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Intramuscular tramadol *vs.* diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised, double-blind study

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Abstract The aim of this prospective, randomised, double-blind study was to evaluate the efficacy of intramuscular (IM) tramadol 100 mg in emergency department treatment of acute migraine attack and to compare it with that of IM diclofenac sodium 75 mg. Forty patients who were admitted to our emergency department with acute migraine attack according to the International Headache Society criteria were included in the study. Patients were randomised to receive either tramadol 100 mg (*n*=20) or diclofenac sodium 75 mg (*n*=20) intramuscularly. Patients rated their pain on a four-point verbal scale (0=none, 1=mild, 2=moderate, 3=severe) at the beginning of the trial and at 30, 60, 90 and 120 min. At each time interval, severity of associated symptoms were also questioned and recorded. Global evaluation of the drugs by patients and doctors were also recorded. Patients were also asked if they would prefer the same injection in future visits. Any adverse events, whether related to the drug or not, were also recorded. Patients were followed up by telephone 48 h later to check for any headache recurrence. Two-hour pain response rate, which was the primary endpoint, was 80% for both tramadol and diclofenac groups. There were no statistically significant differences among groups in terms of 48-h pain response, rescue treatment, associated symptoms' response, headache recurrence and adverse event rates. Fifteen (75%) patients in the tramadol group and 16 (80%) patients in the diclofenac group stated that they may prefer the same agent for future admissions. In selected patients, tramadol 100 mg IM may be an effective and reliable alternative treatment choice in acute migraine attacks.

Key words Migraine treatment • Tramadol • Diclofenac • Randomised controlled trial

Introduction

Migraine headache is a common presenting complaint to the emergency department (ED). Aims of treatment include rapid pain relief, improvement in associated symptoms, minimisation of length of stay and prevention of recurrence. Many treatment alternatives have been shown to be effective in the treatment of acute migraine attack including non-steroidal anti-inflammatory drugs (NSAID), antiemetics, phenothiazines, narcotics, ergot alkaloids and triptans [1–9].

Although it is not the recommended first-line therapy, in nearly half of migraine headaches emergency physicians in the USA prefer parenteral opioids [10]. Tramadol is an opioid agent with central activity. Mechanism of its analgesic activity involves two components: low-affinity binding to opioid receptors and inhibition of monoamine reuptake [11]. Tramadol has a proven analgesic activity for many acute and chronic pain conditions [12–16]. Adverse effects, nausea in particular, are dose-dependent and therefore considerably more likely to appear if the loading dose is high. Other adverse effects are similar to those of other opioids but they appear to be less severe [11]. Potential dependence, tolerance and abuse rates of tramadol are also reported to be relatively low [17]. With these features tramadol appears to have a potential role in the treatment of headaches. However, there is limited data on its use in headache [10, 18] and we could not find any study on its use in acute migraine attack.

The aim of this study was to evaluate the efficacy of intramuscular (IM) tramadol 100 mg in ED treatment of acute migraine attack and to compare it with that of IM diclofenac sodium 75 mg, an agent shown to be effective in treatment of acute migraine attacks [1–4], in a prospective, randomised and double-blind fashion. The primary outcome measure of the study was 2-h pain response after the injection of the study drug. A sample size of 32 patients was determined to achieve 80% power to detect an effect size of 0.5 using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Methods

This prospective, randomised, double-blind trial was conducted in a university hospital ED with an annual census of about 26 000. The study was designed according to the second edition of guidelines for controlled trials of drugs in migraine [19]. The institutional review board and ethics committee approved the study (Decision number: 2003-24-03). Informed consent of all eligible patients was obtained before the study. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

All patients between 18 and 65 years of age with acute migraine attack according to the second edition of the International Headache Society (IHS) criteria for migraine without aura [20] were eligible. Patients with any known sensitivity to either tramadol or diclofenac, patients taking excessive analgesics (more than 10 days per month), patients using antidepressants and antipsychotics regularly within the last 3 months, patients with history of epilepsy, alcohol or drug abuse, patients over 50 years of age with new onset migraine and pregnant or lactating patients were excluded from the study.

Patients with other types of headache (e.g., tension-type headache) together with migraine were included in the study if they could clearly differentiate the type of headache. Patients who had taken analgesics or anti-migraine medication prior to ED admission were included only if there was no response to drug and if more than 6 h had passed between use of the drug and ED admission. Regular prophylactic migraine medications, other than antidepressants and antipsychotics (as they may interact with central nervous system effects of tramadol), were allowed. Patients were allowed to participate in the study only once.

