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Full Length Research Paper

Comparison of the glycemic control of insulin and triple oral therapy in type 2 diabetes mellitus

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To compare the glycemic control of triple oral therapy with sulfonylurea, metformin and acarbose with insulin in type 2 diabetes mellitus patients. This was a prospective observational study, carried out in Sardjito Hospital in Yogyakarta Indonesia, from May 2007 - September 2008. The target population in patients diagnosed with type 2 diabetes who failed with oral antidiabetic medications. At baseline and at 3 -month intervals, level of HbA_{1C}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), hypoglycemic episodes, and adverse events were evaluated. Test for differences between the two groups were performed by Chi-Square test for categorical variables and by independent-samples t-test for continuous variables. Paired t-test was performed for pre-post measurements. All tests were performed using a two-tailed test at a significance level of 0.05. One hundred and fifthteen patients (58 men and 57 women), aged 62.35 ± 8.88, and diabetes duration of 12.53 ± 6.97 years were studied. Over the 6 - month treatment period, HbA_{1c} levels decreased from 8.85 ± 2.02 to 8.33 ± 1.94% with insulin group (P = 0.011) and increased from 8.08 ± 1.89 to 8.73 ± 2.37% with triple oral therapy (P = 0.041). FPG and PPG levels decreased from 169.42 - 138.44 mg/dl (P = 0.002) and 238.26 - 197.97 mg/dl (P = 0.001) with insulin and increased from 160.39 - 170.71 mg/dl (P = 0.183) and 210.31 - 218.67 mg/dl (P = 0.458) with triple oral therapy, respectively. Addition of insulin in poorly controlled type 2 diabetic patients on metformin/sulfonylurea achieved a significantly greater reduction in HbA_{1c}, fasting plasma glucose, and postprandial plasma glucose versus those treated with sulfonylurea, metformin, and acarbose.

Key words: Insulin, triple oral therapy, glycemic effect, type 2 diabetes mellitus, Indonesia.

INTRODUCTION

Control of glycemia is a priority in diabetes management, and is reflected in target values for HbA_{1c} level endorsed by professional organizations. The glycemic goal recommended by the American diabetes association, selected on the basis of practicality and the projected reduction in complications over time is, in general, an HbA_{1c} level of < 7% (Nathan et al., 2009). The American Diabetes Association (ADA) recommended a goal of HbA_{1c} < 6.0% in individuals to the extent that, it can be achieved without such adverse effects as hypoglycemia, with a population goal of < 7.0% (American Diabetes Association, 2009).

Type 2 diabetes is a progressive disease and patients are likely to require the addition of glucose- lowering medications over time (Nathan et al., 2009) . As the disease progresses, many patients with type 2 diabetes will eventually unable to adequately achieve or maintain glycemic control, if neither monotherapy nor combination oral therapies are given. The reason for diminishing antihyperglycemic effects with oral agents over time is multifactorial and includes progressive loss of -cell function, co-morbidities, lifestyle factors, and glucotoxicity (Kuritzky, 2006). For patients with type 2 diabetes whose glucose control has deteriorated when on oral hypoglycemic agents, if treated with intensive insulin therapy, they gain, the improvement of glycemia

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associated with improved insulin secretion and action (Ryan et al., 2004). In general, insulin is the most cost-effective intervention in patients who have not obtained their glycemic goal although taking 2 or more oral agents (Mooradian et al., 2005).

Despite poor glycemic control on average in the general population of patients with type 2 diabetes, there is often a refuse to initiate insulin therapy because of concerns from both physicians and patients (Barnett et al., 2006). The decision to initiate insulin therapy ultimately belongs to the patient. Common barriers among patients include beliefs and negative stigma that insulin is a personal failure, that insulin is not effective, insulin causes complications or even death, or that insulin injections are painful, as well as fear of hypoglycemia, loss of independence, weight gain, and cost (Funnel, 2008). In the treatment of type 2 diabetes with insulin, refuse to inject oneself and fear of weight gain or hypoglycemia may hinder compliance (White et al., 2003). Oral therapy (often using combinations) has been frequently prescribed for type 2 diabetes (because many subjects have a fear of needles that may affect compliance with insulin therapy) (Schwartz et al., 2003). A patient treated with three oral drugs is subjected to an additive risk of adverse effects, and dose adjustments may become complex. In addition, there are cost considerations of adding a second or third class of oral antidiabetic agent to a therapeutic regimen (Schwartz et al., 2003; Rosenstock et al., 2006). Therefore, this study is conducted with the aim to compare the effectiveness, safety, and cost of two possible approaches for managing failure of combination therapy with oral medication: 1) switching treatment to insulin or, 2) combination of therapy with oral medication (sulfonylurea, metformin, and acarbose) for patient who refuses to initiate insulin.

