THE EFFECTIVENESS OF INSULIN COMBINATION THERAPY IN TYPE 2 DIABETES MELLITUS HOSPITALIZED PATIENTS

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ABSTRACT
The combination of Neutral Protamine Hagedorn (NPH) with Regular Human Insulin (RHI) and Glargine with Aspart insulin are two types of insulin combinations most frequently used to treat patients with type 2 diabetes mellitus who are hospitalized in the Sanglah Central General Hospital. This research has been conducted to compare the ability of these two insulin combinations to lower Blood Glucose Levels as well as to determine the percentage of the incidence of side effects. This research applied the observational analytic design (cohort). The characteristics of the patients and the incidence of side effects were analyzed descriptively while the data on blood glucose levels were analyzed evaluatively using paired T-test and independent T-test methods at 95% of confidence level. The results of the evaluative analysis showed that both combinations can reduce the Fasting Blood Glucose Levels, Postprandial Blood Glucose Levels and Random Blood Glucose Levels significantly, where the combination of Glargine insulin and Aspart insulin showed a greater reduction in blood sugar glucose level compared to the combination of NPH with RHI. The combination of NPH with RHI caused a greater incidence level of hypoglycemia but causes a lower incidence level of edema than the combination of Glargine with Aspart did. There’s no allergies found both from two types of insulin combinations.

Keywords: type 2 diabetes mellitus, blood glucose level, NPH, RHI, Glargine, Aspart, side effect.
INTRODUCTION

Diabetes mellitus (DM) belongs to a group of metabolic diseases with the characteristics of hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action, or both (Dipiro et al., 2009; PERKENI, 2011). Approximately 90-95% of DM patients suffered from type 2 diabetes mellitus, and generally occurs due to a combination of insulin resistance and reduced insulin secretion because of the pancreatic beta cell hypofunction (Tjay and Rahardja, 2007; AACE, 2011).

Although oral antidiabetic drug can actually be used to lower and control blood glucose levels, however, in type 2 diabetic patients who had fasting blood glucose levels > 250 mg / dL and blood glucose levels as > 300 mg / dL (Garty et al., 2006), and for those who had worsening insulin deficiency and newly diagnosed patients with severe hyperglycemia, the therapy treatment can be directly using an insulin as a first line therapy. Blood glucose control should be able to mimic the physiological insulin secretion pattern, that is basal and prandial insulin secretion (Soegondo et.al., 2006). Hamati (2011), showed that the combination of bolus insulin to basal insulin can result in better glycemic control and fewer variations in blood glucose levels. The combination of basal insulin and bolus insulin that is used as the first line therapy in Sanglah General Hospital, is the combination of Neutral Protamine Hagedorn insulin (NPH) with Regular Human Insulin (RHI) and the combination of Glargine with Aspart insulin. The combination of RHI with NPH insulin is used when the price becomes the main consideration. Meanwhile, the use of the combination of Glargine with Aspart insulin is because it can result in the better control of glycemia, blood glucose fluctuation and the incidence of hypoglycemia; and because it can result in lower possibility of weight gained (Hamati, 2011).

There has been no evidence-based research in Sanglah Hospital that compared the effectiveness of these two type insulin combinations. The effectiveness of insulin therapy is assessed by its ability to reduce blood glucose levels. The ability to reduce blood glucose levels can be measured by the achievement of the targeted fasting blood glucose levels, post-prandial blood glucose levels, and random blood glucose levels.

A medicine is expected to work effectively with minimal side effects. The absence of research that described the incidence of side effects, as a result of the use of these two type insulin combinations makes it necessary to conduct this study. The incidence of side effects is described by a percentage of side effects during the time the patients are hospitalized. Based
on the researches that have been conducted, insulin therapy may lead to hypoglycemia, lipodystrophy, weight gain, edema, changes in vision, infections, and immunological reactions (Klisic et. al, 2002; Calambokis et.al, 2004; Radermecker, 2007; Anonim, 2009; PERKENI, 2011). Side effects that will be examined in this study are hypoglycemia, edema, and allergic reactions.

