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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 Amitriptyline 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 Amitriptyline versus Gabapentin administration for diabetic neuropathic pain in geriatric.

Methods: A prospective cohort study involving 70 elderlies 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 Amitriptyline 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 sedation (sleepiness) followed by dizziness, dry mouth, and fatigue. Low doses administration showed that Amitriptyline 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 Amitriptyline compared to Gabapentin.

Keywords: Diabetes Neuropathic Pain, Side Effect, Amitriptyline, Gabapentin, Geriatric.

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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 Amitriptyline and Gabapentin. According to Beers Criteria, the use of Amitriptyline in elderly patients should be avoided because of the many potential side effects, particularly in elderly patients. In contrast, several researches concludes that Amitriptyline administration still considered safe at a maximal dose of 100 mg/day.[5,6,7] 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.[8,9]

Based on these problems, further research is needed to compare safety use of Amitriptyline 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 Amitriptyline or Gabapentin therapy. The inclusion criteria were defined as men and women aged ≥ 60years, patients with diabetes mellitus type 2 with controlled blood sugar levels, patients with a

Table 1 Subjects Baseline Characteristics

Baseline Characteristics	Amitriptyline Group (n = 35)	Gabapentin Group (n = 35)	p Value
Age (Year)	62.11 ± 3.47	63.46 ± 4.90	0.709
Gender			
Male [n (%)]	23 (65.71%)	22 (62.86%)	0.803
Female (P) [n (%)]	12 (34.29%)	13 (37.14%)	
BMI (Kg/m^2)	26.73 ± 3.71	26.15 ± 2.96	0.469
High (cm)	164 ± 6.67	162 ± 6.86	0.118
Weight (Kg)	72 ± 10.69	68 ± 8.92	0.128
Risk Factor			
1. Smoking [n (%)]	7 (20%)	10 (28.57%)	0.403
2. Hypertension [n (%)]	18 (51.43%)	24 (68.57%)	0.143
SBP (mmHg)	135 ± 20.10	133 ± 16.72	0.845
DBP (mmHg)	86 ± 9.00	83 ± 10.36	0.412
3. Dyslipidemia [n (%)]	20 (57.14%)	21 (60%)	0.808
Total Cholesterol (mg/dL)	163.83 ± 55.20	165.37 ± 46.97	0.810
LDL (mg/dL)	96.20 ± 35.14	88.91 ± 29.92	0.385
HDL (mg/dL)	42.91 ± 14.48	43.26 ± 12.81	0.604
TG (mg/dL)	151.29 ± 95.17	147.31 ± 71.72	0.729
Duration of Diabetes Mellitus (Year)	7.46 ± 4.02	8.74 ± 3.80	0.079
Another Therapy			
1. Neuroprotector [n (%)]	25 (71.43%)	30 (71.43%)	0.145
B complex Vitamin	10 (28.57%)	12 (34.28%)	
Mecobalamin	15 (42.86%)	18 (51.43%)	
2. Antihypertension Drug [n (%)]	18 (51.43%)	24 (68.57%)	0.143
3. Antidiabetic Drug [n (%)]	35 (100%)	35 (100%)	1.000
4. Antidyslipidemia Drug [n (%)]	20 (57.14%)	21 (60%)	0.808
Baseline Pain Score	3.37 ± 1.06	3.14 ± 1.00	0.376
Compliance (%)	90.67 ± 6.95	91.95 ± 5.83	0.332
Polypharmacy (amount of drug)	4.69 ± 1.32	5.14 ± 1.09	0.110

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

Table 2 Total Incidence Side Effects of Amitriptyline and Gabapentin

Parameter	The Research Group		p-value
	Amitriptyline Group (n = 35) [n (%)]	Gabapentin Group (n = 35) [n (%)]	
Occur	32 (91,43%)	18 (51,43%)	0,000 Sig
Not Occur	3 (8,57%)	17 (48,57%)	

n = Number of Subjects; Sig. = Significant (p < 0.05)

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.

