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INTRAVENOUS CHLORPROMAZINE IN THE ACUTE TREATMENT OF EPISODIC TENSION-TYPE HEADACHE

A randomized, placebo controlled, double-blind study

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ABSTRACT - Acute headache is a very frequent symptom, responsible for a significant percentage of caseload at primary care units and emergency rooms. Chlorpromazine is easily available in such settings. The aim of this study is to conduct a randomized, placebo-controlled, double-blind study to assess the efficacy of chlorpromazine on the acute treatment of episodic tension-type headache. We randomized 30 patients to receive placebo (10 ml of saline intravenous injections) and 30 patients to receive 0.1 mg/Kg chlorpromazine intravenously. We used 7 parameters of analgesic evaluation. Patients receiving chlorpromazine showed a statistically significant improvement ($p < 0.05$ and $p < 0.01$) of pain compared to placebo, far up to 30 minutes after the drug administration. The therapeutic gain was 36.7% in 30 minutes and 56.6 % in 60 minutes. The number needed to treat (NNT, the reciprocal or the therapeutic gain) was 2.7 in 30 minutes and 1.8 in 60 minutes. There were reductions in the recurrence and in the use of rescue medication in the chlorpromazine group. We can conclude that intravenous chlorpromazine is an effective drug to relief the pain in tension-type headache.

KEY WORDS: tension-type headache, acute treatment, chlorpromazine.

Clorpromazina parenteral no tratamento agudo da cefaléia do tipo tensional episódica: estudo randomizado, com mascaramento duplo, controlado por placebo

RESUMO - Cefaléia aguda é queixa frequente, responsável por percentual significativo dos casos atendidos em unidades básicas de saúde e unidades de emergência. A clorpromazina é droga usualmente disponível nessas unidades. Apresentamos dados de estudo randomizado, controlado por placebo e com mascaramento duplo, que avaliou a eficácia da clorpromazina no tratamento agudo da cefaléia do tipo tensional episódica. Trinta pacientes foram randomizados para receber placebo (10 ml de solução salina endovenosa) e 30 pacientes para receber clorpromazina endovenosa, na dose de 0,1 mg/Kg. Foram usados 7 parâmetros de avaliação analgésica. Pacientes que receberam clorpromazina mostraram significativa redução da dor quando comparados com o grupo placebo ($p < 0,05$ and $p < 0,01$), 30 minutos após a administração da droga. O ganho terapêutico foi de 36,7% em 30 minutos e 56,6 % em 60 minutos. O número que se necessita tratar (NNT, a recíproca do ganho terapêutico) foi 2,7 em 30 minutos e 1,8 em 60 minutos. Houve redução nos índices de recorrência e de utilização de medicação de resgate no grupo que recebeu clorpromazina. Podemos concluir que clorpromazina em administração parenteral é droga efetiva para o alívio da dor de pacientes com cefaléia do tipo tensional, seu uso sendo justificado nesses casos.

PALAVRAS-CHAVE: cefaléia tipo tensional episódica, tratamento agudo, clorpromazina.

Tension-type headache (TTH) is the most common type of headache, with a lifetime prevalence of 78% and a yearly prevalence of 38%[1], even thought studies concerning its acute treatment do not reflect this enormous prevalence. This might be explained by the lower intensity of pain, the absence of associated symptoms, the lower impact to the health system and in the quality of life, when compared to migraine. In spite of that, a very significant number of patients with this diagnosis seek for medical help in the emergency rooms. A study of 6006 patients seen at basic health units in Brazil showed that this type of headache was seen in 0.8% of the adult examined, and 7.3% of all headaches[2] . A total of 222 visits due to TTH attacks occurred at an emergency unit over a period of one year[3] .

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Chlorpromazine (CPZ) is the prototype phenothiazine - a neuroleptic agent, first developed in 1950 for use as a pre-anesthetic medication[4] . The phenothiazines have in common a three-ringed structure, with two benzene rings linked by S and N atoms. In the central nervous system, CPZ acts in post-synaptic cells as a DA antagonist, especially in the limbic system and the basal ganglia. It has a particular effect in the chemoreceptor trigger zone of the reticular formation, and hence is a powerful antiemetic. It was initially termed a neuroleptic because it induced "an indifference to pain"[5,6].

