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Comparison of ibuprofen and AAC (acetaminophen, Aspirin, Caffeine) for treating acute migraine episodes

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Abstract

Background and Objective: Migraines are the third most prevalent diseases and the seventh most debilitating diseases in the world. Medical treatment options for acute migraine episodes are various while none are infinitely effective for all patients. The aim of the present study was to compare fixed combination of acetaminophen, aspirin and caffeine with ibuprofen (AAC) with ibuprofen.

Materials and Methods: This double-blind clinical trial (Registration No. IRCT2017052930680N4) was performed upon patients attending the neurology clinic at Shahid Mostafa Khomeini General Hospital with complaint of headache. Treatment protocol for this study consisted of 2 medications prescribed for 4 consecutive episodes: Ibuprofen 400 mg and AAC tablets. Each patient received two sets of medication each for two episodes of headaches consisting of 2 of each drug. Pain perception was evaluated by 11-point Box Scale at three stages: prior to administration of the medication, and 2 and 6 hours after taking the medications and daily functions of the patient were assessed 6 hours after administering the medications by filling the Behavioral Rating Scale (BRS-6) which is a clinical assessment tool.

Results: Results of this study demonstrated that difference in severity of pain after taking 2 Ibuprofen tablets and AAC in the first and second episodes of migraine was statistically significant. Furthermore, AAC as compared to Ibuprofen, helped considerably more by allowing patients to regain enough focus to continue their daily life (P=0.001).

Conclusion: The results of this study showed that in patients with migraine, AAC is more effective than ibuprofen on improving patient's function and reducing pain.

Key words: Migraine disorders, Acetaminophen, Aspirin, Caffeine, Ibuprofen, Treatment.

1. Introduction

Migraine headache is a disorder with primary origin which recurrently debilitate the sufferer, is pulsatile and unilateral in nature and is sometimes accompanied by a myriad of other symptoms such as nausea, vomiting, sensitivity to light (photophobia), sound (hyperacusis), smells (osmophobia) and also disorders of the autonomic nervous system (1,2). Migraines are the third most prevalent diseases and the seventh most debilitating diseases in the world (3,4). In 2016, Global Burden of Disease (GBD) stated that more than one billion people are afflicted by this disorder which is ranked at sixth most common in the world. Moreover, the index Years Lived with Disability (YLD) for this disease is estimated to be well over 45 million (5). In a meta-analysis conducted in 2016 in Iran on thirty-four thousand subjects, the prevalence was calculated at 14% (6).

Medical treatment options for acute migraine episodes are various while none are infinitely effective for all patients (7). These medication are best taken at

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the earliest time after the onset of symptoms. Most patients suffice to self-medication, with a popular drug class of choice being off-the-counter (OTC). In this category, non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen can relieve the symptoms of migraine and act by inhibiting the synthesis of cyclooxygenase (COX) enzyme (8-10).

The combo drug AAC consists of Acetaminophen, Aspirin and Caffeine. Acetaminophen is antipyretic and analgesic agent with unknown mechanism of action (thought to be linked to inhibition of synthesis of prostaglandins in the CNS). Aspirin, thought to reduce pain and inflammation through its effect on the hypothalamus, inhibition of prostaglandin synthesis (COX inhibition) and blocking the impulse of pain, and lastly Caffeine, is a minor stimulant of the CNS which can alleviate the symptoms of migraine headaches. In several studies, it has been suggested that this medication can be helpful in treating acute episodes of migraine headaches (7,11).

The debilitating effects of migraines are well established, with more than a third of the cases missing at least one working day in a three-month period, 80.1% losing at least a day of house chores and 64.9% fail at least for a day to keep up with social activities (12,13). Moreover, this disorder can independently operate as a risk factor for other disorders such as multiple sclerosis or stroke (14-16). In 15% of the population suffering from migraines, the medical treatment fails to result in symptom alleviation; also, for more than 20 years, no new medical treatment has been discovered for treating acute episodes of migraines. In addition, the Triptan drug class which serves as a last resort for treating acute episodes of migraines, causes hypersensitivity in some patients in need (12). As a result, investigating further with the purpose of reaching better treatment options is helpful for sufferers of this disorder. The present study proved the astonishing efficacy of the medications AAC in patients who did not respond to other treatment options. Moreover, we decided to compare AAC with another common drug of choice in treatment of acute migraine headaches, i.e. ibuprofen.

