

## Meta-Analysis: The Effect of Acupuncture Therapy in Reducing Migraine Recurrence

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### ABSTRACT

**Background:** Acupuncture therapy is an effective treatment for reducing headache intensity, migraine recurrence, and improving quality of life. This study aims to analyze and estimate the effect of acupuncture therapy on reducing migraine recurrence.

**Subjects and Method:** This study used a systematic review and meta-analysis by following PICO, Population: migraine patients. Intervention: acupuncture therapy. Comparison: no acupuncture therapy. Result: reduction in migraine recurrence. The data used were obtained from scientific research articles from the Pubmed, Google Scholar, Science Direct, and Springerlink electronic databases with a Randomized Control Trial (RCT) design from 2011 to 2022 which reports effect sizes with Mean and SD. The keywords used in the search for scientific articles are “Acupuncture” AND “Profilaxis Migraine” AND “Migraine Frequency”. The selection of articles was carried out using the PRISMA flowchart. Data were analyzed using Review Manager software version 5.4.1.

**Results:** A total of 9 articles with qualified RCT designs from Asia, America, Australia and Europe were selected for the systematic review and meta-analysis. The results of the meta-analysis, showed that patients with migraine who received acupuncture therapy experienced migraine recurrence 0.31 units lower than those who were not treated with acupuncture (SMD= -0.31; 95% CI= -0.61 to -0.01; p=0.040).

**Conclusion:** Acupuncture therapy reduces migraine recurrence.

**Keywords:** acupuncture, relapse, migraine.

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### Sitasi:

Tursina E, Prasetya H, Murti B (2023). Meta-Analysis: The Effect of Acupuncture Therapy in Reducing Migraine Recurrence. *Indones J Med.* 08(01): 47-58. <https://doi.org/10.26911/theijmed.2023.08.01.05>.



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### BACKGROUND

Migraine is a complex disorder characterized by episodic headaches with varying intensity, frequency and duration in individuals (Abyuda and Kurniawan, 2021). Migraine pain is usually localized to the frontotemporal and ocular areas. Migraine manifestations that often occur are hypersensitivity to visual, auditory, olfactory, and somatosensory stimuli, nausea and vomiting (Marco and Orlando, 2022). In severe cases, migraines can trigger neuropsychiatric symp-

toms such as epilepsy, sleep disturbances, depression and affective disorders. In addition, migraine sufferers have a higher risk of developing cardiovascular and cerebrovascular disease (ischemic stroke) than those who do not suffer from migraines (Kurth et al., 2016).

Globally, more than 30% of adults aged 18-65 in the world have experienced migraines (WHO, 2016). WHO ranks migraine as the third most common medical condition and the second most disabling ne-

urological disorder in the world. The average prevalence of migraine is 18% with the highest incidence occurring in North America, followed by South America, Central America, Europe, Asia and Africa. As many as 36 million people in the United States experience recurrent migraine attacks, with an estimated 16%-18% experiencing women and 6%-8% of men. In fact, an annual fee of 9.2 billion dollars was spent by the United States government on the medical management of migraine between 2004 and 2013. Of course, this is a burden for public health problems (Raval and Shah, 2017).

Approximately 25% to 38% of migraine sufferers require migraine relapse prevention therapy because migraine is a recurrent, episodic disease. Although prophylactic drugs such as beta-blockers or anti-epileptic drugs are recommended for migraine sufferers, they have not been developed specifically to treat migraines (IHS, 2018). In addition, pharmacotherapy treatment is often associated with an increased risk of side effects, including weight gain, sleep disturbances, and gastrointestinal intolerance.

Excessive use of analgesics or certain anti-migraine treatments can also cause headaches and an increase in headache frequency. Due to the limitations associated with these conventional treatments, several attempts have been made to identify effective, low-risk interventions to treat migraine (CNSF, 2012).

Several studies report that acupuncture is effective in reducing headache intensity, migraine recurrence, and improving quality of life. Research conducted by Musil et al. (2018) stated that acupuncture reduces migraine frequency and drug use, both short and long term, so that acupuncture is recommended as an adjuvant treatment for migraines. Meanwhile, Foroughipour et al. (2014) showed no significant difference in the frequency of migraine attacks between

pharmacotherapy and acupuncture treatment. However, after 1 month, the frequency of migraine decreased more in patients who received acupuncture intervention.