MATERIAL and METHODS
a. Study Population and Data Administration
Random selection technique was used to select 30 patients, which has been confirmed passed the inclusions and exclusions during the period of 1 July to 31 December 2013. The inclusion criteria cover the patients in the age of 18 up to 65 years and the patients who agreed to participate in the study through informed consent. Where as exclusion criteria cover patients with pregnancy, patients given other drugs that may affect their blood glucose levels significantly such as dexamethasone, prednisolone, aspirin, paracetamol, buspiron, furosemide, spironolactone, and oral contraceptives, and patients with changes in their skin and or in their subcutaneous adipose tissue at the insulin injection area (such as lipohypertrophy, lipoatrophy, and infection) upon the hospital admission. The data were collected by the observational analytic method (cohort).

b. Statistical Analysis
The data concerning the characteristics of the patients and the incidence of side effects were analyzed descriptively while the data concerning blood glucose levels were analyzed evaluatively using paired T-test and independent T-test methods at 95% of confidence level.

RESULT
a. Characteristics of the Reasearch Subjects
The characteristics of the research subjects are distinguished by gender, age, length of stay and the insulin combination used. The distribution of diabetes mellitus type 2 by gender showed that the number of male patients is more than female, being the most affected while those patients aged 45 years and above, with a range of treatment time varies from 4 days to a maximum of 38 days, and the use of the combination of aspart insulin with glargine insulin for treating patients with type-II diabetes mellitus is more frequent than the use of the combination of NPH insulin with RHI (Table 1).
Table 1 Characteristics of the Research Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
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<tr>
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<tr>
<td>Total</td>
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<tr>
<td>Age:</td>
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</tr>
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<td>35-40</td>
<td>3</td>
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<tr>
<td>41-45</td>
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<tr>
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<td>61-65</td>
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<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Length of stay in hospital:</td>
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</tr>
<tr>
<td>4-8</td>
<td>12</td>
<td>40.00</td>
</tr>
<tr>
<td>9-13</td>
<td>6</td>
<td>20.00</td>
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<tr>
<td>14-18</td>
<td>4</td>
<td>13.33</td>
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<tr>
<td>19-23</td>
<td>4</td>
<td>13.33</td>
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<tr>
<td>24-28</td>
<td>1</td>
<td>3.33</td>
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<tr>
<td>29-33</td>
<td>2</td>
<td>6.67</td>
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<tr>
<td>34-38</td>
<td>1</td>
<td>3.33</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

The use of Insulin

<table>
<thead>
<tr>
<th>Insulin Combination</th>
<th>NPH-RHI</th>
<th>Glargine-Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH-RHI</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Glargine-Aspart</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

b. The Incidence of Side Effects

The combination of NPH with RHI leads to a greater incidence level of hypoglycemia but with a lower incidence level of edema compared to the combination of Glargine with Aspart. The use of these two types of insulin combinations does not cause allergies (Table 2).

Table 2 The Percentage of the Incidence of Side Effects

<table>
<thead>
<tr>
<th>Insulin Combination</th>
<th>NPH-RHI (%)</th>
<th>Glargine-Aspart (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Edema</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
c. The Ability in Reducing Blood Glucose Levels

The results showed that both combinations can reduce Fasting Blood Glucose Levels, Postprandial Blood Glucose Levels, and Random Blood Glucose Levels significantly where the combination of Glargine with Aspart showed a greater reduction than the combination of NPH with RHI (Table 3).

Table 3 The Comparison of Blood Glucose Levels in Type 2 Diabetes Mellitus Patients using NPH with RHI or Glargine with Aspart Combination

<table>
<thead>
<tr>
<th>Output Results</th>
<th>Fasting Blood Glucose Levels (mg/dL)</th>
<th>Postprandial Blood Glucose Levels (mg/dL)</th>
<th>Random Blood Glucose Levels (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPH-RHI</td>
<td>Glargine-Aspart</td>
<td>NPH-RHI</td>
</tr>
<tr>
<td>+SD before</td>
<td>237.14±76.225</td>
<td>261.38±54.284</td>
<td>264.21±85.045</td>
</tr>
<tr>
<td>+SD after</td>
<td>158.36±50.174</td>
<td>133.31±48.716</td>
<td>184.07±71.636</td>
</tr>
<tr>
<td>+SD reduction</td>
<td>78.79±45.967</td>
<td>128.06±64.269</td>
<td>80.14±49.564</td>
</tr>
<tr>
<td>Independent T test</td>
<td>0.024*</td>
<td>0.022*</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