After a detailed headache history, a general physical and neurological examination was performed in all eligible patients by the attending emergency physician. Diagnosis and eligibility for the study were then confirmed by a neurologist. Baseline headache characteristics and presence or absence of associated symptoms (nausea, vomiting, photophobia and phonophobia) were recorded. Severity of the headache was rated on a four-point verbal scale (0=none, 1=mild, 2=moderate, 3=severe) [19].

After the collection of baseline data, patients were randomised to receive either tramadol 100 mg IM or diclofenac sodium 75 mg IM. Randomisation was achieved by computer-based generation of random numbers. To assure blindness, tramadol preparation, which was 2 ml, was completed to 3 ml with normal saline solution to look identical to diclofenac sodium 75 mg 3 ml preparation. Injections were prepared and applied by a nurse who was not a part of the study. Neither the patient nor the physician was allowed to learn the contents of the injection until the end of the study period.

After the injection, patients rated the severity of pain on the four-point verbal scale at 30, 60, 90 and 120 min. At the end of the study period (2 h), the presence or absence of associated symptoms was recorded. Patients were questioned about whether or not they would prefer the same injection for future admissions. Any adverse events that could be related or not related to the drug were also recorded. Patients and doctors globally evaluated the drug on a 5-point verbal scale (0=very poor, 1=poor, 2=no opinion, 3=good, 4=very good). After these data were obtained the doctor and the patient were informed of the content of the injection. Then, the patients with a pain score of 2 (moderate) or 3 (severe) or with unbearable associated symptoms received rescue treatment at the discretion of the emergency physician. Patients were followed up by telephone 48 h after the ED admission and questioned about any headache recurrence, use of additional analgesics and any search for medical assistance.

The primary outcome measure of the study was 2-h pain response and positive response was defined as pain score dropping from 3 or 2 to 1 or 0 within 2 h after the injection. Secondary outcome measures were 2-h pain-free response, 48-h pain response, 48-h pain-free response, response to associated symptoms, rescue treatment, recurrence and adverse event rates. Two-hour pain-free response was defined as pain score dropping from 3 or 2 to 0 within 2 h. Positive 48-h pain response was defined as patients with a positive 2-h pain response without rescue treatment and recurrence at 48-h follow-up. Positive 48-h pain-free response was defined as patients with a positive 2-h pain-free response without rescue treatment and recurrence at 48-h follow-up. Response to associated symptoms was accepted as positive if the symptom improved or was completely relieved.

All demographic, baseline, study and follow-up data were recorded on a standard study form by a resident or attending

physician. Data was then entered into SPSS 10.0 statistical software package (SPSS Inc. Chicago, IL) after the follow-up data were recorded.

The SPSS 10.0 statistical software package (SPSS Inc. Chicago, IL) was used for statistical analysis. Power analysis was performed with the NCSS-PASS 2000 Statistical software package (Number Cruncher Statistical Systems, Kaysville, UT). For categorical variables chi-square and Fisher's exact chi-square tests were used. A two-tailed alpha value ≤0.05 was accepted as statistically significant. Data were presented descriptively as means±standard deviation when appropriate. Odds ratios (OR) and 95% confidence intervals (95% CI) of odds ratios of groups were calculated to evaluate the probability of whether one drug was superior to another. The closer the odds ratio value is to 1, the more likely it is that the analysed parameter is similar in both groups.

Results

Forty-seven patients with acute migraine headache admitted to the ED of Uludag University School of Medicine between October 2003 and May 2004 were randomised to tramadol (*n*=23) and diclofenac (*n*=24) groups (Fig. 1). Of these 47 patients, 7 were excluded from final analysis due to protocol violations (2 in tramadol, 3 in diclofenac groups) and patients' decision to leave the study (1 in tramadol and 1 in diclofenac groups). Demographic features and migraine characteristics of the 40 patients that completed the study are shown in Table 1.

Pain response rates and pain-free response rates at 2 and 48 h were similar for both drugs. Pain response rates at 2 and 48 h for each trial arm are shown in Figure 2. At