METHODS

This was a prospective observational study conducted in Sardjito Hospital in Indonesia. Patients included were based on the following criteria: subjects > 18 years of age with type 2 diabetes and failed with oral antidiabetic medication, HbA1c levels between 7.5 and 10.5%, and fasting blood glucose (FBG) levels > 130 mg/dl (> 6.7 mmol/l). Subjects were excluded for any of the following criteria: evidence of renal disease (elevated creatinine > 1.4 mg/dl) or a liver disease (alanin aminotransferase > 2.5 times the upper limit of normal).

Study medications and treatments

Forty nine of the patients received sulfonylurea, metformin, and acarbose combinations. Slightly, more than half of the patients (55.1%) received sulfonylurea were taking gliquidone; and 44.9% were taking glyclazide. Patients, who were taking glyclazide, also took 80 mg/d - 400 mg/d or 60 mg/d - 120 mg/d gliquidone. During the screening and titration phase, patients not on the maximum metformin dose were titrated to 2,550 mg/day. Patients who were on acarbose therapy were taking 150 - 300 mg/d. All subjects in insulin group received a premixed insulin twice daily subcutaneous injection before breakfast and at bedtime. The dose was titrated monthly according to fasting plasma glucose levels (FPG) and postprandial plasma glucose (PPG). Subjects were seen in the department of endocrinology Sardjito hospital Yogyakarta “between” May 2007 till September, 2008.

Outcome measures

The primary end point was the reduction in HbA_{1c} values from baseline to the end of the study. Values for HbA_{1c} profiles were obtained at study baseline in 3 and 6 month. Secondary objectives included assessment of hypoglycemia profile, changes in fasting plasma glucose and postprandial plasma glucose, proportion of patients achieving HbA_{1c} 7%, and cost of therapy. Values for fasting plasma glucose and postprandial plasma glucose were observed monthly.

Safety assessment

Safety was assessed by physical examination findings, clinical laboratory evaluation, and reporting of adverse events and hypoglycemic episodes. Minor hypoglycemic episodes were defined as blood glucose values of < 56 mg/dl with or without symptoms that were self-treated. Major hypoglycemia was an episode with neurological symptoms consistent with hypoglycemia that required assistance and had a plasma glucose value of < 56 mg/dl.

Cost analysis

The economic costs of glycemic control were compared by combining selected measures of resource use with unit-cost estimates. Resource measures included diabetes intervention, syringes for insulin, glucose testing for groups, laboratory evaluation, and drug treatment for complications. These costs were estimated using average wholesale prices expressed in 2008 U.S. dollars (9,500 rupiahs = 1 USD) and were based on the numbers actually dispensed.

Statistical methods

Descriptive statistics, including means ± SD and median (range) for continuous variable and n (%) for categorical variables, were used to compare the study groups with respect to demographic and disease characteristics. Test for differences between the two groups (group 1 with insulin treatments and group 2 with combination of antidiabetic oral medications) were performed by Chi-square test for categorical variables and by independent-samples t-test for continuous variables. Differences between values at the start of the study and at 6 months were tested using paired t-test. All tests were performed using a two-tailed test at a significance level of 0.05.

RESULTS

Demographic characteristics and baseline values of patients are summarized in Table 1. The treatment groups were generally comparable for variables such as duration of diabetes, age, fasting plasma glucose, and postprandial plasma glucose. Over the 6-month treatment period, HbA_{1c} levels decreased significantly from 8.85 ± 2.02 - 8.33 ± 1.94% with insulin group (p= 0.011) and

Table 1. Baseline characteristics of patients.

Therapy	Insulin	Triple oral	p
n	66	49	
Age (years)	61.98± 9.61	60.88± 12.33	p = 0.613*
Men/Women	36/30 (54.55/45.45)	22/27 (44.90/55.10)	p = 0.308**
Diabetes duration (years)	12.98± 7.57	11.92 ± 6.09	p = 0.420*
HbA1c (%)	8.85 ± 2.02	8.08± 1.89	p = 0.041*
FPG (mg/dl)	169.42± 72.84	160.39 ± 60.24	p = 0.481*

Data are means ± SD, **t* test** Mann-Whitney test.