Beyond its antidopaminergic function, CPZ has important effects in other neurotransmissory systems. It is a powerful adrenergic antagonist with some anti-cholinergic properties and acts in some serotoninergic and hystaminergic receptors[7] .

These neurochemical properties, especially regarding the antidopaminergic ones, might explain the function of chlorpromazine in migraine and also in episodic tension-type headache. In spite of the initial theories about the pathophisiology of tension-type headache had considered muscle contraction and tension stress as the fundamental keys, actually we think that this headache, as migraine, might be the clinical manifestation of a neuronal hyper-excitable state, associated with problems in pain modulation. These abnormalities may be correlated to the basal nuclei, limbic system or serotoninergic neurons, specially those located on the rafe dorsal nucleus. Pharmacological and biochemical studies had initially indicated two subclasses of DA receptors, D1 and D2[7]. Five different DA receptor genes had been identified. The genes products are classified into D1 family (D1 and D5) and the D2 family (D2, D3 and D4). Functional interactions exist, moreover, between serotoninergic and dopaminergic systems in the mesolimbic system, prefrontal cortex and substantia nigra[7].

CPZ is well absorbed orally and parentally, the first one being more unpredictable. Intramuscularly use results in measurable levels at 15-30 minutes. CPZ is tightly bound to albumin and to cell membranes. Central nervous system concentrations are 10 times those of the blood. In the liver, CPZ is conjugated with glucuronic acid, but its excretion is extremely variable[6].

Some dopamine antagonists such as chlorpromazine are commonly used in emergency rooms for the acute treatment of migraine[8,9], studies finding high levels of efficacy following intramuscular[10] and intravenous[11] injections. There is, however, a lack of studies evaluating its use in the treatment of tension-type headache.

The aim of this study is to report a randomized, placebo-controlled, double-blind study evaluating the efficacy of chlorpromazine in the acute treatment of episodic tension-type headache.

METHOD

We used the same methodological approach that we utilized in other similar studies performed by our group[12,13] described above.

Study duration and setting - The study was performed at two public health units in the cities of Ribeirão Preto and São Carlos, State of São Paulo, Brazil, from April 1, 1997 to December 31, 1999.

Inclusion criteria - A. Minimum age of 18 years; B. Diagnosis of episodic tension-type headache according to the criteria of the International Headache Society[14]. C. Agreement to participate in the study by signing an Informed Consent Form, after approval by the Research Ethics Committee of the University Hospital, School of Medicine at Ribeirão Preto, University of São Paulo.

Exclusion criteria - A. Presenting known and reported intolerance to or contraindication for the use of chlorpromazine. B. Having taken any type of medication for that attack before seeking the Health Unit in order to relieve pain or any other accompanying symptoms. C. Have presented an attack of pain that fulfill criteria for migraine in the last 6 months. D. Proven or assumed pregnancy.

Study Design

The patients were randomized by drawing lots. We used randomization with a fixed number of participants[15], 30 patients being randomized to receive any substance.

We first determined how long the patient had been in pain and defined this time as $T\text{-}_0$. We then applied scales for the evaluation of pain immediately before the administration of chlorpromazine at T_0 and at 30 minutes (Time 30 – T_{30}) and 60 minutes after its administration (Time 60 – T_{60}). The patients were then questioned again by telephone 24 hours after the administration of the study drugs.

The patients had a peripheral vein maintained with 0.9% physiological saline (0.9% PS), 0.5 ml (10 drops) per minute. Then, according to the group they had been randomly assigned to, they were treated following the protocol bellow:

1- Placebo: IV injection of 10 ml of 0.9% PS.

2- Intravenous injection of 5.0 ml/Kg of 0.9% PS, immediately followed by intravenous chlorpromazine, 0.1 mg/Kg diluted, to 10 ml of 0.9% PS.

If the symptoms did not improve after one hour of the administration of chlorpromazine, a second drug (rescue medication) was administered, its effect not being assessed in this study.

Parameters for the assessment of pain - Analgesia was assessed according to the parameters indicated below.

Parameter 1 - Pain intensity measured by a 10-point verbal-analogical scale[16].

Parameter 2 - Pain intensity measured by the traditional 4-point scale, 0-no pain, 1-mild pain, 2-moderate pain, 3-severe pain. Positive headache response was a patient's pain changing from 2 or 3 to 1 or 0 after study drug at particular endpoints.

Parameter 3 - Pain free: Pain intensity changing from 2 or 3 to 0 at predetermined time point.