Several studies on the effect of acupuncture for migraine prophylaxis have shown varying effect sizes. Comprehensive research is needed from various primary studies that discuss the effect of acupuncture as a migraine prophylaxis treatment. Meta-analysis is a study design that combines numerical summary results on effect sizes extracted during a systematic review process from independent studies to be synthesized in order to obtain better and more generalizable effect size results (Khan, 2020). This study aims to analyze and estimate the effect of acupuncture therapy on reducing migraine recurrence using a meta-analysis of primary studies conducted by previous researchers.

## SUBJECTS AND METHOD

### 1. Study Design

This study used a systematic review and meta-analysis method. The data used comes from article searches primers from databases such as Google Scholar, Science Direct, and Pubmed from 2012 to 2022. The search was carried out using the keywords "Acupuncture" AND "Profilaxis Migraine" AND "Migraine Frequency".

### 2. Steps of Meta-Analysis

Meta analysis was carried out in 5 steps as follows:

- 1) Formulate research questions in PICO format (Population, Intervention, Control/Comparisons, Outcomes)
- 2) Looking for primary study articles from various electronic and non-electronic data based such as PubMed, Google Scholar, Science Direct, SCOPUS and so on
- 3) Perform screening to determine inclusion and exclusion criteria and carry out critical assessments

- 4) Extract the data from the primary study and synthesize the effect estimates using the Revman 5.3 application
- 5) Interpret the results and draw conclusions

### 3. Inclusion Criteria

The inclusion criteria in this study included full text articles using the Randomized Controlled Trial (RCT) research method from 2012 to 2022 which used acupuncture interventions and analyzed outcomes to reduce the frequency of migraine recurrence reported by Mean and Standard deviation (SD).

### 4. Exclusion Criteria

Exclusion criteria in this study were studies prior to 2012 and using languages other than Indonesian and English.

### 5. Operational Definition of Variables

The study was conducted by considering the eligibility criteria which were defined using the PICO Population: Adult model. Intervention: Acupuncture therapy. Comparison: No acupuncture therapy. Outcome: Decreased migraine recurrence.

**Acupuncture** is a physical therapy procedure using fine needles (Filiform needles) that are inserted into the body at acupuncture points and manipulated at a certain depth to reduce symptoms or as a healing modality for disease.

**Reduction in migraine recurrence** is a reduction in the frequency of migraine attacks after the patient performs acupuncture therapy

### 6. Instrument

The research was guided by the PRISMA flowchart and the research quality in this study was conducted based on the Center for Evidence-Based Medicine (CEBM) worksheets.

### 7. Data Analysis

Data analysis was performed using Review Manager software version 5.4.1. The odds ratio with 95% CI is calculated from the adjusted Mean and SD. The Forest Plot was used to describe effect sizes and the Funnel

Plot to describe publication bias. The analysis was carried out by looking for the heterogeneity consistency value ( $I^2$ ) of the research results used.

