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Original Article

Analgesic Potency of Ibuprofen, Paracetamol, and Mephenamic Acid: A Randomized Controlled Trial

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Abstract

Background : Analgesics are a group of drugs to relieve pain. The use of analgesics is quite high, around 22.8% is used per year. Selection of analgesic drugs having adequate potency and minimal side effects is needed. Common analgesics publicly known involve paracetamol 500 mg, mefenamic acid 500 mg, and ibuprofen 400 mg. This study aims to compare the analgesic potency of paracetamol 600 mg, ibuprofen 600 mg and mefenamic acid 500 mg.
Methods : This study used a double blind randomized control trial. The study population was healthy subjects. The study sample consisted of 30 subjects with the inclusion criteria involve normal vital signs, while the exclusion criteria involve history of allergy to NSAID class drugs. This study consisted of three groups namely group 1 (K1)= paracetamol 600 mg, group 2 (K2)= mefenamic acid 500 mg, group 3 (K3)= ibuprofen 600 mg. Each subject was given medication according to the group and their pain latency (the time of onset of constant and unbearable pain) was measured every 30 minutes
Results : The repeated ANOVA test shows P= 0.1507 meaning that no significantly different analgesic potency was found between groups.
Conclusion : Paracetamol 600 mg, mefenamic acid 500 mg and ibuprofen 600 mg have equal analgesic potency.

Keywords : Analgesic, Parasetamol, Ibuprofen, Mefenamic Acid

INTRODUCTION

Analgesic derives from the word an – meaning not and algesia meaning pain, so analgesia means no pain. One of analgesic class is Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).[2] NSAIDs work by inhibiting the action of the cyclooxygenase enzyme disrupting the biosynthesis of prostaglandins . Some of analgesics in the NSAID class are acetaminophen/paracetamol, mefenamic and meclofenamic acids, and ibuprofen.[3]

Mild to moderate acute pain can be treated with NSAIDs as first-line agents. Acetaminophen or commonly known in Indonesia as paracetamol, is a non-opioid antipyretic analgesic which is very popular in the community to relieve mild to moderate pain. Paracetamol is different from other NSAIDs as it has less anti-inflammatory activity. The usual dose of paracetamol is 500 mg per consumption.[4] Mefenamic acid is an NSAID included in BCS (Biopharmaceutic Classification System) class II having low solubility with high membrane penetration.[5] Mechanism of action mefenamic acid is by inhibiting the cyclooxygenase enzyme.[6] Mefenamic acid and other NSAIDs can cause gastrointestinal disturbance involving stomach irritation if used in high doses or in the long period. The general dose of mefenamic acid for adults and children over 14 years is 500 mg per consumption.[7] Ibuprofen is also well known in Indonesia having anti-inflammatory and antipyretic effects, with a general dose of 400 mg effective for relieving pain. Ibuprofen is an NSAID considered having the least side effects and the safest NSAID among others.[8]

A report from The Oxford League Table of Analgesic Efficacy in 2006, NSAIDs have varying strength profiles. This study recorded data on the number needed to treat (NNT) or the value of the proportion of patients who are pain free within 4–6 hours compared to placebo, where the patients suffered from moderate to severe pain. NSAIDs involving ibuprofen 400 mg and paracetamol 500 mg have NNT 2.5 and 3.5 respectively,[9] while data on mefenamic acid has not been stated for its analgesic potency, whereas some of these NSAIDs is a non-selective class of NSAIDs commonly used by health care facilities in Indonesia.[10]

Research data in Brazil in 1 year found the overall analgesic consumption was 22.8%. Of them, 25.9% of analgesics was cumsumed by adults (18 years and over). The data for the use of non-opioid analgesics is 18.5%, NSAIDs 6.9%, and 0.5% opioid analgesics. The most widely used drugs were metamizole (37.8%) then paracetamol (25.3%). The prevalence of analgesic use may increase in certain conditions such as presence of chronic disease (regardless of the number of analgesic combinations ranging from one to three or more), five or more medication consumption (besides analgesics), possession of health insurance, use of emergency services within last year, or hospitalization within las year.[11] Based on the 2013 Riskesdas regarding data on NSAID use in Indonesia, the province with the highest NSAID consumption was East Java with 94%, followed by West Java province with 56%.[12] NSAIDs have been available for decades and their use has been described in many guidelines. Most guidelines recommend that "choice of a particular NSAID should be based on a balance between benefits and risks for the individual patient". However, studies are often incomplete.[13] The common side effect of NSAIDs is gastrointestinal disturbances with peptic ulcer as the most severe side effect. In the United States, 100,000 cases of peptic ulcers occurs due to NSAIDs consumption, so assessment of the NSAID potency is important so appropriate medication is selected and no NSAID with the same mechanism of action and potency is combined.[14] For that reason, this study aims to compare the analgesic potency of paracetamol, mefenamic acid, and ibuprofen as NSAIDs commonly used by the public.

