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Clinical Trial

Intravenous caffeine versus intravenous ketorolac for the management of moderate to severe migraine headache

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Abstract

The aim of this study was to determine if intravenous caffeine is as effective as intravenous ketorolac for the treatment of moderate to severe migraine headaches. Eligible patients randomly received 60 mg caffeine citrate or 60 mg ketorolac infused intravenously. Their pain score were measured at baseline, one hour and two hours after infusion. Therapeutic success was defined as decreasing of at least 3 points on the pain score. In total 110 patients were enrolled (75.5% women). Therapeutic success after 60 min was achieved by 63.6% of patients in the caffeine and 70.1% of patients in the ketorolac group (p = 0.23). After 120 min, 87.3% of the caffeine group and 83.6% of the ketorolac group achieved therapeutic success (p = 0.49). In this multi-center, randomized double blind study, intravenous caffeine was as effective as intravenous ketorolac for first line abortive management of acute migraine.

Introduction

Migraine is a neurologic disorder that its prevalence is estimated as high as 17% in women and 6% in men and accounts for 1.3% of productive years lost due to medical disability (Natoli et al., 2010). Despite efforts to keep patients out of hospitals, migraine headaches are still sometimes managed in emergency departments and urgent care centers with intravenous medications. A large variety of agents are available for abortive migraine management in Emergency Department (ED). Ketorolac is a potent nonsteroidal anti-inflammatory drug (NSAID) that has been shown to be effective in this regard (Baratloo et al., 2016; Taggart et al., 2013). Despite its favorable effects, there are known side effects, contraindications and incomplete effectiveness. The search to find an alternative or adjunct medication has lead to the suggestion of caffeine for acute migraine management (Lipton et al., 1998; Pini et al., 2012). What makes caffeine attractive to conduct research is the fact that it has also been proposed to be one of the triggers for migraine headaches (Baratloo et al., 2015; Rogers et al., 2005). Parenteral caffeine has never been studied for acute migraine in a double blind fashion. This double blind clinical trial was designed to determine if intravenous caffeine is as effective as intravenous ketorolac in managing moderate to severe migraine headaches.

Materials and Methods

Study design

This double blind clinical trial was conducted in two tertiary care emergency departments in the city of Tehran, Iran. The goal of this study was to compare the effectiveness of caffeine versus ketorolac in managing migraine headaches.

Study population

Sampling was conducted between January and December 2014 on patients admitted to the care centers who met international classification of headache disorders, 2nd edition criteria for migraine for at least a year prior to the presentation day. Participants were between 18 and 65 years of age. Inclusion also required 2 episodes of headaches in the previous 3 months followed by a symptom free period or an episode of only mild symptoms. The following exclusion criteria were used to minimize confounding factors and to further homogenize the study population: Complex migraine, medication overuse headache, presence of other co-existing primary headaches (e.g. tension, cluster etc.). We also excluded patients for any of the following medication contra-indications: History of or current atrial or ventricular tachycardia, uncontrolled hypertension (defined as systolic BP $\geq$150 mmHg), ischemic heart disease, peptic ulcer disease, inflammatory bowel disease, obsessive compulsive disorders, pregnancy, lactation (nursing), coagulation disorders, renal or hepatic disease, sleep disorders, diabetes, respiratory disorders (asthma and COPD), drug or alcohol abuse and hypersensitivity to caffeine or ketorolac. Initially 193 patients were enrolled (Figure 1). Thirty four patients met at least one of the exclusion criteria. Forty nine patients refused to participate. Finally 110 patients were equally divided between the treatment groups- 55 in each study arm.

Intervention

Using an online random number generator, patients were assigned to 60 mg of caffeine citrate in 100 mL of normal saline or to 60 mg of ketorolac in 100 mL of normal saline. Each intervention was infused over 10 min. This dosage of caffeine was adopted from a previously published study to ensure safety and efficacy and to also avoid significant side effects (Baratloo et al., 2015). The ketorolac arm used manufacturer suggested dosages. For choosing the proper drug dosage, a meeting of academic neurologist, pharmacologist and emergency medicine experts was formed and the decision was made. Permuted randomization blocks without stratification were used in this study. Medication packages were prepared and packaged in identical thick plastic containers and were coded by an independent pharmacist. Thus, researchers, clinicians and patients were blinded to the intervention received. The medication packages were given to the study coordinators at each site. The name of the medication was only to be released if a serious side effect happened. In these cases the patient had to be excluded from the study and a treatment failure was supposed to be registered in the affected group. If the headache was not reasonably managed in the first 120 min after the end of the medication infusion, an attending physician was allowed to use an alternative medication such as a narcotic to treat the pain

