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Efficacy of Acetaminophen Plus Amitriptyline Compared to Acetaminophen to Reduce Pain Intensity in Nonspecific Chronic Lower Back Pain

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Abstract

Background: There was 90% of Lower back pain (LBP) are non-specific. Acetaminophen is the first an analgesic in the treatment of LBP, but some cases of chronic LBP need additional antidepressant drugs. Amitriptyline is an antidepressant drug often used in cases of pain, but the evidence research in the case of non-specific chronic LBP is still a contradiction.

Method: The study was a Double-Blind Randomized Controlled Trial using consecutive sampling admissions. The subjects were divided into 2 groups; acetaminophen plus amitriptyline group and acetaminophen plus placebo group.

Results: There was no significant difference in pain intensity of acetaminophen plus amitriptyline and acetaminophen plus placebo groups either statistically or clinically (p = 0.498; OR = 0.667; CI 95% 0.20-2.16; ARR = -0.07 or -7%). The significant improvement of pain intensity in the treatment group Acetaminophen plus Amitriptyline was 24 (72.7%), while in the control group Acetaminophen plus Placebo was 24 (80.0%). In the treatment group was 9 (27.3%) who did not experience a significant improvement in pain intensity, and in the control group was 6 (20.0%).

Conclusion: There was no difference in efficacy between acetaminophen plus amitriptyline with acetaminophen plus placebo to reduce pain intensity in non-specific chronic LBP.

***Keywords**: Non-specific chronic LBP, Amitriptyline, Acetaminophen, VAS*

Introduction

Lower back pain (LBP) is a health problem in adults that most often occurs in developing countries around the world [1]. Approximately 90% of LBP patients are non-specific, and one-third of them have chronic symptoms about a year after an acute episode. According to the World health organization (WHO) International classification of functioning definition, disability, and health; nonspecific LBP is an unknown LBP that underlying pathology in the absence of tissue damage to corresponding symptoms of LBP[3]. Acetaminophen is still the first-line analgesic recommended by almost all pain guidelines in the treatment of chronic LBP[4] , but in some cases, additional treatment is required, such as antidepressants or anti-convulsions. Amitriptyline is one of the most widely used tricyclic antidepressant drugs as an adjuvant analgesic primarily for chronic neuropathic pain and fibromyalgia [5]. Amitriptyline 25 to 125 milligrams each could reduce neuropathically and fibromyalgia pain Relative risk (RR) 2.3, (95% CI, 1.8-3.1) with number needed to treat 4.6 (3.6-6.6), however 64% of participants in the study experienced adverse events RR = 1.5, (95% CI 1.4-1.7) with needed to harm

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4.1 (95% CI 3.2-5.7). Another result mentioned that in the case of temporomandibular joint pain, amitriptyline at a dose of 10-30 milligrams/day was effective in relieving pain with pain reduction occurring within 6 weeks.

In addition, there were other objectives such as; [6]Assessing the intensity of pain in chronic non-specific LBP patients by receiving acetaminophen 3x500 milligrams daily; [7] Assessing pain intensity in non-specific LBP patients chronically treated by acetaminophen 3x500 milligrams plus amitriptyline 10 milligrams daily; [5] Comparing pain intensity changes in chronic non-specific acetaminophen LBP patients by receiving acetaminophen 3x500 milligrams plus amitriptyline 10 milligrams daily with non-specific chronic LBP patients that receiving acetaminophen 3x500 milligrams. Therefore, the study aimed to prove that acetaminophen 3x500 milligrams plus amitriptyline 10 milligrams each day was better in reducing the intensity of pain than the administration of acetaminophen 3x500 milligrams each day in non-specific chronic LBP.