## RESULTS

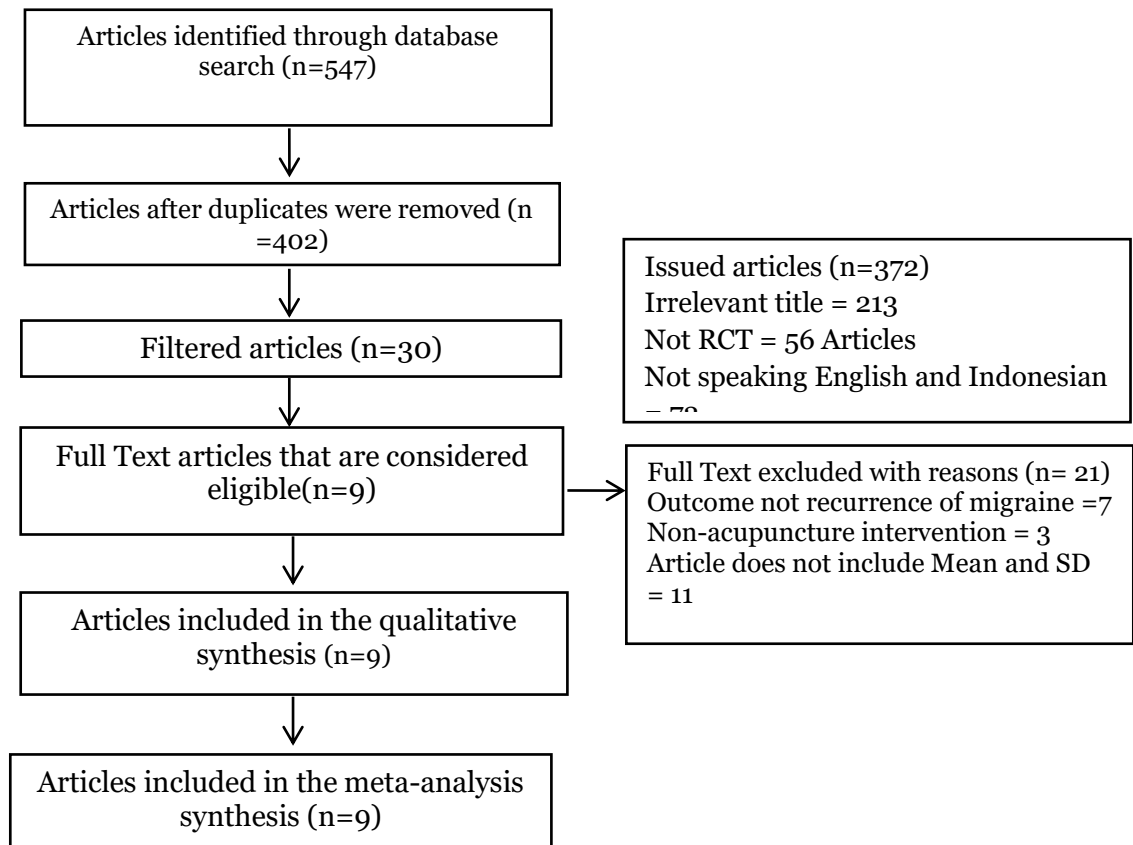
The data used comes from searching primary articles from databases such as Google Scholar, Science Direct, and Pubmed from 2012 to 2022. The search was carried out using the keywords "Acupuncture" AND "Profilaxis Migraine" AND "Migraine Frequency". The process of selecting and reviewing articles is carried out using the PRISMA flowchart.

In this meta-analysis, a number of articles with RCT research designs will be used. The initial search results obtained a number of 692 articles from a predetermined database and from other searches. After removing duplicate articles, 402 articles were obtained. At the screening stage, 30 articles were obtained by removing 372 articles because these articles did not meet the criteria on the grounds that they were irrelevant, not RCT, not full-text and not in English or Indonesian. The researcher reviewed the 30 articles that had been obtained and found 9 articles that met the requirements. 21 articles were excluded because the outcome was not migraine recurrence, the intervention was not acupuncture and the articles did not include the Mean and SD. There were 9 articles included in the qualitative synthesis, then 9 articles that met the criteria were selected again. In these 9 articles a quantitative synthesis of the meta-analyses will be carried out (Figure 1).

This research related to the effect of acupuncture therapy on reducing migraine recurrence consists of 9 studies originating from 4 continents including Asia, America, Australia, and Europe. A total of 6 studies from the Asian continent were all from China; 1 study came from America, namely the

USA, 1 study came from Australia, namely Melbourne, and 1 study from the European continent, namely from Italy. The distri-

bution of the description of the study area is depicted on the map (Figure 2)



**Figure 1. PRISMA flow diagram**



**Figure 2. Map of the research area on the effect of acupuncture therapy on reducing migraine recurrence**

**Table 1. Assessment of the quality of randomized controlled trial studies on the effect of acupuncture therapy on reducing migraine recurrence**

Primary Study	Criteria of Questions												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Biçer <i>et al.</i> (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12
Foroughipour <i>et al.</i> (2015)	1	1	1	1	1	1	1	1	1	0	1	1	11
Musil <i>et al.</i> (2018)	1	1	1	1	1	1	1	1	1	1	1	1	12
Giannini <i>et al.</i> (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Wang <i>et al.</i> (2011)	1	1	1	1	1	1	1	0	1	0	1	1	10
Xu <i>et al.</i> (2020)	1	1	1	1	1	1	1	1	1	1	0	1	11
Wang <i>et al.</i> (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Zhao <i>et al.</i> (2014)	1	1	1	1	1	1	1	1	1	1	0	1	11
Naderinabi <i>et al.</i> (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12