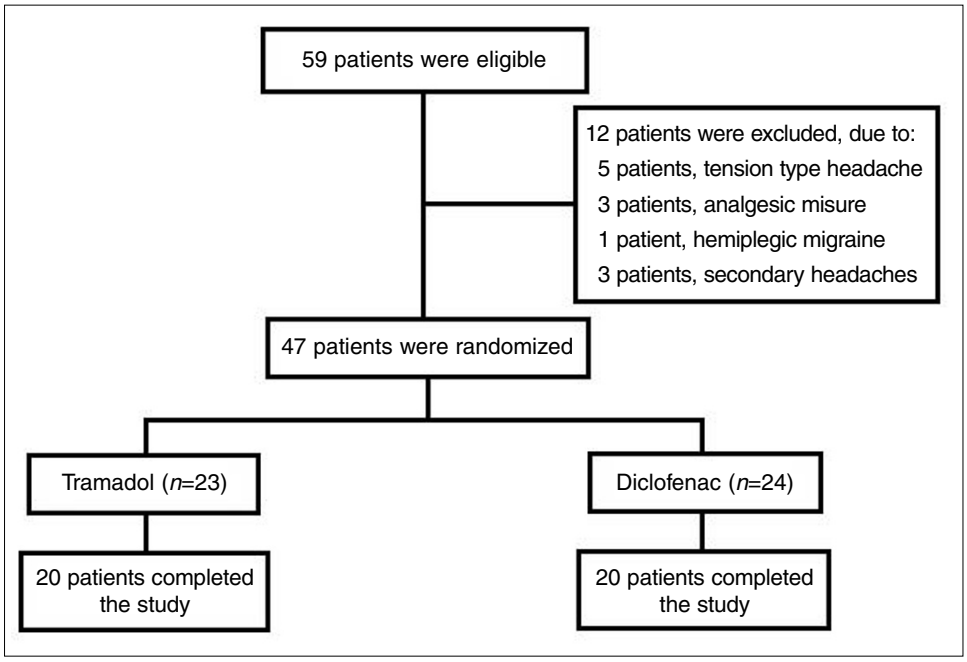

Fig. 1 Randomisation of the patients

Table 1 Demographic features and migraine characteristics of the patients

	Tramadol	Diclofenac
Male, *n* (%)	6 (30)	3 (15)
Female, *n* (%)	14 (70)	17 (85)
Mean age±SD	37.9±13.3	37.0±11.06
Mean diagnosis duration, years±SD	6.47±4.70	6.05±3.52
Mean number of attacks per month±SD	2.70±1.17	2.40±1.23
Patients on prophylactic treatment, *n* (%)	3/20 (15)	3/20 (15)
Patients taken analgesic before ED, *n* (%)	5/20 (25)	6/20 (30)
Nausea, *n* (%)	18/20 (90)	15/20 (75)
Vomiting, *n* (%)	7/20 (35)	7/20 (35)
Photophobia, *n* (%)	17/20 (85)	18/20 (90)
Phonophobia, *n* (%)	16/20 (80)	18/20 (90)