2. Materials and Methods

This double-blind clinical trial (Registration No. IRCT2017052930680N4) was performed on patients attending the neurology day-clinic at Shahid Mostafa Khomeini general hospital with a complaint of headache. The subject selection process was through "convenience sampling" method (confidence interval 95%, statistical power 80%, standard deviation of degree of headache was 1.5 and 55 subjects were selected, and it was raised up to 60 in order to ensure sample size authenticity. Prior to selection, a thorough neurological examination was performed on the outpatients complaining of headache. The patients selected for this study met all criteria such as age between 20 and 45 years, established diagnosis of migraine headaches based on International Headache Society (IHS) criteria (17), prior to this visit, patient was suffering from migraine headaches for an overall period of at least 6 months, each month consisted of at least 3 episodes and each episode had a duration of at least 30 minutes, no previous preventative medication has ever been used. Moreover, patients suffering from other forms of headaches (tension headache and rhinosinusitis-related headache) were excluded, along with other patients affected by active peptic ulcers or severe gastrointestinal distress, a history of current or former psychiatric disorders, and also patients on any of the following medication: beta blockers, calcium channel blockers, tricyclic antidepressants (TCA's), anti-convulsants, MAO inhibitors, corticosteroids, botulinum toxin and those with chronic substance abuse problem. Also, among the patients excluded from the study were those with a prior history of relevant medication hypersensitivity and those without personal consent to take part in the study.

Treatment protocol for this study consisted of 2 medications prescribed for 4 consecutive episodes: Ibuprofen 400 mg and AAC tablets (containing Acetaminophen 162.5 mg, Aspirin 325 mg and Caffeine 32.5 mg). Each patient received two sets of medications, each for two episodes of headaches consisting of 2 of each drug (first and second episodes: 800 mg Ibuprofen each, and third and fourth episodes: 2 tablets of AAC each). Both the patients and the physicians administering the medications were unaware of the drug being taken by the patient. Afterwards, the subjects completed a questionnaire scoring their pain at 2 and 6 hour intervals after taking the medication. Pain perception was evaluated by 11-point Box Scale at three stages: prior to administration of the medication, and 2 and 6 hours after taking the medications, while the lowest and highest score being 0 and 10 respectively (18). Daily functions of the patients were assessed 6 hours after administering the medications by filling the Behavioral Rating Scale (BRS-6) which is a clinical assessment tool (19). The score each patient gave to the medication was documented into 4 categories: for each patient a first and second episode for each ibuprofen and AAC.

Finally, the accumulated data was analyzed using SPSS software (IBM, v.16), using tests such as t test and Chi-squared. Significant value for all analyses were appointed at $p<0.05$.

The researchers were committed to the ethical guidelines of the Declaration of Helsinki and approval for the study was obtained from the Institutional Review Board at Shahed University. The goal, the wanted effects and unwanted side-effects of the treatment were explained, and informed consent forms were obtained from all participants. Further, the subjects were reassured that their information is kept private and the final result are published without subject information and the cost of treatment are entirely upon the research team.

3. Results

In this study which consisted of 60 patients suffering from migraines, patients were trialed for the comparative efficacy of Ibuprofen and AAC on treating acute migraine episodes; 47 patients (78.33%) were females and 13 (21.67%) were male; all were 20 to 45 years old with an average age being 32.02±2.44 years.

In regards to the first episode of migraine occurring in patients, 2 hours after administering the medications, 55 subjects (91.66%) treated with AAC and 31 subjects (51.67%) treated with Ibuprofen had a pain score of 0 to 3. Thus, the difference in efficacy between AAC and ibuprofen in treating acute migraine episodes was statistically significant after 2 hours ($p<0.001$). Moreover, 6 hours after treatment, 93.33% of patients taking AAC and 63.33% of patients taking Ibuprofen scored on the pain scale between 0 and 3. This too meant that the difference in efficacy of AAC and Ibuprofen in treating acute migraine episodes is statistically significant ($p=0.001$). (Fig. 1)