Parameter 4 - Therapeutic gain (TG): TG was defined as the "Active Response Rate - Placebo Response Rate". We used the end-point efficacy (parameter 2) for calculations.

Parameter 5 - Number Needed to Treat (NNT): NNT was defined as the reciprocal of TG, i.e. 1/TG.

Parameter 6 - Recurrence of pain: recurrence was considered to be present when the patient reported pain free at any time after administration of chlorpromazine with a headache returning afterwards.

Parameter 7 - Use of rescue medication: Use of rescue medication was noted if the patient used some type of analgesic medication before the reevaluation performed 24 hours after the administration of the study drug.

Criteria for discharge and reevaluation - After one hour, patients who felt better were discharged even if they had received the placebo. Those whose clinical improvement was not satisfactory, with the need for further treatment, were treated with the rescue medication. Patients were reevaluated, by phone, 24 hours after the administration of the substance under study. This reevaluation consisted of the application of the same scales as applied previously.

Statistical analysis - Data were analyzed statistically by descriptive statistics for all variables studied. The demographic variables were analyzed by the Chi-square test and by contingency tables, and the efficacy of the medications were compared by the nonparametric Mann-Whitney test. We considered $p < 0.05$ as statistically significant. The statistician responsible for the analysis worked in a blinded fashion.

The study was approved by the Research Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, USP.

RESULTS

A total of 30 patients were randomly assigned to receive placebo. Fifty percent of them were males. Mean age was 37.6 years old. The chlorpromazine group consisted of 30 patients, 43.3 % of them males. Mean age was 39.9 years. The female: male ratio was 1.0 for the placebo group and 1.3 for the chlorpromazine group. The mean for T_{-0} was 4.1 and 4.2 hours. There were no significant differences between these variables.

Assessment of analgesia

The comparison of pain intensity evaluated by the pain scale (parameter 1) is presented in Figure 1. Patients who received chlorpromazine had significantly less pain, evaluated by this parameter, than patients randomized to receive placebo, in all evaluated times.

Table 1 presents the comparison of treatment efficacy (parameter 2) and pain free (parameter 3). Chlorpromazine was superior to placebo in both parameters.

TG (parameter 4) and NNT (parameter 5) are shown in Figures 2 and 3. We obtained high therapeutic gains and low number needed to treat on both evaluated times.

Recurrence (parameter 6) and the need for rescue medication (parameter 7) are shown in Figure 4. Patients receiving chlorpromazine had significantly less recurrence and need for rescue medication, when compared to placebo.

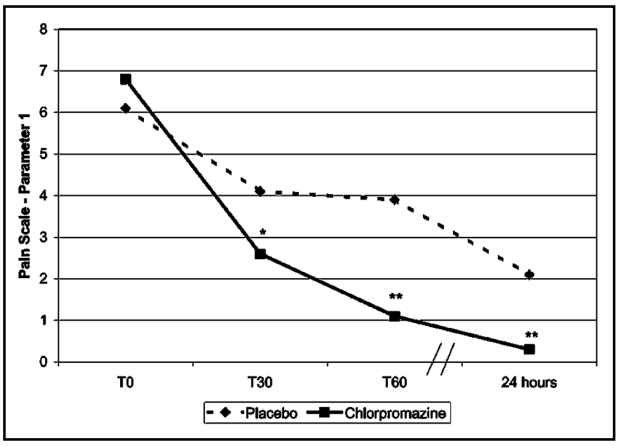

*Fig 1. Time vs. Pain intensity. Comparison between chlorpromazine and placebo. *p<0.05; **p < 0.01.*

Table 1. Comparison of the efficacy of the drug and pain free in patients randomly assigned to receiving placebo or chlorpromazine.

	Placebo	Chlorpromazine
Efficacy	%	%
T_{30}	10.0	46.7
T_{60}	26.7	83.3
24 hours	66.7	91.3
Pain free		
T_{30}	6.7	36.7
T_{60}	20.0	70.0
24 hours	63.3	86.9

*p<0.05; **p<0.01.

