - 5] However, the 20% success rate of $\leq$ 7% HbA1c in this study as compared with 40-60% in others may be due to the following reasons.

1. The differences in the frequency of fingertip SMBG: Other studies provided glucose meters for all subjects. Patients were also requested to perform daily finger-stick capillary blood glucose monitoring.[2 - 5] Therefore, close monitoring of changes in glucose levels allowed for proper and better planning for behavioral and insulin adjustment.[6]

2. The frequency of insulin dosage adjustment: The INSIGHT[4] study required daily upward titration of 1 unit of insulin until the glucose target was reached. Hermansen et al[5] used average records of plasma glucose from 3 consecutive days for insulin titration. In study conducted by Riddle MC et al[2] insulin dosage was titrated weekly according to daily self-monitored capillary fasting blood glucose. The approach helped informed patients to be aware of daily plasma glucose for their behavioral motivation and adjustment such as in modification of diet and exercise in the normalization of blood glucose levels.

3. The FPG target: Most studies set fasting blood glucose of < 100 mg/dl.[2 - 5]

4. The threshold for insulin dosage adjustment: For every 20 mg/dl of fasting capillary blood glucose that was higher than the goals, insulin doses in most studies were increased 1-10 unit each.[2 - 5] The advantage of this approach was that the patients must be well-informed with titration scheme and have the capability and competency in dealing with adverse effects, particularly hypoglycemia.

5. Patient compliance in insulin dosage adjustment: In most studies, most subjects (>90%) adhere to titration schedule.[2 - 4] However, in the present study 71.9% of the patients adhered to the protocol due to concerns from both patients and caretakers. In addition, medical staffs that provided blood glucose tests at local DHPHs should be reinforced for the understanding and consistency of the protocol to increase patients' confidence and trust.

The authors found that the only difference between the achieved group and the failed group was baseline HbA1c (table 5). This is consistent with the study of Dale J et al[7] which patients who achieved target HbA1c also had lower HbA1c at baseline after 3 years follow-up.

The adverse effect of daytime hypoglycemia in this study was comparable with those in Lee P et al[8] (40.0% vs. 41.0%, respectively). Nocturnal

hypoglycemia from the present study, however, was evidently lower (14.4% vs. 34.0%). Key factors attributable to lower incidence of nocturnal hypoglycemia were insulin dosages, fasting capillary blood glucose target, and frequency of dose adjustment. The lower rate of nocturnal hypoglycemia in this study was similar to that of the INITIATE study (10 - 13%) despite mean insulin dose was up to 56 - 62 unit/day at the end of the study.[3] This was probably due to effective intervention in INITIATE study by systematic and regular patient monitoring management through phone calls, as well as a remote patient monitoring that allowed real time blood glucose results via internet access while talking with patients. During the call, the nursing staffs reviewed patient's information and encouraged self-adjustment of insulin dose, and asked for possible undesirable effects, and provided immediate solutions to the problems.

The benefits of adding pioglitazone to an insulin regimen was also explored, especially in patients with insulin resistance but at the cost of increased edema and weight gain.[9] The PROactive study suggested that patients who developed edema or weight gain after receiving pioglitazone should not be treated with pioglitazone in combination with insulin.[10] Therefore, to prevent possible non-compliance and reduce patient's concern regarding adverse effects associated with pioglitazone, health care professionals should inform the patients and report such events to doctors for appropriate management.Key interventions associated with good glycemic control include:

1. Information given to the patients from all parties including doctor, nurse, and pharmacist must all be correct and in total consistency so the patient could rely on.

2. Role of patient participation in self-care and self-monitoring of glycemic control at home for proper adjustment of insulin dosage either by the patient or caretaker.

3. Telemonitoring intervention through telephone calls for consultation and follow-up, especially in early phase of initial treatment when inexperienced patient and caretaker may be unsure and, therefore, reluctant to adjust insulin doses because of fear of hypoglycemia. This also alleviates patient's concern by allowing phone contact for more information and psychological support.

This study is not without limitations. The design was retrospective in nature; hence, no control group was included. The poor compliance (28.1%) with the study tool, the titration schedule for insulin dose adjustment, was probably associated with concern in hypoglycemic side effect. A better study design in providing education and support to lessen such concern plus a development of effective and easy access monitoring system may help fine tune the future study.

Conclusion

Bedtime basal insulin injections in type 2 diabetic patients whose blood sugar levels remain poorly controlled even at high doses of oral hypoglycemic agents in conjunction with weekly fingertip SMBG, and self-adjustment of insulin

dose using simple titration scheme can clearly help improve glycemic control without significant increase in hypoglycemia. The presented study provides the evidence and proof of concept that this is a particularly useful practice because it is associated with low incidence of hypoglycemia and weight gain that are of concerns for insulin injections. To substantiate and extend the technique into clinical practice, the team of physicians, nurses, pharmacists, and caretakers in addition to the patient must be specifically trained in the integrated treatment of patients with diabetes in a community hospital or in building a network of diabetes care among DHPHs.

Suggestion from research finding

In patients with HbA1c less than 8.3%, a combination of oral hypoglycemic agents and basal insulin often effectively controls glucose levels.

Therapy with basal insulin in combination with capillary blood glucose (finger prick) monitoring and appropriate titration scheme can help patients achieve glycemic target.

Suggestion from research finding

Simplified titration scheme for dose adjustment of basal insulin injection appears to increase patient's acceptance and improve dose titration. The weekly fingertip blood glucose test at local DHPHs may serve as an alternative way for glucose monitoring for patients who are unable to afford glucose meter.

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