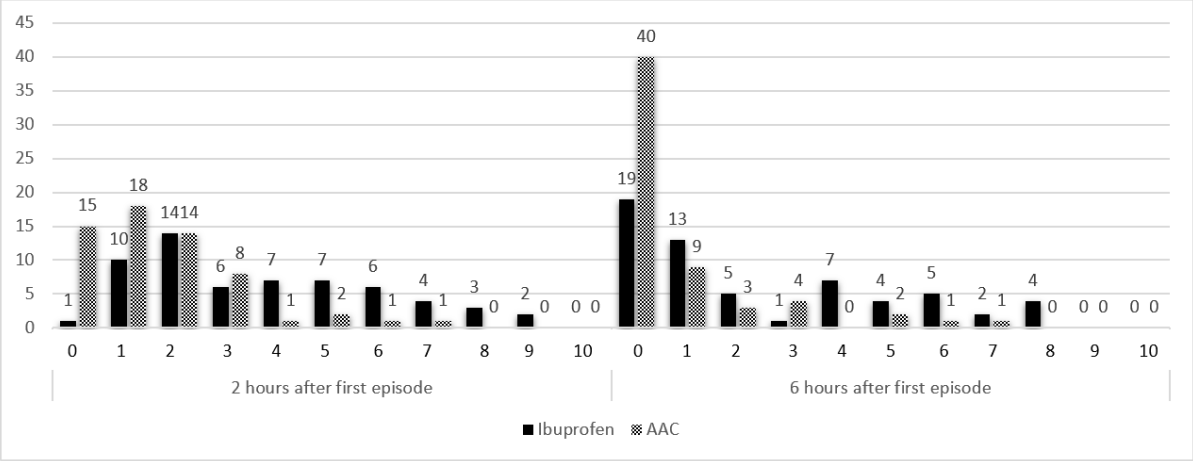

Figure 1. Severity of pain, 2 and 6 hours after taking 2 Ibuprofen tablets and AAC in the first episode of migraine based on BS-11

In regards to the second episode of migraine occurring in patients, 2 hours after administering the medications, 54 subjects (90%) treated with AAC and 42 subjects (70%) treated with Ibuprofen had a pain score of 0 to 3. The difference in pain relief between AAC and ibuprofen in treating acute migraine episodes was statistically significant after 2 hours ($p<0.005$). Furthermore, 6 hours after treatment, 93.33% of patients taking AAC and 68.33% of patients taking Ibuprofen scored on the pain scale between 0 and 3, meaning that the difference in efficacy of treating migraine episodes between AAC and Ibuprofen was statistically significant ($p<0.001$) (Fig. 2).

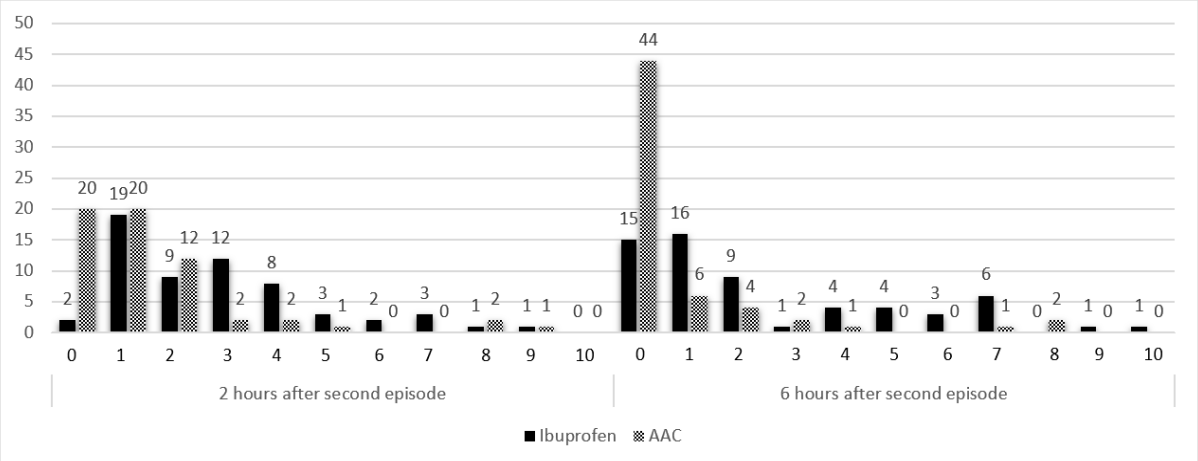

Figure 2. Severity of pain, 2 and 6 hours after taking 2 Ibuprofen tablets and AAC in the second episode of migraine based on BS-11