R: Average values; SD: Standard Deviation

DISCUSSION

Hyperinsulinemia and insulin resistance can induced by obesity and lower levels of adiponectin (Hussein et al., 2010). Man had a greater possibility for being obese (Pinkney, 2001; Tatttarani, 2002; Rana et al., 2007), and in addition, men also have lower levels of adiponectin compared with women (Wever, 2001). The incidence of type 2 diabetes mellitus increases as the age increases; this is due to the combination of increased insulin resistance and function impairment of the pancreatic islet as a result of aging (Kirkman et al., 2012). As a result of the aging process, there is shrinkage of pancreatic beta cells and the progressive accumulation of amyloid in the vicinity. The remaining pancreatic beta cells are generally still active but lead to decreased insulin secretion and decreased sensitivity of receptors to insulin (Tjay and Rahardja, 2007). The age of 45 years and above is the productive range of age where people are very susceptible to stress. Stress does not only serve as one of the risk
factors causing the increase in blood glucose levels, but stress also results in irregular eating and activity patterns thus causing people with stress prone to obesity (Epel and Tanja, 2007).

To maintain stability and minimize fluctuations in blood glucose levels, research showed that a continuous glucose monitoring through hospitalization for approximately 5 days is needed (Martin, 2006; Fraze, 2010). Differences in length of stay are not only depending on the achievement of the targeted blood glucose levels, but also depending on the patients’ condition improved from the complications of diabetes or other diseases that are the main complaints on their admission to hospital.

The selection of the insulin combination is based on its action profile to work normally imitating the insulin secretion patterns in the body (Dipiro et. al, 2009; Hamaty, 2011). In comparison, the combination of Glargine with Aspart provides a faster onset of action with a longer duration of action so that it can better imitate the body’s normal insulin profile. This has become one of the basic considerations to the use of this type of the insulin combination in patients with type 2 diabetes mellitus in Sanglah Hospital.

The percentage of the incidence of hypoglycemia in the use of the combination of NPH insulin with RHI is greater than the combination of Glargine with Aspart. This is caused by the difference in their profiles. NPH insulin can lead to an increased risk of nocturnal hypoglycemia because NPH insulin has a peak action during the night which appears during about 4 up to 10 hours after an injection (Soegondo, 2006; Fowler, 2008; Dromgoole 2012). The long peak action of RHI as bolus insulin leads this insulin to cause an increased risk of delayed post-meal hypoglycemia (Soegondo; 2006; Dromgoole, 2007; Fowler, 2008, Katzung; 2011).

The insulin mechanism in causing edema involves the changes of vasomotor balance induced by the rapid changes in glycemic control (Sukandar 2009). These occurrences lead to the activation of the RAAS (Renin Angiotensin Aldosterone System). The activation this system can subsequently cause the retention of sodium and fluid which contributes to the onset of edema (DeFronzo, 1975; Klisic, 2002; Kalambokis, 2004; Hernawati, 2006). The absence of more specific research to distinguish the capability of these two types of insulin combinations gives rise to edema. However, the higher number of edema was found in the use of glargine with aspart combination, it is likely due to the faster onset and longer duration of the activity
of this insulin combination compared to the combination of NPH insulin with RHI; thus, the activities that contribute to the occurrence of edema will be higher.

Protamine added to the NPH insulin to produce long action can act as the allergen (Radermecker, 2002; Dromgoole, 2012). The characteristics of the allergen are also supposed to exist in both analogues insulin like Glargine and Aspart, because their amino acid sequence modifications brings new epitopes for the detection of immune system, which then potentially alter the antigenicity and immunogenicity of insulin (Radermecker, 2002). Although RHI is not an analogues insulin, and don’t have additional agents to prolong the activity, it is said that its immunogenicity properties are equivalent to aspart (Katzung, 2011). This generates, all insulin combination has a same chance for induce an allergic reaction. But in this research there’s no allergies finded both from two types of insulin combinations.