Outcome measures

Data were collected by the chief resident at each site. Pain intensity was measured using a 10-point visual analog pain scale prior to medical intervention and then 60 and 120 min post medical intervention. The 120 min endpoint was chosen based on similar previous clinical trials, where 120 min was found to be standard (Coppola et al., 1995; Shahrami et al., 2015). Our primary outcome was therapeutic efficacy, which was defined as an improvement in three points on the visual analog scale without requirement of rescue medication. Patients were followed for 120 min from medication administration for observations of any side effects of the medication. Common side effects to be considered were tachycardia, hypertension, nausea, vomiting, site,

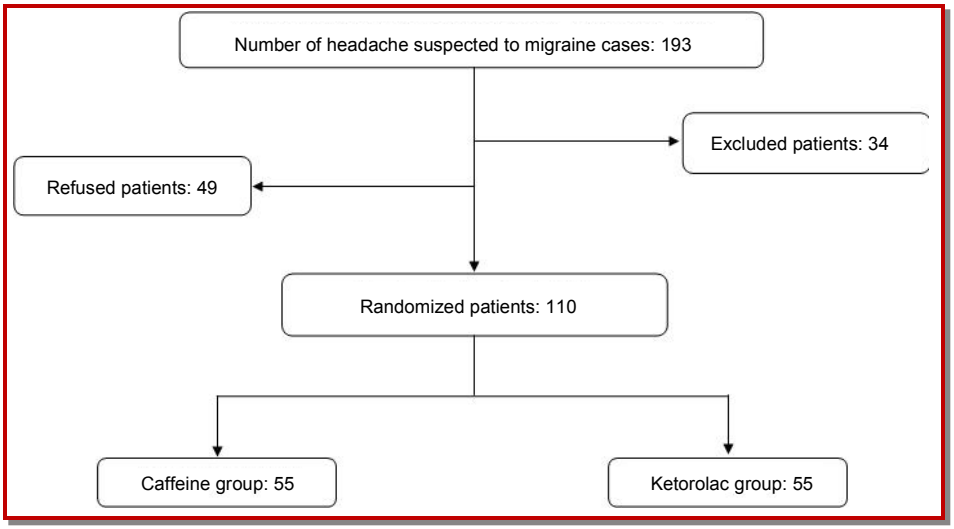

Figure 1: Enrolment of patients

pruritus, agitation, restlessness and pain in the injection. Lastly, if patients experienced a significant decrease in their pain score (of at least three) and did not show any adverse effect, they were discharged from the department (Alschuler et al., 2012; Jensen et al., 2001; Kelly, 2001; Mark et al., 2009; Zelman et al., 2005). We also followed all patients after pain control to ensure the maintenance of at least 2 additional pain-free hours.

Data analysis

Sample size in this study was calculated based on the anticipated therapeutic successes of the caffeine group (44%) and the ketorolac group (74%) with $\alpha = 0.05$ and $ß = 0.1$. Using these parameters, sample size was calculated to be at least 51 per group. Data analysis was done by STATA version 11 software (Stata Corp. TX, USA). Since the data distribution was not normal ($p<0.05$, based on Kolmogov-Smirnov test) the Mann-Whitney and Wilcoxon signed-rank test were used for ordinal pain score data. The Chi-square test and Fisher's exact test were used for dichotomous outcomes. A non-parametric (Wilcoxon-type) test for trend was used to compare the effect of the drugs in the first and the second 60 min. Sub-group analyses for males versus females and for age groupings younger and older than 40 were also done. Therapeutic success was defined as a minimum of a three-point drop in the pain score and maintenance of at least a 2 hours pain-free period. In all analyses, $p<0.05$ was considered statistically significant.

Results

Forty four (80.0%) members of the caffeine group and 39 (70.9%) members of the ketorolac group were female ($p = 0.27$). The average ages in the caffeine and ketorolac groups were 30.3 ± 8.6 and 36.0 ± 2.6 years, respectively ($p = 0.01$).

The average pain score upon initial emergency department evaluation in the caffeine and ketorolac groups were 8.4 ± 1.5 in both groups ($p = 0.96$). After 60 min post-intervention, pain scores were 5.4 ± 1.5 and 4.9 ± 1.9 in the caffeine and ketorolac groups respectively ($p = 0.23$). After 120 min, pain scores were 3.5 ± 2.6 and 3.5 ± 2.1 in the caffeine and ketorolac groups, respectively ($p = 0.49$) (Table I).