Method

Double-blind randomized controlled trial was used in the study. The subjects were non-specific chronic Lower back pain (LBP) patients at the Outpatient Neurology Unit of Dr. Soetomo Teaching Hospital Surabaya that fulfilled the criteria of inclusion and exclusion. The inclusion criteria were; [6] the samples have not received treatment yet, [7] Not treatment anti-pain drugs within a week before joining the study. [5] Age ranges of 20-49 years. [73] Visual analogue scale (VAS) ≥4. [7] And willing to participating in the research by sign informed consent. Whereas, the exclusion criteria were: [6] Depression, [8]such as the heart is relatively unknown and noticed by radiographers and cardiologists. Objective: To analyse the image quality of 4 chamber sections of Cardiac Magnetic Resonance Imaging with and without the use of shim volume on Steady State Free Precession (SSFP Allergy to acetaminophen or amitriptyline, [5] The drugs consumption that could interact with acetaminophen or amitriptyline, [7] History of heart disease, [3] Cardiac arrhythmias, [7] History of liver disease, [9] The result of transaminase enzyme was more than normal, [10] Epilepsy, [11] Pregnant or breastfeeding and, [12] Gastrointestinal disease.

Additionally, drop out criteria during the study were: [6] Resigned from participation in research, [4] In the process, the patients showed an allergy symptoms and/or signs to a given drug, [5] In the patient's research process showed side effects symptoms and/or signs of a given drug that interferes with the patient's activity, [7] Not taking any capsule medication within 2 days in a row, [3] Not any taking tablet medicine within 3 consecutive days, [7] In the research process, the patient showed red flags signs and, [9] The patient moved the address without notice so it could not be followed. The study was conducted at the Neurology Department of Dr. Soetomo Teaching Hospital for 4 months. This research involves participants in the process using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic regulation.

The data collection was obtained the basic data: identity, history, physical examination, laboratory examination, and cardiac consultation, as well as Visual analogue scale (VAS) at the beginning [8]such as the heart is relatively unknown and noticed by radiographers and cardiologists. Objective: To analyse the image quality of 4 chamber sections of Cardiac Magnetic Resonance Imaging with and without the use of shim volume on Steady State Free Precession (SSFP. Data on the intensity change of pain was obtained from the difference between before and after the treatment[7], then it will be analyzed using a Chi-square test (X2).The preliminary study of 30 people was obtained 80% of the subjects that had experienced a treatment success (VAS1-VAS2 ≥2 difference) on the 14th day of treatment, so the cut point taken of treatment was 13 days.

Results

Tabel 1: The Characteristics of Baseline Age Data in Treatment and Control Groups

Treatment			**Control**		
Variable	**(Asetaminofen +Amitriptilin)**		**(Asetaminofen+Plasebo)**		**p**
	Median	Minimal-Maximal	Median	Minimal - Maximal	
Ages	42.00	20-49	37.50	20-49	0.524 (Mann-Whitney)

Tabel 2 The Characteristics of Research Subjects By Sex, Education Level, and Occupation

Variable	Group		Total	*p*
	Treatment	Kontrol		
Sex				
Female	26 (55.3%)	21 (44.7%)	47 (100%)	0.424
Male	7 (43.8%)	9 (56.3%)	16 (100%)	
Education				
Junior High School	7 (41.2%)	10 (58.8%)	17 (100%)	0.279
Senior High School	26 (56.5%)	20 (43.5%)	46 (100%)	
Jobs				
Moving Around	19 (48.7%)	20 (51.3%)	39 (100%)	0.458
Stay Still	14 (58.3%)	10 (41.7%)	24 (100%)	

Tabel 3 The Characteristics of Pain Intensity Visual analogue scale (VAS) of the Initial Research Subjects

Variable	Treatment (Asetaminofen+Amitriptilin)	Control (Asetaminofen+Plasebo)	*p*
	Median (minimal-maximal)	Median (minimal-maximal)	
Early VAS	5.00 (4.20-8.50)	5.20 (4.10-8.20)	0.540 (*Mann-Whitney)*

Tabel 4. The Changes in Pain Intensity in The Treatment and Control Group

Variable	Treatment (Asetaminofen+Amitriptilin)		Control (Asetaminofen+Plasebo)		*p*
	Mean	Standard Intersection	Mean	Standard Intersection	(IK95%)
Difference of VAS1-VAS2	3.50	2.09	4.07	2.04	0.28 (IK95% -1.16- 0.47)

Tabel 5. The Treatment successes in the Treatment Group and Control Group

Group	Success	Failed	Total	*P*
Treatment (Asetaminofen+Amitriptilin)	24(72.7%)	9 (27.3%)	33 (100%)	0.498
Control (Asetaminofen+Plasebo)	24 (80.0%)	6 (20.0%)	30 (100%)	
Total	48 (76.2%)	15(23.8%)	63 (100%)	

Rasio Odds : 0.667 (IK95% 0.20-2.16)

Tabel 6 The Occurrence of Drug Side Effects in the Treatment Group and Control Group.