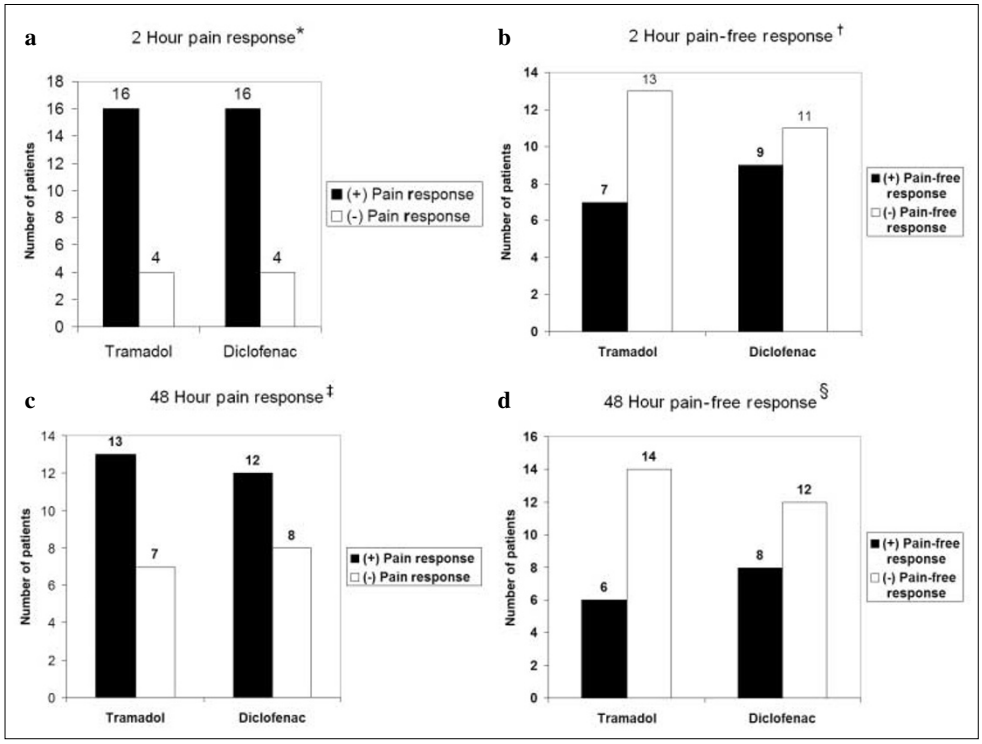

Fig. 2a-d Pain response rates at 2 (**a**, **b**) and 48 h (**c**, **d**). *p>0.05, OR=1.00, 95% CI=0.22–4.35). †p>0.05, OR=1.52, 95% CI=0.43–5.29. ‡p>0.05, OR=0.81, 95% CI=0.23–2.84. §p>0.05, OR=0.64, 95% CI=0.17–2.31

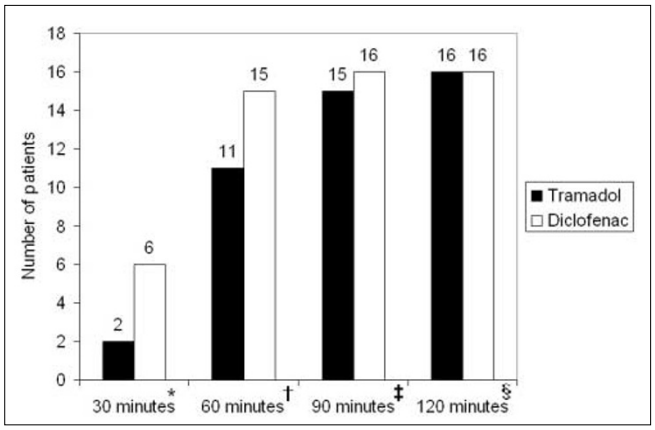

Fig. 3 Change in pain response rates in relation to time. *p>0.05, OR=0.26, 95% CI=0.04–1.48. †p>0.05, OR=2.45, 95% CI=0.64–9.39. ‡p>0.05, OR=1.33, 95% CI=0.30–5.92. §p>0.05, OR=1.00, 95% CI=0.21–4.70

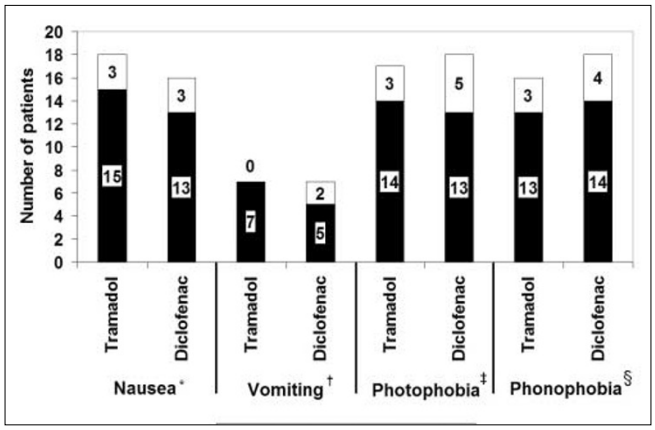

Fig. 4 Response to associated symptoms. *p>0.05, OR=1.30, 95% CI=0.22–7.54. †p>0.05, OR=0.36, 95% CI=0.25–5.10. ‡p>0.05, OR=0.56, 95% CI=0.12–2.60. §p>0.05, OR=0.81, 95% CI=0.16–3.94. (■) Positive response; (□) negative response

60 min, pain score of 9 patients in tramadol group declined to 1 (mild) and 2 patients' pain was relieved completely. On the other arm of the trial, at 60 min, 12 patients pain severity decreased to mild pain and 3 patients were pain-free. Although there was a tendency towards earlier response to diclofenac, no statistically significant difference was detected between the two groups in terms of pain response rates at 30, 60, 90 and 120 min. Changes in the number of patients with (+) pain response during the study period at 30-min intervals is shown in Figure 3.

There was no statistically significant difference between tramadol and diclofenac groups in terms of response rates to nausea, vomiting, photophobia and phonophobia (Fig. 4). Rescue treatment was necessary for 8 patients, 4 (20%) in the tramadol and 4 (20%) in the diclofenac groups. Adverse events were observed in a total number of 3 patients. Orthostatic hypotension was observed in one patient in the tramadol group during discharge who recovered spontaneously with a few minutes rest in sitting position without need for IV flu-

ids. In the diclofenac group, one patient described epigastric discomfort and one patient complained of worsening of nausea. Both events responded quickly to symptomatic treatment.