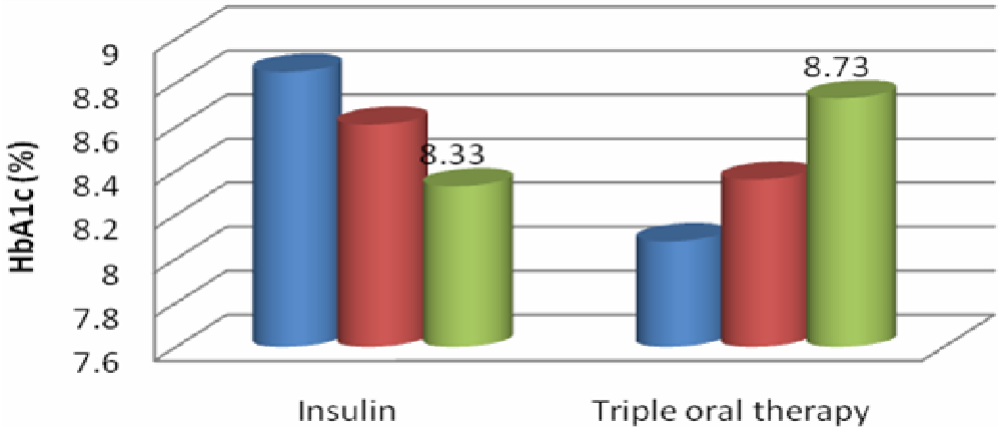

Figure 1. HbA1c levels (%) from baseline to end point.

increased significantly from 8.08 ± 1.89 - 8.73 ± 2.37% with triple oral therapy (p= 0.041) (Figure 1) . At 6-month, no statistically significant difference in HbA_{1c} between the two groups was observed (final value at month 6 were 8.33 ± 1.94% for insulin and 8.73 ± 2.37% for triple oral therapy [p= 0.325]). The distribution of HbA_{1c} values at study end was comparable in both treatment groups. The percentage of subjects achieving HbA_{1c} < 8% was 52% for insulin and 47% for triple oral therapy. Thirty-two percent and 27% of subjects were able to reach targeted HbA_{1c} values of < 7% in the insulin and triple oral therapy groups, respectively.

Fasting plasma glucose (FPG) levels decreased significantly from 169.42 - 138.44 mg/dl with insulin (p= 0.002) and increased from 160.39 - 170.71 mg/dl with triple oral therapy, but was not significant (p= 0.183). At the end of the study, 39.39% of insulin group patients had reductions of FPG by > 40 mg/dl, whereas only 16.33% of triple oral therapy group patients had a glycemic response of this magnitude. Final postprandial plasma glucose (PPG) values were lower for insulin therapy than triple oral therapy. PPG levels decreased significantly from 238.26 - 197.97 mg/dl with insulin (p= 0.001) and increased from 210.31 - 218.67 mg/dl with triple oral therapy, but was not significant (p = 0.458).

There was one patient in either treatment group who experienced major hypoglycemic episodes. Minor hypoglycemic episodes occurred in 36.36% of the patients of the insulin group compared with 28.57% of the patients in the triple oral therapy group. Minor episodes (symptoms with confirmed blood glucose < 56 mg/dL, no assistance required) was once in both treatment groups (1 of 14 episodes in triple oral therapy and 1 of 24 episodes in the insulin group). There were 12 events (24.49%) associated with symptoms only (without confirmed blood glucose reading) for triple oral therapy and 22 events (33.33%) in the insulin group. The most frequent adverse event in both groups was gastrointestinal disturbance (28.57% of insulin vs. 61.11% of oral triple therapy group). Adverse events occurring in both group included flatulence, abdominal discomfort, diarrhoea, and nausea.

The total cost of glycemic control was $305 in the insulin group and $242 in the triple oral therapy group. The mean cost of diabetes intervention was higher in the insulin group ($204 ± $72) than in triple oral therapy group ($109 ± $36). However, the cost for complications was higher in triple oral therapy group ($107) than in

insulin group ($78).