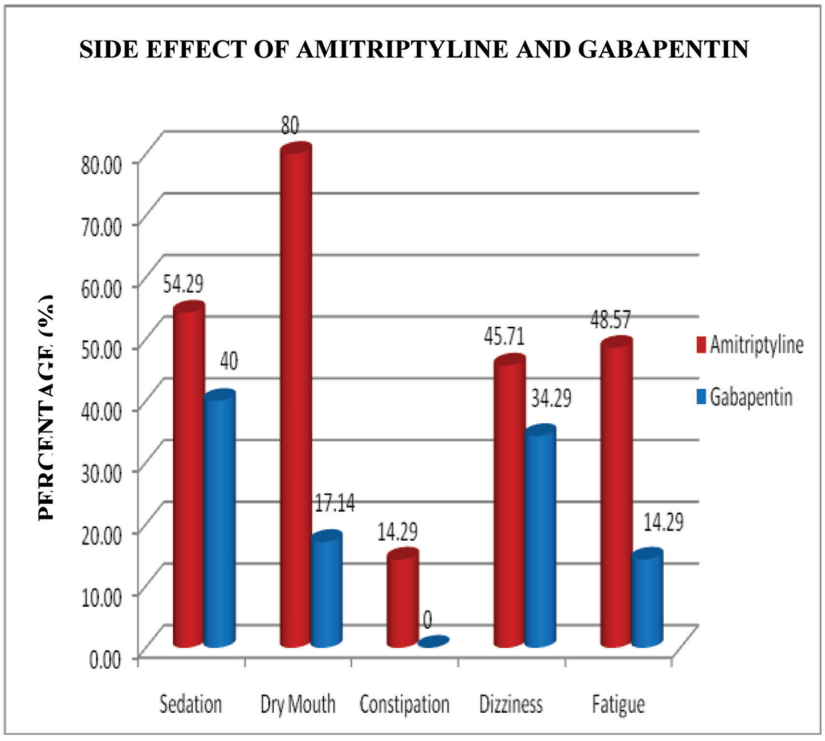

Figure 1 Incidence Side Effect of Amitriptyline and Gabapentin

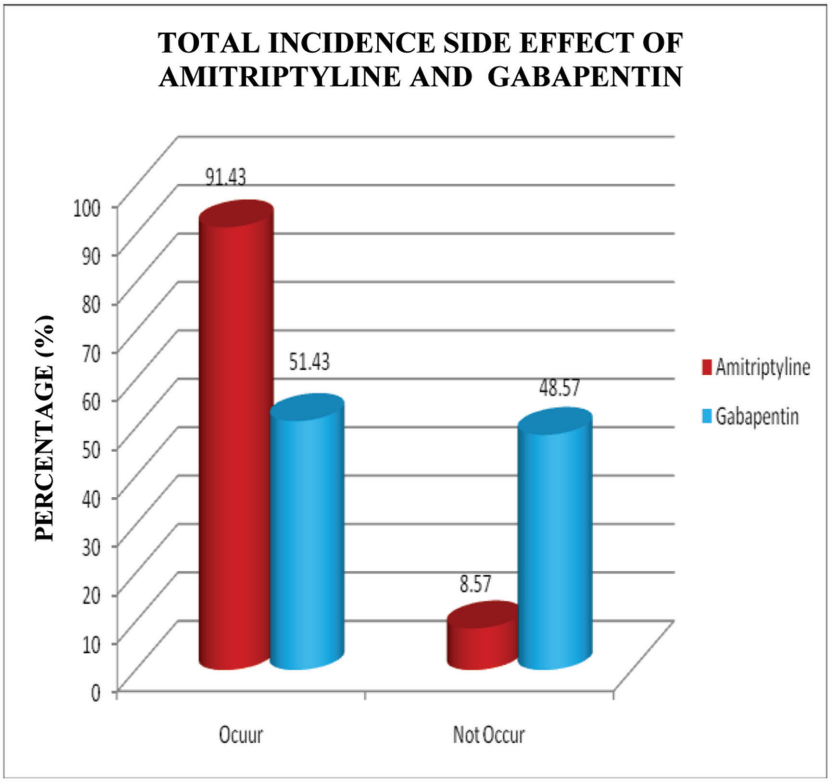

Figure 2 Total Incidence Side Effect of Amitriptyline and Gabapentin

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.

Table 3 Incidence Side Effects of Amitriptyline and Gabapentin at Sub Therapeutic Doses

The Research Group	Side Effects (%) (-)	Side Effects (%) (+)	p Value
Amitriptyline Group (< 25 mg/ day) (n=6)	1 (2.9%)	5 (14.3%)	0.002* Sig
Gabapentin Group (< 300 mg/ day) (n=19)	17 (37.1%)	2 (5.7%)	

n = Number of Subjects; Sig = Significant ($p < 0.05$); * = Fisher Exact Analysis

Table 4 Incidence Side Effects of Amitriptyline and Gabapentin at Usual Doses

The Research Group	Side Effects (%) (-)	Side Effects (%) (+)	p Value
Amitriptyline Group (25 mg/ day) (n= 29)	2 (6.9%)	27 (93.1%)	1.000* NS
Gabapentin Group (< 300 mg/ day) (n=16)	1 (6.3%)	15 (93.8%)	

n = Number of Subjects; NS = Not Significant ($p > 0.05$); * = Fisher Exact Analysis

DISCUSSION

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 antidepressant 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.[5,6,7,8,9]

The findings in our study, however, confirm the traditional notion that Gabapentin is actually safer compared with Amitriptyline. Incidence of adverse events was found to appear more on Amitriptyline group, the incidence rate was statistically significant ($p < 0.05$). In the study conducted Dallocchio, et al., 2000 and Candis, 1999 also showed similar results where the incidence of side effects on Amitriptyline group larger than Gabapentin.[13,14] The greater incidence of side effects of Amitriptyline is suspected because of the pharmacokinetics and pharmacodynamics of the drug. Amitriptyline is more lipophilic (log p [octanol / water] = 4.94) with greater plasma protein bound (91-97%) compared to Gabapentin (Log p [octanol / water] = - 1.10; binding protein < 3%), which cause the absorption of Amitriptyline to be larger with longer half-life (t½) and elimination time. This phenomenon causes Amitriptyline will be in the blood longer than Gabapentin, so that more receptors are occupied and potentially to produce adverse effects.[14,15]

Another possibility of higher incidence of side effects in Amitriptyline is because of its main route of elimination (80%) through metabolism in the liver. Liver metabolisms of Amitriptyline produce active metabolites such as Nortriptyline, Didesmethyl-amitriptyline, 10-Hydroxy-derivative, and Amitriptyline N-oxide. These metabolites have a high potential to bind to specific receptor and generate side effects. On the other hand, Gabapentin is not metabolized. 99% of Gabapentin excreted by kidney is 99% unchanged which is the reason why its side effects are relatively modest compared to Amitriptyline.[9,14,16]

CONCLUSION

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

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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.

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