METHODS

This research is a double blind randomized controlled trial. The study was conducted at the Pharmacology Laboratory of the Medical Faculty of Tadulako University and the Ear, Nose and Throat–Head and Neck, Functional Medical Unit of Undata General Hospital, Palu. The population is healthy subjects, not suffering from any illness. The sample size formula used is the Federer formula and the results are 9 subjects per group plus 10 percent of the drop out to 10 subjects per group. The inclusion criteria were willing to participate and signing consent to become s reserarch subject and having normal vital signs. The exclusion criteria were having a history of allergy to NSAIDs, history of taking NSAIDs within <24 hours before study, history of taking corticosteroid and gastrointestinal disturbance. This research was approved by the research ethics committee of the Medicine faculty of Tadulako University number 7245 A / UN 28.1.30 / KL / 2022. Informed consent and physical examination were carried out for each subject. The medication used in this study were paracetamol 600 mg, mefenamic acid 500 mg and Ibuprofen 600 mg. These medictions were chosen as they were the most widely used analgesics by public.[15] The dosage was adjusted according to a report from The Oxford League Table of Analgesic Efficacy regarding the effectiveness rates of various kinds of analgesics and adjusted for the doses available at the pharmacy. The 500 mg mefenamic acid and 400 mg ibuprofen is a common dose in the community, while the 600 mg paracetamol was chosen as previous study reported the use of this dose for acute pain.[15]

Based on the number of medications studied, this study divided subjects into 3 treatment groups: Group 1 (K1)= 600 mg paracetamol, Group 2 (K2)= 500 mg mefenamic acid, Group 3 (K3)= 600 mg Ibuprofen.