DISCUSSION

Recommendations for monitoring glycemic control include daily self-monitoring of blood glucose levels and periodic measurement of glycated haemoglobin. The glycated haemoglobin assesses the long-term adequacy of the treatment in meeting glycemic goals (Mooradian et al., 2006). Only one-third of subjects in either treatment were able to achieve an HbA_{1c} value below 7%. A few subject in both treatment groups were able to achieved near normal HbA_{1c} levels. Limitation to achieving normal HbA_{1c} may be due to the severity of diabetes or physiology such that, certain classes of antidiabetic agents are less effective, fear of hypoglycemia by either subject or physician limiting further aggressive control, and non-compliance with recommended regimen (Schwartz et al., 2003). Treatment compliance may suffer if polypharmacy is involved in glycemic control with oral medications for comorbid conditions of type 2 diabetes (Winocour, 2002)

Diabetes is a progressive disease, and while oral antidiabetics may initially achieve a level of glycemic control, most patients will eventually require insulin therapy (Cook et al., 2005). In this study, mean HbA_{1c} rose from 8.08 - 8.7% for triple oral therapy group. -cell deterioration occurs progressively over many years in type 2 diabetes mellitus and is part of the natural history of the disease. When -cell secretor capacity falls below the requirements for insulin to maintain glycemic level, even in the presence of oral agents, exogenous insulin is required. A patient with -failure on optimal doses of oral agents may present with the following profile: fasting blood glucose levels >140 mg/dL (7.7 mmol/L) on more than one occasion, postprandial glucose levels > 180 mg/dL (9.9 mmol/L) on more than one occasion, and HbA_{1c} levels at least 2% higher than the upper limit of normal. Such patients need exogenous insulin supple-mentation because they no longer adequately respond to oral antidiabetic medications (Gavin, 2007). When A_{1c} is close to the treatment goal (< 8.0%), addition of a third oral agent could be considered; however, this approach is relatively more costly and potentially not as effective in lowering glycemia compared with adding or intensifying insulin (Nathan et al., 2006) . Because the addition of a third oral agent is unlikely to decrease HbA_{1c} levels by > 1.5 - 1.7%, insulin is often the only means of lowering HbA_{1c} to target levels when the baseline is > 8.5 - 9.0% (Riddle et al., 2003). To achieve glycemic control, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommended the early use of basal insulin (with or without oral antidiabetic agents) or basal bolus insulin therapy (premixed insulin preparations are recommended for those who require additional insulin during meals). The AACE and ACE guidelines acknowledge the effectiveness of insulin therapy, the decreased risk of hypoglycemia, and the simplified therapy with minimal daily injections associated with insulin analogs (Spellman, 2007). In many patients, basal insulin alone, when added to oral antidiabetics, is sufficient to achieve glucose goals. Due to the natural history of type 2 diabetes, many patients eventually progress to a level of insulin deficiency that requires initiation of prandial insulin in addition to basal insulin (Edelman et al., 2007).

In our study, the regimen of premix-insulin formulation showed a limited ability to achieve targets for glycated haemoglobin (32%). Premixed insulin is more convenient and less prone to errors in dosing but limit flexibility in diet and lifestyle (Mooradian et al., 2006). Janka et al. (2007) reported that in patients with type 2 diabetes poorly controlled on oral therapy, adding a single injection of insulin glargine to glimepiride and metformin can provide more effective glycemic control than stopping oral antidiabetic drugs (OADs) and starting twice-daily pre-mixed insulin. The glargine plus oral antidiabetic regimen enabled nearly 50% of patients to reach HbA_{1c} 7% without experiencing nocturnal hypoglycemia, whereas < 30% of patients on 70/30 insulin achieved target HbA_{1c} 7% in the absence of nocturnal hypoglycemia. Patients with type 2 diabetes on split-mixed or premixed twice-daily insulin regimens who are unable to achieve or maintain target HbA_{1c} goals may also benefit from conversion to basal-prandial insulin regimens. Because the timing of the dose is fixed in such regimens, they may be ineffective in patients with an unstable daily routine (De Witt and Hirsch, 2003).