Also, the difference in efficacy of treating migraine episodes with AAC between first and second episodes of migraines occurring was not statistically significant ($p>0.05$). Moreover, the BRS-6 scale analysis yielded

that 35 patients (58%) using AAC and 15 patients (25%) using Ibuprofen felt well enough to do daily chores without difficulty. Furthermore, AAC compared to Ibuprofen, helped considerably more by allowing patients to regain enough focus to continue with their daily life (p=0.001).

4. Discussion

This study was designed based on the experienced-based observation that AAC is effective in controlling symptoms of acute migraine headaches. Another commonly used medication for this condition, Ibuprofen, was chosen to compare against AAC in efficacy of treatment. Since each patient has different tolerance to pain, each patient was compared to themselves. The outcome was that patients' pain score, 2 and 6 hours after taking AAC was considerably lower than those who had taken ibuprofen. Additionally, patients regained considerably more focus to continue with their daily routine 6 hours after taking AAC compared to 6 hours after taking Ibuprofen. In the study conducted by Lipton et al., efficacy of AAC in treating migraine episodes was compared with a placebo which resulted in AAC being statistically better at treatment as compared to placebo (20). The present study is in concordance to Lipton et al. study. Moreover, the various studies published by Goldstein et al. over 15 years on AAC (dosage: Acetaminophen 500 mg, Aspirin 500 mg, Caffeine 130 mg) compared with Sumatriptan and Ibuprofen (most common drugs in treating acute migraines) all resulted in the fact that both AAC and Ibuprofen as compared to placebo are effective in treating acute migraine episodes and AAC is better than Ibuprofen in both the amount of pain lowered and the speed in which the pain was lowered (21). Furthermore, it was established that AAC is considerably more effective at treating migraines as compared to the single-dose therapy with Ibuprofen and placebo (11). Also, triple therapy with AAC is faster at treating symptoms compared to Sumatriptan (22) and again in another study, AAC was better at reducing pain as compared to placebo (23). The present study is in concordance to the publications of Goldstein et al.

Diener et al. conducted a study in 2005 comparing the efficacy of several treatment plans to treat symptoms of migraines, with the combo medication AAC (dosage: Acetaminophen 500 mg, Aspirin 400 mg, Caffeine 50 mg) being considerably better than AA (Acetaminophen and Aspirin) and each individual drug and lastly placebo. On the other hand, caffeine as single therapy was the only treatment regimen which was not statistically better than placebo (24). Moreover, Diener et al. stated in a study published in 2011 that the combination of Aspirin, Acetaminophen and Caffeine was tremendously effective in treating acute episodes of migraine headaches when compared to placebo (25). The present study's findings are congruent with Diener's study.

The important hallmarks of this study were "efficiency evaluation by function improvement and degree of focus regained for daily life and chores" using BRS-6 Scale comparing AAC and Ibuprofen (19). The data yielded that function improvement 6 hours after taking AAC was reported considerably more compared to Ibuprofen. Despite treating the subjects with lower dosages of the combo medication AAC in the present study compared to similar studies, the outcome was still analogous with them when treating patients with migraines refractory to Ibuprofen.

The limitation of the present study was the lack of a control group which would be difficult since pain perception and threshold varies among different subjects, so each patient's scoring of the two medications were compared to themselves. It is suggested that to further this study, "focus regain" be targeted and evaluated after treatment in different time periods. Also, the medication AAC and its effect on focus regain in migraine sufferers should be targeted and compared to other medications. Moreover, a bigger sample size should help reinforce the findings on the effect of AAC in treatment of acute migraine headaches and also, randomized clinical trials to evaluate the effect of AAC on other types of headaches.

To conclude, the results of this study showed that in patients with migraine, AAC is more effective than ibuprofen on improving patient's function and reducing pain.

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Conflict of interest

The authors declare that they have no conflict of interest.

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