Group	Side Effect (Yes)	Side Effect (No)	Total	*p*
Treatment (Asetaminofen+Amitriptilin)	21 (63.6%)	12 (36.4%)	33 (100%)	0.275
Control (Asetaminofen+Plasebo)	15 (50.0%)	15 (50.0%)	30 (100%)	
Total	36 (57.1%)	27 (42.9%)	63 (100%)	

Basic Demographic and Clinical Data of Subject

The basic characteristics of subjects by age (Table 1) showed that the median age in the treatment group Acetaminophen plus Amitriptyline was 42.00 (20-49), while in the control group Acetaminophen plus Placebo was 37.50 (20-49). The homogeneity test of the age variables in the two groups (Table 1), showed no significant difference age between treatment and control group with Mann-Whitney p = 0.345.

Characteristics of basic data of research subjects based on sex, educational level and type of job are shown in Table 2. Overall, there were 47 females and 16 males. The treatment group was 26 (55.3%) of female subjects and 7 (43.8%) of male subjects.

Clinical data of study subjects before treatment shown in Table 3. In the treatment group, the median data of initial VAS was 5.00 (4.20-8.50), whereas in the median control group the initial VAS was 5.20 (4.10-8.20). The homogeneity test of early VAS variables in both groups had no significant difference in initial VAS variable between treatment and control group, with Mann-Whitney p = 0.540.

Effect of therapy on the improvement of pain intensity Changes in pain intensity were the differences between the initial Visual analogue scale (VAS), on day 14th (VAS1-VAS2 differences). The mean of pain intensity change in the treatment group was 3.51±2.01, and in the control group was 4.08±2.05 (Table 4).

The test of variable distribution of pain intensity change in both groups showed an abnormal distribution pattern, so the comparative test used to compare the variety of pain intensity change in both groups using an unpaired t-tes[4] The unpaired t-test of VAS1-VAS2 differences between the two groups showed no statistically significant difference, with p = 0.28 (CI 95%

1.16-0.47).

Result Data based on the success of treatment

A significant improvement in pain intensity was considered successful, for example, the initial VAS value difference and the VAS day value of 14 (VAS1-VAS2 difference) was ≥2. Overall, 48 (76.2%) of the subjects who succeeded in the treatment (decreased pain intensity ≥2) and 15 subjects (23.8%) were unsuccessful in the treatment. The significant improvement of pain intensity in the treatment group Acetaminophen plus Amitriptyline was 24 (72.7%), while in the control group Acetaminophen plus Placebo was 24 (80.0%). In the treatment group was 9 (27.3%) who did not experience a significant improvement in pain intensity, and in the control group was 6 (20.0%). The result of the statistical test comparing the treatment success between the treatment group and control group was not statistically significant, with p = 0.498; Odds Ratio = 0.667 (CI 95% 0.20-2.16).

Drug Side Effects in the treatment and control group

During the study, the side effects were found in both control and treatment groups, with results as shown in Table 6. The incidence of adverse drug effects in the study subjects of treatment group was 21 people (63.6%), whereas in the control group was 15 (50.0%).

Discussion

The study, there were no significant differences in both the outcome of decreased pain intensity and treatment success, between the treatment group and the control group. It was not following previous studies suggesting that amitriptyline was more effective in the second week of treatment in reducing pain intensity (t = 4.43, p <0.001) than acetaminophen (t = 3.30, p <0.01) LBP 45. Some of the reasons that might explain the difference between our study and previous research were the inclusion criteria were non-specific LBP cases that exclude depression, did not take into account psychological factors (anxiety and coping mechanisms), and use low doses of Amitriptyline.