The numbers of hypoglycemic events were lower in the triple oral therapy group than in the insulin group. The lower rate of hypoglycemia with the triple oral therapy regimen is of particular interest because fear of hypoglycemia remains one of the key obstacles to both initiating and optimizing insulin therapy (Korythowski, 2002) . The difficulty of managing multiple injections and the associated requirement for multiple daily glucose measurements is another barrier to achieving recom-mended glycemic level targets (Celalu, 2002). Although hypoglycemia is a possibility with any form of antidiabetic therapy, the choice of therapy influences the risk (Janka et al., 2005). The goal of insulin therapy is to mimic normal insulin levels throughout the day as closely as possible, thereby preventing preprandial glucose troughs and postprandial glucose peaks. Insulin analogs have made the potential for delivery of near -physiologic insulin therapy (De Witt and Hirsch, 2003). The basal insulin injection is intended to provide a steady, low- level, ideally with once-daily administration, as well as to prevent hypoglycemia between meals. The bolus (or prandial) insulin injection is taken shortly before meals to prevent postprandial glucose peaks. Of these treatment options, combining once-daily basal insulin with bolus insulin before meals can provide intensive, near-physiologic

delivery of insulin to help patients achieve glycemic goals while minimizing hypoglycemia. Near-physiologic insulin therapy with a basal bolus regimen also provides flexibility with respect to changing meal times, skipping meals, activity and adjusting doses (Spellman, 2007).

The incidence of gastrointestinal disturbance (flatulence, nausea, diarrhoea, and abdominal pain) associated with metformin was lower for the insulin groups (7.58%) than for the triple oral drugs (34.69%).

Gastrointestinal side effects of metformin are common but can minimize by slow dosage titration (Kimmel and Inzucchi, 2005). Many patients fail to tolerate maximum doses due to gastrointestinal side effects. Acarbose is rarely used in the UK due to common side effects such as flatulence and diarrhoea, but it used regularly in other countries such as Japan (Srinivasan et al., 2008). There were 67.35% of patients in triple oral drugs group and 18.18% of patients in the insulin group who experienced side effects. Abdominal discomfort occurred in 16.33% of the patients of the triple oral therapy group compared with 4.55% of the patients in the insulin group. The most frequent adverse event in both groups was flatulence (46.94% of triple oral group vs. 13.64% of the insulin group). Diarrhoea occurred in 4.08% of the patients of the triple oral therapy group.

The total cost of glycemic control was $305 in the insulin group and $242 in the triple oral therapy group. The mean cost of diabetes intervention was higher in the insulin group ($204 ± $72) than in triple oral therapy group ($109 ± $36). However, the cost for complications was higher in triple oral therapy group ($107) than in insulin group ($78). Schwartz et al. (2003) have reported the regimen of insulin 70/30 mix plus metformin showed substantial cost savings relative to a triple oral therapy approach, whereas the glycemic improvement and safety findings of the two treatment approaches were largely similar. Other trials demonstrate a cost advantage with add-on insulin, as well as the potential for superior glycemic control only limited by hypoglycemia (Riddle et al., 2003).

Rosenstock et al (2006) demonstrated that low-dose insulin glargine combined with a sulfonylurea and metformin resulted in similar A1C improvements except for greater reductions in A1C when baseline was 9.5% compared with add-on maximum-dose rosiglitazone. Further, insulin glargine was associated with more hypoglycemia but less weight gain, no edema, and salutary lipid changes at a lower cost of therapy. The annual mean direct cost for each person with diabetes was estimated to be Pakistani rupees 11,580 (US$ 197). Khowaja et al. (2007) compared the mode of treatment with direct cost, they found significant difference ($p < 0.001$) between those with non-pharmacological lifestyle management to oral medication and insulin, while indirect cost was not significant ($p = 0.950$). Patient education is particularly important in overcoming reluctance to insulin therapy (Bethel and Feinglos, 2005). The patient is the key player in the diabetes care team and should be trained to prevent and treat hypoglycemia, as well as adjust medications with the guidance of health care providers to achieve glycemic goals (Nathan et al., 2006).

Patients need not only initial education about insulin but also continued to follow up and support it, to obtain diabetes self- care behaviours. Office staff can be helpful in supporting and reinforcing patients' self-management efforts related to insulin therapy, particularly in the early phases, when doses are being titrated frequently. Establishing a plan with patients to following up on blood glucose results by telephone or in person will also facilitate the appropriate dose of insulin and its effectiveness (Funnel, 2008).

Conclusion

Addition of insulin in poorly controlled type 2 diabetic patients on metformin and sulfonylurea achieved a significantly greater reduction in HbA_{1c}, fasting plasma glucose, and postprandial plasma glucose versus those treated with sulfonylurea, metformin, and acarbose. Compared with triple oral therapy, insulin was associated with more hypoglycemia but fewer adverse reactions.

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