At 48 h follow-up, recurrence was reported by 2 (10%) patients in the tramadol and 3 (15%) patients in the diclofenac groups. One patient in the diclofenac group was re-admitted to the ED due to recurrence. Tramadol was rated good by 11 and very good by 3 of the patients. Diclofenac was rated good by 14 and very good by 2 of the patients. There was no statistically significant difference between the groups in terms of global evaluation of the drugs by patients. Fifteen (75%) patients in the tramadol and 16 (80%) patients in the diclofenac groups stated that they may prefer the same injection for the future admissions.

Discussion

Acute migraine headache is a common presenting complaint to the ED and there is no defined standard abortive treatment for acute attacks. Many specific (ergots and triptans) and non-specific treatment options are used with varying degrees of success. Opioids are one of the most commonly chosen agents for the ED treatment of headaches in the USA [10]. In this prospective, randomised, double-blind trial, efficacy of tramadol in abortive treatment of acute migraine attack was evaluated and compared with that of diclofenac sodium.

Many studies used different outcome measures defining pain relief for migraine headache. Generally, pain response rates for different drugs studied have ranged between 45% and 88% [2, 3, 5–9]. In our study, 2-h pain response rate for both tramadol and diclofenac was found to be 80% and 2-h pain-free response rates were 35% and 45% respectively. Sustained pain response at 48 h was found to be 65% for tramadol and 60% for diclofenac. These rates are comparable to many of the drugs studied for the treatment of acute migraine headache and are also clinically acceptable.

Associated symptoms generally subside with cessation of headache pain. In our study, both drugs performed well in relieving associated symptoms in parallel with pain. Rescue treatment rates for different agents have been reported to be between 11% and 33% [2, 4, 7, 8]. Rescue treatment was necessary for a total number of 8 patients (4 in the tramadol, 4 in the diclofenac groups) in our study. Headache recurrence rates of different treatments have been found to be between 8% and 50% [3, 4, 8, 9]. 2/20 patients in the tramadol and 3/20 patients in the diclofenac groups reported headache recurrence at 48-h follow-up. Need for rescue treatment and recurrence rates of both drugs evaluated in our study were comparable to those of other treatment options previously studied.

Side effects were observed in 1/20 patients in the tramadol and 2/20 patients in the diclofenac groups. None of the observed side effects were severe. Both drugs are well tolerated by patients as 15 patients in the tramadol and 16 patients in the diclofenac group stated that they would prefer the same drug for future admissions. As tramadol is a weak opioid, it is expected that it may cause nausea and vomiting. Nausea or vomiting rates after tramadol therapy have been reported between 0 and 16.5% [12–16]. In our study, we did not observe any nausea or vomiting due to tramadol therapy. However, as our study is small, our results may not reflect the real side effect profile.

One of the limitations of the study is that time to partial and/or complete relief was not recorded as a continuous variable. This limits the value of information about response time and consequently the length of stay at ED. However, more than half of the patients in each group responded well enough to be discharged at 60 min. Other limitations were due to the setting and design of the study; the study was designed for the treatment of a single attack with a single dose with IM route. Therefore, the study does not provide information about usage in multiple migraine attacks or prophylaxis and other routes of administration and dosing regimens.

As tramadol was not compared with placebo, because it is not ethical to give placebo when effective treatment is available, it is not possible to estimate how much of the response was due to a placebo effect. The randomised nature of our study minimises potential biases that may be caused by the placebo effect.

A common limitation of migraine studies originates from selection of patients, as diagnosis of migraine is based on clinical and historical information. Although IHS criteria are widely used in migraine studies, it was reported that only 56% of patients with an ED discharge diagnosis of migraine met the IHS criteria [21]. The same study reported that main deviations from the criteria were observed in headache duration and number of prior episodes. In our study we strictly controlled all the criteria and the diagnosis was confirmed by a neurologist. Also, although the diagnostic criteria are not different from the first edition, we chose to use the second edition of the IHS criteria [20] as it addressed the common problems encountered in interpretation of the criteria.

Although they are not the recommended first-line therapy, opiates are commonly used for the treatment of benign headaches at ED [10]. Tramadol, because it is a weak opioid, is placed in the second step of the analgesic ladder of the World Health Organization [22]. Although

our results suggest that tramadol is an effective agent in the treatment of acute migraine headaches, we do not encourage its use as a first-line treatment. However, tramadol can be preferred in patients who are unresponsive to first-line therapy or patients with contraindications for NSAIDs or triptans. In conclusion, in selected patients, tramadol 100 mg IM may be an effective and reliable alternative treatment choice in acute migraine attacks.

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