Therapeutic success in the caffeine group was 63.6% after 60 min and 87.3% after 120 min. The same measured variables were 70.1% and 83.6% in the ketorolac group respectively (Table II). While the therapeutic success in each group was statistically significantly different after 60 and 120 min when compared to baseline no statistically significant difference was found between the groups.

Fortunately, no patients suffered any of the aforementioned adverse effects. Sub-group analysis of the collected data did not reveal any age or sex dependent significant differences between the groups. All 83 patients who were not enrolled were treated with intravenous acetaminophen. Morphine sulfate was administered as a rescue medication.

Table I

Comparison of mean reduction of pain scores between two groups after one and two hours

Time	Ketorolac group		Caffeine group		p value
	Mean and standard deviation of pain score	Mean of declining of pain score	Mean and standard deviation of pain score	Mean of declining of pain score	
On admission	8.4 ± 1.5	-	8.4 ± 1.5	-	0.96[a]
After one hour	4.9 ± 1.9	3.5 ± 1.6	5.4 ± 2.4	3.0 ± 2.0	0.23[b]
After two hours	3.5 ± 2.1	4.9 ± 2.3	3.5 ± 2.6	4.9 ± 2.2	0.49[b]

[a]Based on Mann-Whitney test; [b]Based on Wilcoxon rank test

Table II

Comparison of success rate between groups after one and two hours

Time	Ketorolac group		Caffeine group		P-value
	Success rate	95% Confidence interval	Success rate	95% Confidence interval	
After one hour	70.1	57.9-81.2	63.6	50.4-75.1	0.42[a]
After two hours	83.6	71.7-91.1	87.3	76.0-93.7	0.59[a]

[a]Based on non-parametric (Wilcoxon-type) test for trend

Discussion

In this randomized, double-blind multi-center ED-based study, we have demonstrated that intravenous caffeine is as efficacious as intravenous ketorolac for the acute treatment of migraine. Ideally, treatment for migraine headaches should be safe, fast and effective. An optimal treatment should have minimum side effects and must decrease the odds of recurrence. To this day, we have yet to find a treatment regimen that contains all of these qualities simultaneously. Studies in this field are still underway. The present study shows that caffeine and ketorolac have similar therapeutic success in controlling the pain in moderate to severe migraine headaches.

While there have been studies conducted on the effects of these two drugs on migraine headaches, to our knowledge this study is the first of its kind to perform a head to head comparison of caffeine and ketorolac. In a meta-analysis, Tagart et al., examined the effects of ketorolac on decreasing the pain intensity of severe headaches in adults. They found that ketorolac has therapeutic effects on this type of headache that are comparable to standard treatment regimens. Therefore, these authors recommended ketorolac as a second line therapy in these cases (Taggart et al., 2013). In a randomized study not included in the meta-analysis, Friedman et al., reported similar findings in regards to the effectiveness of ketorolac in managing migraine headaches—a decrease in pain scale scores of 3.9 units (Friedman et al., 2014). Meredith et al., compared the effectiveness of sumatriptan and ketorolac on emergency department migraine management, finding the latter to be more effective (Meredith et al., 2003).

We were unable to identify any randomized studies of intravenous caffeine. Goldstein et al., showed in a study that oral combinations containing caffeine are faster and more potent compared to ibuprofen in the ED management of migraines (Goldstein et al., 2014). In another study by Di Monda et al., a caffeine containing cocktail (indomethacin, prochlorperazine and caffeine) was found to be superior to sumatriptan in the management of acute migraines (Monda et al., 2003).

We only followed patients during their ED stay. A longer follow-up period would have revealed the frequency of recurrence of symptoms after caffeine and ketorolac. Another limitation to this study is the lack of a placebo arm. Although including a placebo arm would have provided useful data, doing so is hard to ethically justify, given that patients admitted to the emergency department would not receive any pain management for at least 120 min. Since the 30% non-inferiority margin that we prospectively defined based on previous published data was a rather subjective number. Although we found caffeine to be non-inferior to ketorolac in acute migraine management, this study was under-powered to show a non-inferiority of this margin size and the conclusions need to be made cautiously.

Conclusion

Caffeine is as effective as ketorolac and can be a reasonable first line abortive medication in emergency department management of acute migraine.

Ethical Issue

The sampling phase was performed after final approval was received from the ethics committee of the Shahid Beheshti University of Medical Sciences. Patients were enrolled to this study voluntarily after giving informed consent. The declaration of helsinki ethical principles were followed and respected throughout the study. The study was conducted using the manual of the "International Conference on Harmonization of Guidelines for Good Clinical Practice". The study protocol is available at www.IRCT.IR with the registration number IRCT2013120315640N1.

Conflict of Interest

All authors declare that there is no conflict of interest in this study.

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