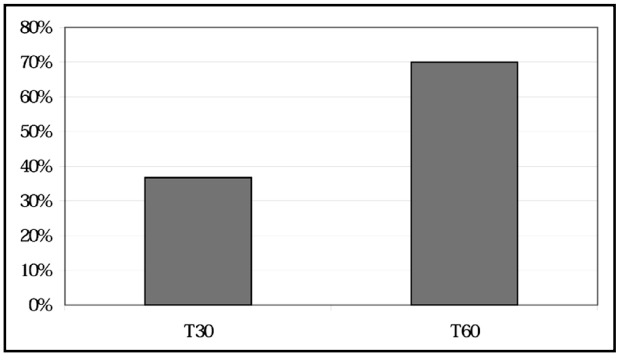

Fig 2. Therapeutic gain of chlorpromazine, 30 and 60 minutes after its administration.

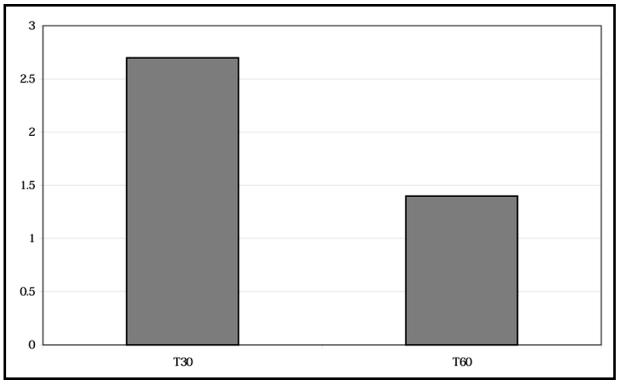

Fig 3. Number needed to treat of chlorpromazine, 30 and 60 minutes after its administration.

DISCUSSION

The present randomized, placebo-controlled and double-blind study shows that chlorpromazine is highly and rapidly effective in episodic tension-type headache (Fig 1 and Table 1), with a high therapeutic gain (Fig 2), a low NNT (Fig 3), as well as low levels of recurrence and rescue medication utilization (Fig 4). Episodic tension-type headache is the second most common primary headache in public health units in Brazil[3] and, probably, in other countries. The administration of intravenous chlorpromazine had been described in the treatment of migraine[17], generic non-migrainous headaches[18] and cluster headaches[19], but not in the acute treatment of episodic tension-type headache. Another important aspect to be emphasized in this study is that there are not specific drugs to be used in the acute treatment of TTH as there are for migraine.

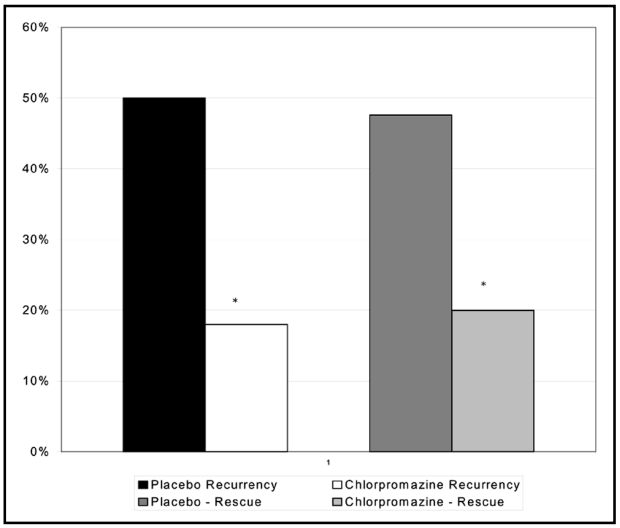

*Fig 4. Recurrence and rescue medication needs. Comparison between chlorpromazine and placebo. *p < 0.05.*

Our methodology involved the assessment of approximate previous duration of pain (T_{-0}) and of pain and associated symptom intensity at T_0, 30 and 60 minutes and within 24 hours after drug administration. The fact that we limited our first evaluation of efficacy to only one hour may be criticized. However, this option was dictated by the needs of the health service where the study was conducted. Since this was a public health unit in a developing country, with overcrowding, excess demand and all other problems presented in these places, we though it would be inappropriate to maintain a patient under observation for more than one hour unless his clinical needs required it. We tried to minimize this limitation by re-contacting the patients 24 hours after drug administration. This procedure, in spite of minimizing the above drawbacks, has its own limitations. After 24 hours there is an increase in subjectivity with a proportional decrease in the precision of information, a fact that might generate possible deviations and distortions. Although the guidelines of the International Headache Society recommend an evaluation of two hours[20], we consider our procedure to be justified. We also guarantee that, although the methodology was not ideal, the study was conducted under the closest possible conditions of real utilization of these medications in the most part of the emergency rooms. We also tried to minimize another bias, excluding patients with history of migraine. Treating the patients 4.1 to 4.2 hours, in mean, after the beginning of the pain, almost exclude the possibility of having treated the beginning.

