Safety comparison between amitriptyline versus gabapentin on neuropathic pain therapy in geriatric with type II diabetes mellitus

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ABSTRACT

Background: Neuropathy in diabetes mellitus is a disorder that occurs in the peripheral nervous system. Diabetic neuropathy is more prevalent in elderly (44%) compared to adult (24%). The most commonly used agent in diabetic neuropathy are Amifrapine and Gabapentin, mostly to treat the neuropathic pain. However, there were variations in the results of the studies that have been done related to safety between both drugs. Thus, further research is needed to confirm the safety of both drugs in diabetic neuropathy treatment especially in geriatrics patients.

Objective: The aim of this study was to compare the safety of Amifrapine versus Gabapentin administration for diabetic neuropathic pain in geriatric.

Methods: A prospective cohort study involving 70 elders were observed during 4 weeks. The outcome targets were incidence of side effect and comparison incidence of side effect between both drugs. Non-parametric Mann Whitney U, Chi-Square, and Fisher’s Exact test were used to analyze the outcome.

Result: Most side effects have appeared in the group Amifrapine is a dry mouth followed by sedation / drowsiness, fatigue, dizziness, and constipation. In the group of Gabapentin, the incidence of adverse events that most often arises is dizziness followed by dry mouth, and fatigue. Low doses administration showed that Amifrapine has significantly greater adverse effects (p < 0.05) compared with Gabapentin. However, no significant differences were found in therapeutic dose (p > 0.05).

Conclusion: The incidence of adverse events was more common in geriatric patients receiving Amifrapine compared to Gabapentin.

INTRODUCTION

Neuropathy in diabetes mellitus is a complication that affects peripheral nervous system. These disorders arise due to damage small blood vessels (microvascular) resulting from high blood glucose level.1-3 Diabetic neuropathy has the highest incidence (60-70%) compared to other diabetic complications. In addition, the incidence of diabetic neuropathy was found more prevalent in elderly (44%) compared to adult (24%).4,5

Amitriptyline and Gabapentin are widely used as mainstay treatment of neuropathic pain. There were many debated issues in the treatment of diabetic neuropathic pain in geriatric using first line anti neuropathic pain agents, such as Amifrapine and Gabapentin. According to Beers Criteria, the use of Amifrapine in elderly patients should be avoided because of the many potential side effects, particularly in elderly patients. In contrast, several research concludes that Amifrapine administration still considered safe at a maximal dose of 100 mg/day.6,7 Gabapentin is an anticonvulsant drug class that is more often used to treat neuropathic pain because the drug is otherwise relatively safe and does not listed to be avoided in Beers Criteria. However, there are many reports stated that the side effects of Gabapentin are more common than predicted in elderly patients.6,9

Based on these problems, further research is needed to compare safety use of Amifrapine versus Gabapentin for diabetic neuropathic pain in geriatric with hope the results can be used as a reference, especially in the local health authority to determine the safest therapy of diabetic neuropathic pain especially on geriatric population.

MATERIAL AND METHODS

Subjects

The population of this study were all patients age group ≥ 60 years with painful diabetic neuropathy who have a pain score at least 2 of Visual Analog Scale (VAS), Numeric Rating Scale (NRS) or Verbal Rating Scale (VRS). Patients were undergoing outpatient care in polyclinic of neurology, endocrine, and internal medicine at Sanglah General Hospital Center in Denpasar-Bali and received Amifrapine or Gabapentin therapy. The inclusion criteria were defined as men and women aged ≥ 60 years, patients with diabetes mellitus type 2 with controlled blood sugar levels, patients with a...
diagnosis of painful diabetic neuropathy, patients who obtain pain therapy of diabetic neuropathy such as Amitriptyline or Gabapentin. The exclusion criteria were defined as patients who were not willing to participate in the study; patients with a history of heart disease, kidney failure, and impaired liver function; patient with contraindications or allergy to Amitriptyline or Gabapentin.9,10

Sampling was carried out after obtaining the approval of research ethics committee with ethical clearance number 185 / UN.14.2 / R & D / 2015 as well as informed consent from the patients. Patients will be involved in this study if they have understood and signed the informed consent that has been prepared by the researcher. This study used a non-experimental analytical method which was prospective cohort study. The subjects were divided into two groups according to treatment obtained by the patients.

Clinical Assessment
Basic characteristics such as demographics, Body Mass Index (BMI), risk factors, lipid profile (total cholesterol, HDL, LDL, TG), the use of drug therapy for other diagnoses (antihypertension, anti-dyslipidemia, and neuroprotection therapy), polypharmacy and compliance recorded were obtained as a baseline characteristic. The data collection method was done by direct measurement technique in which researchers take measurements and recording of subjects with diabetic neuropathic pain. The data collection of Amitriptyline and Gabapentin side effects was performed by an assessment using a Naranjo Algorithm and New Genetic Algorithm (NGA) instruments.11, 12

The sampling technique used was non-probability consecutive sampling where researchers will take all subjects who were diagnosed with diabetic neuropathy in accordance with the inclusion and exclusion criteria, up to the minimum number of subjects met. By using the formula of robustness analysis in a cohort study, the minimum sample to be observed to represent the population in each group was 35 patients.