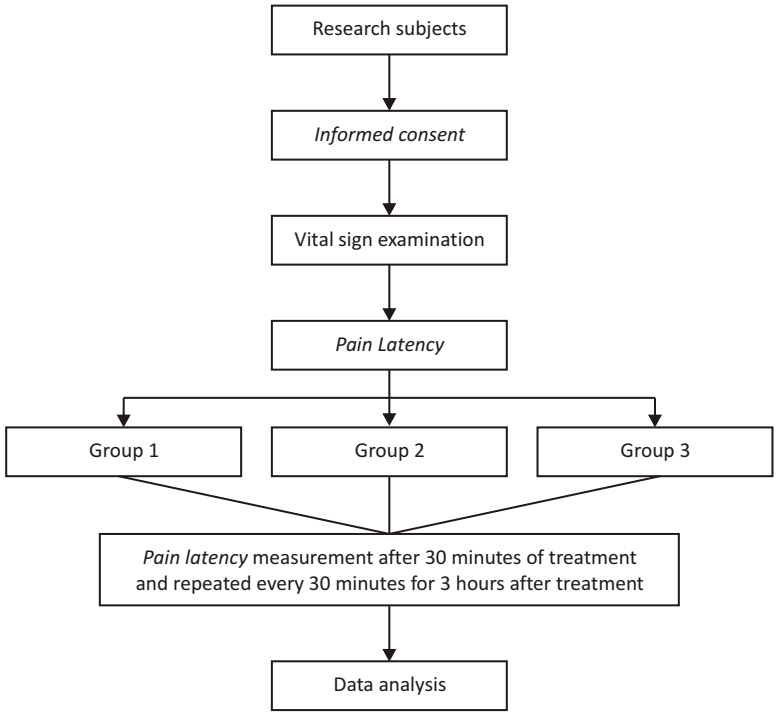

Figure 1. Consort diagram

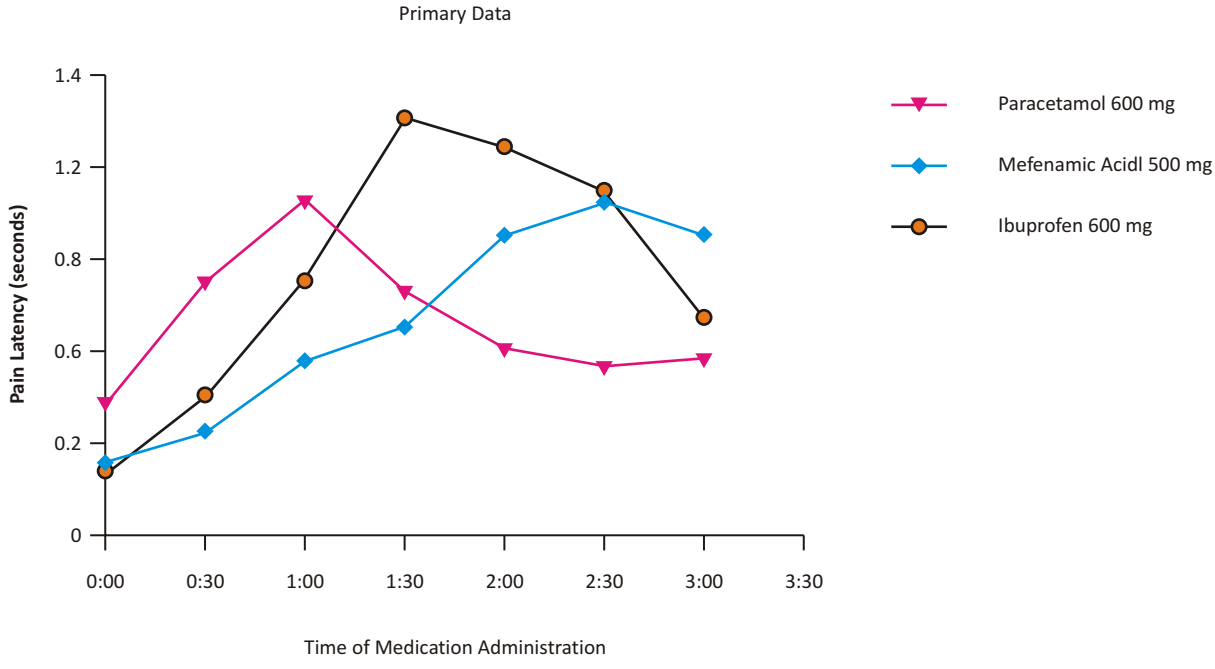

Figure 2. Comparison of the effect of three medications on pain latency (onset of constant pain since the introdution of pain) and time of observation

Thermometer, sphygmomanometer and smartphone were used to assess vital signs, specifically the sphygmomanometer was used to provoke pain in the subject arm by means of a sphygmomanometer cuff installed and pumped up to 180 mmHg and maintained at that pressure, then subjectds were assessed how long it takes to reach constant and unbearable pain (pain latency). Pain latency time was assessed before treatment

TABLE 1
Comparison of Mean Pain Latency in all groups

	Mean pain latency in seconds	P value
Paracetamol 600 mg	62.57	0.1507
Mefenamat acid 500 mg	64	
Ibuprofen 600 mg	67.86	

*Significant P < 0.05

TABLE 2
Comparison between groups

Bonferroni's Multiple Comparisons Test	95.00% CI of Diff	Adjusted P Value
Parasetamol 600 mg vs. Asam Mefenamat 500 mg	-10.31 to 9.965	>0.9999
Parasetamol 600 mg vs. Ibuprofen 600 mg	-15.55 to 4.722	0.5957
Asam Mefenamat 500 mg vs. Ibuprofen 600 mg	-15.38 to 4.894	0.6393

*Significant P < 0.05

(drugs administration) and every 30 minutes up to 3 hours after treatment. Data regarding pain latency time is the primary measurement data analyzed in this study. Research data were analysed using the PRISMA application. The data normality test used the Shapiro-Wilk normality test. The data normality test is to find out whether the data is normally distributed or not. Comparison test used repeated ANOVA and Bonferroni post hoc tests. The consort diagram is shown in Figure 1.

RESULTS

This research has been carried out at Pharmacology Department of Medical Faculty of Tadulako University to prepare materials and tools for research, followed by Functional Medical Unit of Ear, Nose and Throat–Head and Neck of of Undata General Hospital in June 2022. The population involved healthy subjects willing to participate and giving consent as research subjects. The sample size was 30 people based on predetermined inclusion and exclusion criteria. Samples were divided into 3 treatment groups namely Group 1 (K1)= 600 mg paracetamol, Group 2 (K2)= 500 mg mefenamic acid , and Group 3 (K3)= 600 mg Ibuprofen.