A study that evaluated the efficacy of chlorpromazine in the acute treatment of migraine presented its conclusions as follows[21]: "Migraine is a common and frequently incapacitating condition resulting in thousands of Emergency Department visits per annum in Canada. IV CPZ therapy offers a number of theoretical attractions for treating such patients. This study demonstrates that there is merit in proceed-

ing to a full randomized trial to investigate its role in this setting". We could conclude our paper with the same words. Intravenous chlorpromazine showed high efficacy treating patients with tension-type headache. Its therapeutic gain is extremely high. Although its use requires admission in emergency rooms, with corresponding increases of the costs and of the time that patients are in pain, we can conclude that chlorpromazine is an excellent option in these settings.

REFERENCES

1. Rasmussen BK, Jensen R, Olesen J. A population-based analysis of the diagnostic criteria of the International Headache Society. Cephalalgia 1991; 11: 129-134.
2. Bigal ME, Bordini CA, Speciali JG. Etiology and distribution of headaches in two Brazilian primary care units. Headache 2000; 40:241-247.
3. Bigal, ME; Bordini, CA; Speciali, JG. Headache in an emergency room in Brazil. São Paulo Medical Journal 2000; 118:58-62.
4. Goodman AG, Goodman LS, Gilman A. The pharmacologic basis of therapeutics. 6.Ed. Oxford: MacMillan, 1980:654-672.
5. Seeman P, Sellers EM, Roschlan WHE. Principles of medical pharmacology. 3.Ed. Toronto: Univ. of Toronto Press, 1980:123-124.
6. Johnstone EC, Crow TJ, Frith CD, et al. Mechanism of the antipsychotic agents: the treatment of acute schizophrenia. Lancet 1978;22:848-885.
7. Mascia A, Áfra J, Schoenen J. Dopamine and migraine: a review of pharmacological, biochemical, neurophysiological, and therapeutic data. Cephalalgia 1998; 18: 174-182.
8. McEwen JI, Oçonnor HM, Dinsdale HB. Treatment of migraine with intramuscular chlorpromazine. Ann Emerg Med 1987; 16: 758–763.
9. Costa AG, Monzillo PH, Sanvito WL. Uso da clorpromazina para tratamento da cefaléia no serviço de emergência. Arq Neuropsiquiatr 1998; 56:565–568.
10. Iverson KV. Parenteral chlorpromazine treatment of migraine. Ann Emerg Med 1983;16: 756-758.
11. Lane RL, Ross R. Intravenous chlorpromazine: preliminary results in acute migraine. Headache 1985; 25:302-304
12. Bigal ME, Bordini CA, Speciali JG. Intravenous dipyrone in the acute treatment of migraine without aura and migraine with aura: evaluation of the analgesic effect of the drug, of its effect on associated symptoms and adverse events profile. A randomized, placebo controlled, blind study. Headache (in press).
13. Bigal ME, Bordini CA, Speciali JG. Intravenous dipyrone in the acute treatment of tension-type headache. A randomized, placebo controlled, double-blind study. Cephalalgia (in press).
14. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(Suppl 7):1-96.
15. Jadad AR, Rennie D. The randomized controlled trial gets a middle-aged checkup. JAMA 1998; 279:319-320.
16. Von-Korff M, Stewart WF, Lipton RB. Assessing headache severity. New directions. Neurology 1994;44 (suppl 4): 40-46.
17. Lane PL, McLellan B. Comparative efficacy of chlorpromazine and meperidine with dimenydrate in migraine headache. Ann Emerg Med 1989;18:360-365.
18. Barclay CL, Shuaib A, Montoya D, et al. Response of non-migrainous headaches to chlorpromazine. Headache 1990; 30: 85-87.
19. Caviness VS, O'Brien P. Cluster headache: response to chlorpromazine. Headache 1980; 20: 128-131.
20. Tfelt–Hansen P, Block G, Dahlöf C, et al. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765-786
21. Lane RL, Ross M. Intravenous chlorpromazine: preliminarly results in acute migraine. Headache 1985;25:302-304.