**Description of the question criteria:**

- 1 = Does the research address a clearly focused statement/problem?  
2 = Is the randomized controlled trial research method appropriate to answer the research question?  
3 = Are there enough subjects in the study to establish that the findings did not occur by chance?  
4 = Were subjects randomly allocated to the experimental and control groups? If not, could this introduce bias?  
5 = Were inclusion/exclusion criteria used?  
6 = Were the two groups comparable at study entry?  
7 = Were objective, unbiased outcome criteria used?  
8 = Are objective and validated measurement methods used to measure the results? If not, were the results assessed by someone who was not aware of the group assignment (i.e. was the assessment blinded)?  
9 = Is the effect size practically relevant?  
10 = How precise is the estimated effect? Are there confidence intervals?  
11 = Could there be confounding factors that haven't been taken into account?  
12 = Can the results be applied to your research?

**Description of the answer score:**

- 0 = No  
1 = Yes

**Table 2. Summary of randomized controlled trial (RCT) primary study articles with each PICO (N=429)**

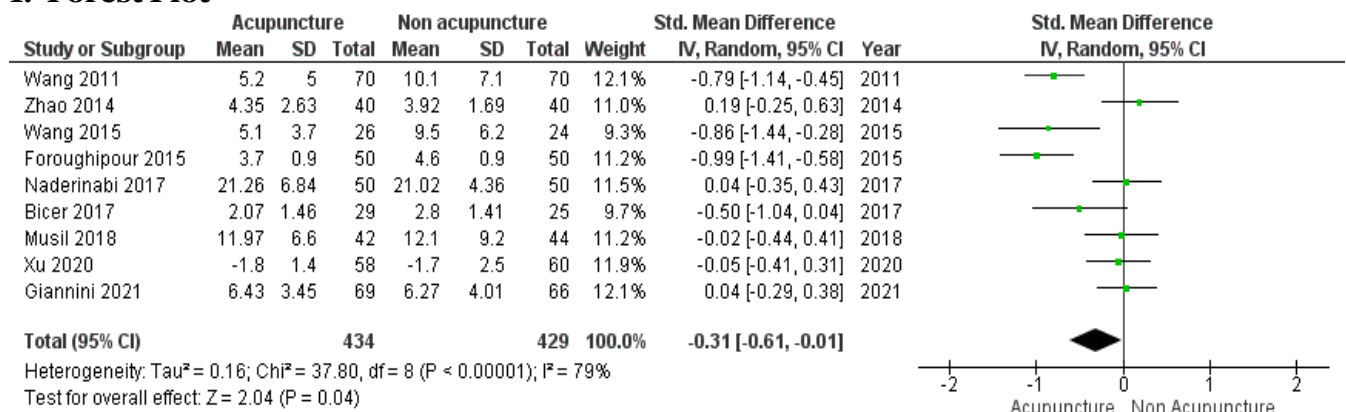
Author (Year)	Country	Sample Size	P	I	C	O
Biçer <i>et al.</i> (2017)	Turkey	54	Migraine patient	Acupuncture therapy	Usual treatment	Reduction of migraine recurrence
Foroughipour <i>et al.</i> (2015)	America	100	Migraine patient	Acupuncture therapy	Sham acupuncture	Reduction of migraine recurrence
Musil <i>et al.</i> (2018)	China	86	Migraine patient	Acupuncture therapy	Pharmacology	Reduction of migraine recurrence
Giannini <i>et al.</i> (2021)	Italy	135	Migraine patient	Acupuncture therapy	Pharmacology	Reduction of migraine recurrence
Wang <i>et al.</i> (2011)	China	140	Migraine patient	Acupuncture therapy	Pharmacology	Reduction of migraine recurrence

Author (Year)	Country	Sample Size	P	I	C	O
Xu <i>et al.</i> (2020)	China	118	Migraine patient	Acupuncture therapy	Sham acupuncture	Reduction of migraine recurrence
Wang <i>et al.</i> (2015)	Melbourne	50	Migraine patient	Acupuncture therapy	Sham acupuncture	Reduction of migraine recurrence
Zhao <i>et al.</i> (2014)	China	80	Migraine patient	Acupuncture therapy	Sham acupuncture	Reduction of migraine recurrence
Naderinabi <i>et al.</i> (2017)	Iran	100	Migraine patient	Acupuncture therapy	Pharmacology	Reduction of migraine recurrence