The combination of Glargine insulin with Aspart insulin that helps reduce Fasting Blood Glucose Levels greater than the combination of NPH insulin with RHI shows that the combination of Glargine insulin with Aspart insulin is better to balance blood glucose homeostasis during the time the patients are fasting. This could be because Glargine insulin acts as basal insulin with a longer duration of activity (11 up to 24 hours or longer) compared to NPH, which also acts as basal insulin in the combination of NPH insulin with RHI. The duration of activity/action of Glargine insulin that reaches 24 hours makes glargine insulin more able to control hepatic glucose production in patients compared to NPH insulin whose action duration only reaches 4 up to 12 hours (Katzung, 2011). According to the research by Colon et al. (2008) on the use of some types of insulin, it is showed that insulin therapy is successful in replacing basal insulin secretion that will also have a significant impact in decreasing Fasting Blood Glucose Levels. Naturally, the body secretes two kinds of insulin, which are basal and prandial insulin (Soegondo et. a.l, 2006). Basal insulin is released to control blood glucose levels each day while prandial insulin is secreted when the body receives food or when there is a rapid increase of glucose Mogensen, 2007; Wade et. al., 2008). The analysis results of Fasting Blood Glucose Levels will describe the secretion of basal insulin in the body so that good control of basal insulin in glargine insulin will certainly have a direct impact on the reduction of Fasting Blood Glucose Levels.

An increase in blood glucose levels will stimulate the pancreatic beta cells to secrete insulin. The body’s insulin secretion occurs in two phases where the first phase is often called the Acute Insulin Response Secretion (AISR). At this phase, insulin is rapidly secreted to cope
with the increase in blood glucose levels after the patient eats (Weyer, 2001). Therefore, in patients with type 2 diabetes mellitus who have insulin resistance, insulin is needed to work quickly to deal with this increase. According to the onset and peak of activity, aspart insulin that acts as bolus insulin, has an onset and can reach the peak of activity faster than the RHI. That’s make the combination of Aspart and Glargine can reduced Postprandial Blood Glucose Levels greater than NPH and RHI combination.

Random Blood Glucose Levels examination is affected by various factors such as the effects of food intake, physical activity and the effect of stress on the patients prior to the test of glucose levels. For example, patients who consume little fiber (more carbohydrates) prior to the test of blood glucose levels will tend to show the graphs rise higher as compared to the patients who consume more fiber foods before the test (Sukandar et. al., 2009). The study result conducted by Ciano et al. (2009) also mentions that, the consumption of foods low in carbohydrates and high in fiber in patients with type 2 diabetes mellitus will improve the control of blood glucose levels, improve insulin activity and even help reduce the risk of cardiovascular complications. In addition, the effect of the the limited space for physical activity in the hospital as well as psychological distress of the patients can be a factor causing a not maximum decrease in Random Blood Glucose Levels in patients after doing a test despite the fact that patients had been treated with insulin. Restrictions of movement and stress can trigger the accumulation of glucose and fatty substances levels in the body. This condition can certainly affect insulin therapy because the accumulating levels of glucose and fatty substances cause reduced insulin sensitivity (Tjay and Rahardja, 2008).

The insulin that plays a role here is the basal insulin. The greater ability from the combination of Glargine with Aspart, is due to the longer duration activity of Glargine as basal insulin and its steady activity profile, make better control of blood glucose level fluctuations than NPH with RHI combination.

CONCLUSION
Overall, the research subjects were dominantly male patients, more patients with the age > 45 years and with longer hospitalization period 4 up to 8 days. The combination of NPH with RHI induced a greater incidence of hypoglycemia but with a lower incidence of edema compared to the combination of Glargine with Aspart. The use either of both types of insulin combinations did not cause any allergies. The results showed that both combinations can
reduce Fasting Blood Glucose Levels, Postprandial Blood Glucose Levels and Random Blood Glucose Levels significantly where the combination of Glargine with Aspart showed more significant reduction in blood glucose levels compared to the combination of NPH with RHI.

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