Another Result included both non-specific LBP and neuropathic LBP in the inclusion criteria, whereas in the study subjects were only non-specific chronic LBP. They also take into account psychological factors such as mild depression, anxiety, and coping mechanisms. The results of the calculations in his study showed that the presence of depression was a predictor of treatment before the treatment of pain intensity after treatment, in addition to the improvement of pain was also associated with anxiety improvement, indicating that amitriptyline also has an anxiolytic effect that could be achieved within a short time. In our study, we excluded depression to examine the efficacy of amitriptyline only in the improvement of pain, but the shortcomings in the study of other psychological factors were not taken into account. In the previous LBP study, the dose of the amitriptyline drug was the dose used for depression (150 mg daily) while in our study used the initial dose as an anti-pain according to the guidelines for pain management, which was 10 mg.

In addition, the data of the research demographics was obtained the median of age in the treatment group was 42 (20-49), and the control group was 37.5 (20-49). According to the epidemiological study, the incidence of lower back pain was high in the third decade and increased prevalence up to age 60-65 years. Whereas from the basic data of sex demography, the number of non-specific Low back pain (LBP) patients with female gender was higher than men, it was not in accordance with epidemiological studies which generally stated that there were no significant gender differences in the prevalence of LBP.

Whereas in the basic data of the demography type of job, it was found that there were heavier types of jobs than the sedentary type of job. It was following epidemiological studies of occupational-type correlation with LBP incidence, that manual workers (often lifting, bending, and spinning) were more (39%) that experiencing LBP than sedentary workers (18%), and were risk factors for LBP. All data analyzed, there was a difference demographic data and clinical data between treatment group and control group but the difference was not statistically significant (p >0.05). The results of drug administration on the success of the treatment, it was found that in the second week of treatment (day 14 of treatment), overall of 63 study subjects, 48 subjects (76.2%) had success treatment (decreased pain intensity ≥2).

In the study, there was an average decrease in the pain intensity score of almost the same between the treatment group and the control group.While the results of research on the success of treatment, from the test results of treatment efficacy statistics between the

treatment and the control groups, were no significant differences. The clinical trial, ARR = -0.07, indicated that statistically and clinically, treatment in the treatment group (Acetaminophen 3x500 mg + Amitriptyline 10 mg) was no improvement in reducing pain intensity than in the control group.

The incidence of adverse events in the treatment group and the control group was also differed. Administration of acetaminophen 3x500 mg plus amitriptyline 10 mg resulted in greater adverse events compared to the control group (Odds ratio: 1.750), but the difference between the two groups was not significant. This suggests that the addition of Amitriptyline at a dose of 10 mg of acetaminophen might have a greater side effect than single acetaminophen in a case of non-specific chronic LBP.

Another study supporting the results of our study was a meta-analysis of tricyclic antidepressant drug administration compared to placebo in the case of chronic non-specific LBP,In addition, a systematic review of the use of antidepressants in chronic LBP cases suggests that tricyclic antidepressants were superior only mild to moderate when compared with placebo on pain intensity output (SMD = 0.43 and SMD = 0.69 in 2 high-quality studies). The mean superior mild to moderate decrease in pain intensity was 0.5-2 points, whereas in our study considered to be significantly improved the pain intensity that was decreased ≥2.

The work of Amitriptyline as an analgesic to strengthen the pathway of descending inhibition by increasing the number of noradrenaline and serotonin neurotransmitters in the synaptic gaps at the spinal and supraspinal levels, especially, nor-adrenaline uptake. There were several possible reasons why the administration of acetaminophen 3x500 mg plus Amitriptyline 10 mg unproven to be better than the administration of acetaminophen 3x500 mg. The first possible mechanism for the onset of pain in non-specific chronic LBP was more due to the release of excessive inflammatory mediators, and not due to reduced levels of Noradrenaline and serotonin neurotransmitters at the supraspinal level, as have excluded depression in the study. Moreover, the possibility at a dose of 10 milligrams Amitriptyline has not reached its optimal dose as an analgesic.

Conclusion

There was no difference in efficacy of Acetaminophen 3x500 mg plus Amitriptyline 10 mg with Acetaminophen 3x500 mg in reducing pain intensity in non-specific chronic Low back pain (LBP).

Conflict of Interest: There is no concflict of interest.

Source of Funding: This study is self-funded.

Ethical Clearance: This study was approved by Ethical Commission of Health Research Faculty of Medicine University of Airlangga.

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