**Table 3. Effect estimates (Mean SD) of all primary studies performed in the meta-analysis (N=429)**

Author (Year)	Acupuncture		Non-Akupunktur	
	Mean	SD	Mean	SD
Biçer <i>et al.</i> (2017)	2.07	1.46	1.80	1.41
Foroughipour <i>et al.</i> (2015)	3.70	4.60	0.90	0.90
Musil <i>et al.</i> (2018)	11.97	6.60	12.10	9.20
Giannini <i>et al.</i> (2021)	6.43	3.45	6.27	4.01
Wang <i>et al.</i> (2011)	5.20	5.00	10.10	7.10
Xu <i>et al.</i> (2020)	-1.80	1.40	-1.70	2.50
Wang <i>et al.</i> (2015)	5.10	3.70	9.50	6.20
Zhao <i>et al.</i> (2014)	2.35	2.19	3.10	2.00
Naderinabi <i>et al.</i> (2017)	21.26	6.84	21.02	4.36

**1. Forest Plot**

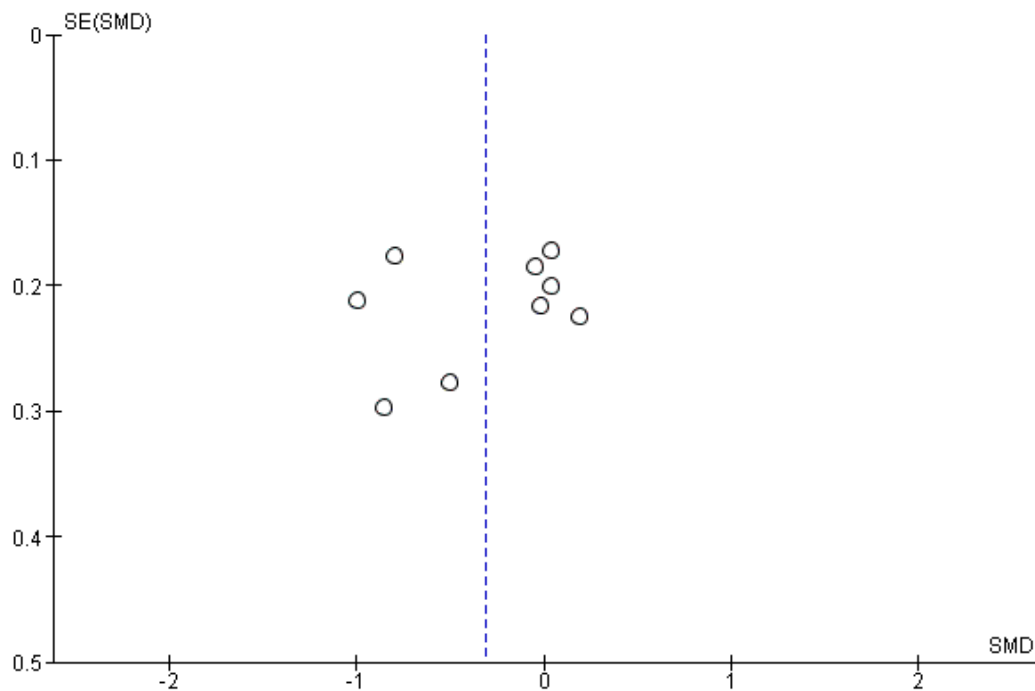


**Figure 3 Forest plot meta-analysis of the effect of acupuncture therapy on reducing migraine recurrence**

The forest plot in Figure 3 shows the effect of acupuncture therapy on reducing migraine recurrence, and this effect is statistically significant. Patients with migraine who received acupuncture treatment experienced migraine recurrence 0.31 units lower than those who did not receive acupuncture treat-

ment (SMD= -0.31; 95% CI= -0.61 to -0.01; p=0.040). The forest plot also showed high heterogeneity in effect estimates between studies (I<sup>2</sup>=79%; p<0.001). Thus, the calculation of the average effect estimate uses the random effect model approach.