Clinical Outcomes
The clinical outcomes observed were incidence of side effects that appear on the subject in the study, which would be exposed by descriptive analysis and the comparison of the incidence of side effect between both drugs by analytical analysis.9,10

Statistical Analysis
Statistical analyses were performed to test the baseline characteristic and study outcomes.

1. Baseline Characteristic Analysis
Analysis of baseline characteristics comparison conducted by the Mann-Whitney U and Chi-Square test for abnormally distributed data and Tow Independent Sample Pair T-Test for normally distributed data.

Table 1  Subjects Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Amitriptyline Group (n = 35)</th>
<th>Gabapentin Group (n = 35)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>62.11 ± 3.47</td>
<td>63.46 ± 4.90</td>
<td>0.709</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>23 (65.71%)</td>
<td>22 (62.86%)</td>
<td>0.803</td>
</tr>
<tr>
<td>Female (P) [n (%)]</td>
<td>12 (34.29%)</td>
<td>13 (37.14%)</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.73 ± 3.71</td>
<td>26.15 ± 2.96</td>
<td>0.469</td>
</tr>
<tr>
<td>High (cm)</td>
<td>164 ± 6.67</td>
<td>162 ± 6.86</td>
<td>0.118</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72 ± 10.69</td>
<td>68 ± 8.92</td>
<td>0.128</td>
</tr>
</tbody>
</table>

Table 2  Total Incidence Side Effects of Amitriptyline and Gabapentin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The Research Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amitriptyline Group (n = 35)</td>
</tr>
<tr>
<td>Occur</td>
<td>32 (91.43%)</td>
</tr>
<tr>
<td>Not Occur</td>
<td>3 (8.57%)</td>
</tr>
</tbody>
</table>

Glossary of terms: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; TG = Triglycerid; B-Complex: Contains Vitamin B1, B6, and B12; Mecobalamin = Vitamin B12

n = Number of Subjects; Sig. = Significant (p < 0.05)
2. Side Effect Evaluation Analysis

The incidences of side effects were analyzed with Chi-square or Fisher's Exact test. Probability values of < 0.05 were considered statistically significant for all analysis. All analysis was conducted using SPSS 17 for windows.

RESULTS

Ninety-one subjects were enrolled during 4-month period. There were 52 patients in Amitriptyline group and 39 patients in the Gabapentin group. Twenty-one subjects were dropped out during the observation period and 70 subjects were observed until the final stages, which consisted of 35 patients in the group of Amitriptyline and 35 patients in the Gabapentin group.

Subjects Characteristics

The demographic characteristics of subjects in this study were determined by age, gender, body mass index, the risk factors, another therapeutic drugs, baseline pain score, adherence, and polypharmacy. The demographic characteristics of patients were found not significantly different between both groups (p > 0.05). The characteristics of patients are shown in Table 1.

Evaluation Side Effect of Amitriptyline and Gabapentin

The most common side effects have appeared in the group Amitriptyline is a dry mouth (80%) followed by sedation / drowsiness (54.29%), fatigue (48.57%), dizziness (45.71%), and constipation (14.29%). In the Gabapentin group, sedation (sleepiness) (40%) and dizziness (34.29%) were commonly found, followed by dizziness (34.29%), dry mouth (17.14%), and fatigue (14.29%) as shown in Figure 1.

The incidence of total side effects on Amitriptyline group has a greater proportion (40%) significantly compared with the incidence of adverse events in the group of Gabapentin as shown in Table 2 and Figure 2.

The dosages of both drugs in this study were varied, so it was necessary to test head to head between Amitriptyline and Gabapentin at sub therapeutic doses (low dose) and the usual dose (therapeutic dose). Low dose group Amitriptyline is < 25 mg / day whereas Gabapentin < 300 mg / day. Amitriptyline usual dose is 25 mg / day whereas Gabapentin is 300 mg / day. Comparisons incidence of side effect head to head between two drugs are shown in Table 3 and Table 4.

The incidence of side effects on Amitriptyline group has a greater significantly on sub therapeutic dose compared the group of Gabapentin, but there was no difference on usual dose between both group.
Neuropathic pain in diabetes mellitus remains to be one of major challenges either for neurologist or endocrinologist. So far, the only treatment for this condition is to relieve the pain by using anti-depressant drug Amitriptyline or anticonvulsant Gabapentin. For long period it is believe that Gabapentin is safer than amitriptyline for geriatric patients. However, conflicting report regarding the safety issue of these agents had been reported in several studies.

The findings in our study, however, confirm the traditional notion that Gabapentin is actually safer compared with Amitriptyline. Incidence of adverse events was more common in patients receiving Amitriptyline compared to Gabapentin in geriatrics.

**CONCLUSION**

The incidence of adverse events was more common in patients receiving Amitriptyline compared to Gabapentin in geriatrics.

**ACKNOWLEDGEMENT**

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**AUTHOR CONTRIBUTION**

All authors contributed in the manuscript, based on their contribution as: study proposal in general (Krisna Adi Jaya [KAJ] and Tuty Kuswardhani [TK]), study design (KAJ, TK), statistical analysis (KAJ, TK), study running (KAJ, TK), manuscript writing (KAJ, TK). We confirmed that all authors have read and agreed to the content of this manuscript.

**CONFLICT OF INTEREST**

This paper was written independently. All authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence the work.
REFERENCES