The study sample consisted of 40 subjects. Anamnesis and examination of vital signs were carried out and informed consents were signed then followed by provoking pain in the arm by inflating sphygmomanometer cuffs, pain latency was measured by using a Visual Analoque Scale (VAS). Subsequently, the treatment was carried out by adminisering medications in a double-blind manner, and measurements were repeated every 30 minutes with a total of 6 measurements during 3 hours of observation. After that, all research results were collected and primary data analysis was carried out.

The Figure 2 shows the onset of the three medications. Paracetamol shows a rapid onset but shorter duration than ibuprofen and mefenamic acid. Normalily test was carried out using the Shapiro–Wilk normality test showing that the research data is normally distributed. A repeated ANOVA was carried out to answer research objectives (Table 1) and Bonferroni's post hoc was carried out to compare groups (Table 2).

The repeated ANOVA (Table 1) showed no significant difference between all groups (p>0.05). The research data was analyzed to compare groups and obtained a P value> 0.05 (Table 2) meaning that no significant difference was found between medications studied. No subject complained any side effects from the medication during 24 hours of observation.

DISCUSSION

Seven observations were conducted and repeated every 30 minutes for 3 hours involving once before medication administration and six times after medication administration, then data were collected and analyzed. The results of this study cfound no significant differences between groups. It was found that paracetamol 600 mg, ibuprofen 600 mg and mefenamic acid 500 mg had equivalent analgesic potency.

The Oxford League Table of Analgesic Efficacy (2007) reported that NSAIDs have varying strength

profiles. This report shows the number needed to treat or the value of the proportion of patients who are free of pain within 4–6 hours compared to placebo, the pain used is moderate to severe pain. Several NSAIDs administered at clinical doses involving ibuprofen 400 mg and paracetamol 500 mg have a number needed to treat of 2.5 and 3.5 respectively. The medication in this study used larger dose involving ibuprofen, increased by a half, and paracetamol, increased by one fifth. As a result, there is a similarity in their analgesic potency.

Different Research findings were put forward by a study comparing visual analogue scale (VAS) in administering oral mefenamic acid, ibuprofen and paracetamol before circumcision. This study found that the ibuprofen group had the lowest VAS followed by mefenamic acid group and paracetamol respectively. Ibuprofen is more potent in treating post-circumcision pain as it strongly inhibits prostaglandins in peripheral tissues, sites of injury during circumcision.[16] Different study findings may arise as this study uses a larger dose, different from that used in other studies.

The side effect of these three drugs is on the gastrointestinal tract. The three drugs tested in this study were NSAIDs (3). A meta-analysis of the variability of the risk of complications of NSAIDs found that ibuprofen has the lowest risk of gastrointestinal complications followed by diclofenac, azapropazone and tolmetin. Ketoprofen and piroxicam showed the highest risk of gastrointestinal complications whereas indomethacin, naproxen, sulindac and aspirin showed moderate risk. High-dose of ibuprofen carries the same risk of gastrointestinal complications as naproxen and indomethacin.[17] No drug side effect was noted during this study as patients was only monitored for 3 hours for data collection and 24 hours for nay side effects. The medication administration is not repeated and the period is very short to cause severe side effects.

A study conducted at a puskesmas (literally means community health centre) in 2017 – 2019, paracetamol was used the most frequently used followed by ibuprofen and mefenamic acid respectively,[18] while a study regarding pattern of osteoarthritis treatment at hospitals found that mefenamic acid is the most frequently used pain killer followed by paracetamol and ibuprofen respectively. These two studies show that these three drugs are widely used and various types of analgesic are used depending on the case. In term of price, ibuprofen 600 mg is the most expensive which costs Rp 2285 followed by paracetamol 600 mg and mefenamic acid 500 mg which cost Rp 650 and Rp 360 respectively.

The limitation of this study is that assessment only uses a simple and subjective parameter. For further research, several objective measurement parameters can be added, such as for assessing bioavailability in the blood.

CONCLUSION

This study concluded that paracetamol 600 mg, mefenamic acid 500 mg and ibuprofen 600 mg had equal analgesic potency. This study recommends administration of NSAIDs should consider their potency as well as provision of several analgesics should not combine analgesics with the same mechanism of action.

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