## 2. Funnel Plot



**Figure 4. Funnel plot meta-analysis of the effect of acupuncture therapy on reducing migraine recurrence**

The funnel plot in Figure 4 shows a more or less symmetrical distribution of effect estimates between studies to the right and left of the vertical mean estimate line. Thus, this funnel plot shows no publication bias in the meta-analysis

### DISCUSSION

Migraine is defined as a complex headache disorder characterized by episodic headaches with varying intensity, frequency and duration for each individual (Abyuda and Kurniawan, 2021). Migraines can occur at any age, and more than half of patients who suffer from migraines experience interference with daily activities, whether at work or school (Chen et al., 2020). In addition, migraine sufferers have a higher likelihood of developing cardiovascular and cerebrovascular disease (ischemic stroke) than those who do not suffer from migraines, especially women and the elderly. Migraines

also increase the risk of various diseases such as epilepsy, depression, and affective disorders. This proves that migraines can affect a person's loss of quality of life (Kurth et al., 2016).

Prophylactic treatment is an important aspect of migraine case management, because migraine greatly affects social and work life, leading to excessive use of analgesic drugs. Predominantly prophylactic treatment is used to reduce the frequency, duration and severity of attacks. This reduces the utilization of acute medication as well as improves the patient's functional status (Biçer et al., 2017).

Although pharmacotherapy (divalproex sodium, topiramate, metoprolol, and propranolol) is recommended as a migraine drug. However, many patients experience side effects due to the drug. Data from clinical trials show that the drug is not acceptable to migraine patients. In recent years,

evidence has emerged showing the negative impact of these drug interventions on patients. Therefore, more and more patients are seeking effective non-pharmacological alternative treatments (Zhang et al., 2020).

Acupuncture, widely used in Eastern Countries, but recently acupuncture therapy is gaining popularity in Western countries. Acupuncture has a long history in the treatment of many painful conditions, including headaches. Acupuncture stimulation causes the release of endorphins, serotonin, enkephalins, gamma-aminobutyric acid, norepinephrine and dopamine which help explain the biomedical and pharmacological effects of acupuncture. Acupuncture can be used as an alternative in treating migraines without any adverse effects (Schiaparelli et al., 2011; Lu and Lu, 2013)

Based on the results of the analysis of 9 primary studies that were carried out systematic review and meta-analysis showed that there was high heterogeneity between experiments ( $I^2= 79\%$ ;  $p < 0.001$ ) so that the analysis used the Random Effect Model (REM). High heterogeneity is based on the variation or diversity between populations as seen from the different number of samples between the experimental group and the control group, the frequency of migraine recurrence which has different ranges, and the number of times the treatment is given varies.

The results of a meta-analysis of 9 articles related to the effect of acupuncture therapy on reducing migraine recurrence showed that acupuncture therapy reduced migraine recurrence higher than those who did not undergo acupuncture therapy (SMD= -0.31; 95% CI= -0.61 to -0.01;  $p= 0.140$ ). There are 3 primary research articles that show significant value in studies of acupuncture therapy in reducing migraine recurrence as indicated by not touching the horizontal line of each study with the vertical

line in the forest plot. This significance value is influenced by several factors, including in the 3 articles the number of samples between the control group and the intervention group is the same so that the number of proportions for both is balanced.

Acupuncture therapy itself is a procedure in which fine needles are inserted into the body at acupuncture points (acupoints) and manipulated at a certain depth to reduce symptoms and achieve disease cure (Zhao et al., 2017). Acupuncture originates from China and has now become a form of treatment that is widely used. The treatment effect of acupuncture is considered as a balancing of disturbances in the human body as a modality for treating disease. The balance is achieved by activating the body's accurate meridians and acupuncture points using various needle insertion techniques, according to the patient's disease and status. Today, acupuncture has been widely used for migraine prophylaxis and treatment of chronic pain worldwide. According to a survey in the US, 9.9% of patients received acupuncture treatment to treat migraines and other headaches (Gao et al., 2018).

Several studies have shown the effect of acupuncture therapy on reducing migraine recurrence, one of which is a study conducted by Biçer (2017) who examined the efficacy of acupuncture therapy in preventing migraine recurrence attacks with a total of 54 study subjects with migraine diagnoses. Acupuncture treatment therapy was given for a total of 26 sessions, first three days a week (12 sessions), then two days a week. Selection of acupuncture points is based on books and related literature. The number of migraine recurrences before acupuncture intervention (Mean= 5.31; SD= 1.67), then migraine recurrences decreased after acupuncture intervention (Mean= 5.31; SD=1.67).



The general theory of acupuncture is based on the premise that there are patterns of energy (Qi) flow through the body that are essential to health. Disruption of this flow is believed to be responsible for disease. The insertion of acupuncture needles results in the release of endogenous opioids by stimulating the free nerve endings of pain receptors known to be involved in pain control. Neurotransmitters involved in the analgesic system such as beta-endorphins, serotonin and enkephalins play an important role in this mechanism (Sahin et al., 2015).

Another study by Liu et al. (2018) also showed findings that support the efficacy and safety of acupuncture in migraine cases. The study involved 60 migraine patients who were randomly divided into two different groups. The intervention group was given acupuncture therapy and placebo drugs, while the control group was given acupuncture sham and original medicine (topiramate). The results showed a reduction in headache recurrence per day, the number of acute headache medications consumed, changes from the Migraine Disability Assessment, quality of life, State-Trait Anxiety Inventory-trait, and Beck Depression Inventory-II Score from baseline to endpoint.

So far, the specific mechanisms by which acupuncture affects migraines have not been fully elucidated. However, according to the gate control theory, the A delta nerve can be stimulated to close the pain gate in the central nervous system, therefore the sensation of pain will not be felt due to failure to reach the thalamus. In addition, many researchers argue that acupuncture can influence calcium signaling and the opioid system. Acupuncture stimulation can produce and release endogenous opioids, which bind to opiate receptors in the brain and mediate analgesia through the descend-

ing pain inhibitory system (Vijayalakshmi et al., 2014).

Another mechanism that can explain the effect of acupuncture therapy on migraine reduction is shown by the results of other studies which state that acupuncture treatment in the long term can modulate and normalize the decrease in the amplitude of low frequency fluctuation (ALFF) of the posterior cingulate cortex (RVM) or the trigeminocervical complex (TCC.) in migraine patients, where a decrease in the ALFF value of either RVM or TCC was associated with an increase in headache intensity. In addition, acupuncture therapy can normalize the disrupted descending pain modulation system (Li et al., 2017).

Acupuncture treatment in migraine cases is also related to the regulation of brain networks that control migraine pain and recurrence. Acupuncture therapy can increase metabolism in brain areas involved in pain processing. Acupuncture therapy can inhibit pain cognitive processing such as the orbitofrontal cortex, parahippocampal gyrus and emotional affective processing of pain which affect migraine recurrence (Liu et al., 2021). Perception of pain is also modulated by the DPMS which consists of cortical, sub-cortical brain networks and brainstem areas that are also stimulated to inhibit nociceptive afferent brain input to the central nervous system and behavioral responses to pain (Goksan et al., 2018).

Research by Gao et al. (2018) mentioned that acupuncture activates the release of opioid peptides in the central nervous system. The release of these peptides can relieve various painful conditions. Not only that, electro-acupuncture treatment can suppress CGRP expression in the trigeminal ganglion, which plays a very important role in triggering migraine attacks. With low CGRP expression, it can reduce migraine recurrence.

Meta-analysis was conducted on 9 primary randomized control trials conducted from 4 continents namely Asia, Australia, Europe and America, with a total sample of 429. Patients with migraine who received acupuncture therapy experienced migraine recurrence 0.31 units lower than those who were not treated with acupuncture. (SMD= -0.31; 95%CI= -0.61 to -0.01; p=0.040). The results also demonstrated high heterogeneity in effect estimates between studies (I<sup>2</sup>=79%; p<0.001). The results of the distribution of effect estimates between studies were more or less symmetrical to the right and left of the vertical mean estimate line indicating that there was no publication bias in this meta-analytic study. The limitation of this study is that it only uses 4 databases, namely PubMed, Google Scholar, Springerlink, and Science Direct, thus ignoring other database sources. In addition, this research also has limitations in translating languages so that it only uses articles published in Indonesian and English and then ignores articles published in other languages.

#### **AUTHORS CONTRIBUTION**

Elsa Tursina is the principal researcher who selects topics, searches for and collects research data. Hanung Prasetya and Bhisma Murti analyzed the data and reviewed research documents.

#### **FUNDING AND SPONSORSHIP**

This study is self-funded.

#### **ACKNOWLEDGMENT**

We are grateful to data-based providers including PubMed, Google Scholar, and Science Direct.

#### **CONFLICT OF INTEREST**

There is no conflict of interest in this study.

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