ABSTRACT
Headache is the most frequent complaint in Neurology, and the principal types are the tension-type headache, and migraine. In addition to the high prevalence in the population, migraine especially has a significant impact on quality of life. It is estimated that headaches comprise 5% of all complaints in the emergency services. Migraine can be treated initially with common painkillers like intravenous dipyrone and/or non-steroid anti-inflammatory medications, followed by antidopaminergic drugs. In refractory cases, intravenous propofol can be used, and in selected cases, intravenous magnesium sulfate, corticosteroids and/or opioids may be added to therapy. For tension-type headache and undifferentiated primary headache, dipyrone, anti-inflammatory and/or antidopaminergic agents are sound options. Oxygen, and then triptan and intranasal lidocaine are good options for the acute treatment of Cluster Headache.

Keywords: Primary headache; Treatment; Emergency department

INTRODUCTION
Headache is the most frequent complaint in Neurology. Nearly 47% of the worldwide population is estimated to have some type of headache, mainly tension-type headache (TTH) (38%) and migraine (10%). In addition, 66% of the population is expected to have at least one attack of headache in life, at an approximate proportion of 46% of tension-type headache and 14% of migraine. (1)

In Brazil, a population-based study carried out in 2008 revealed a prevalence of headache in that year of 72.2%. Of these, 15.2% fulfilled diagnostic criteria for migraine, 13% for TTH and 6.9% for chronic daily headache (CCD). (2)

Besides the high prevalence of headache in population, migraine particularly impacts on the quality of life. A survey
conducted in northeast Brazil found that approximately 50% of Caruaru population suffering migraine showed moderate to severe migraine-related disability affecting mainly female migraineurs. (3)

Approximately 5,000,000 of the worldwide emergency care units attendance per year is accounted for headache, consisting in 5% of all complaints from patients who seek medical care in these units. (4,5)

To face this high rate of prevalence, the relevant degree of incapability and the constant search for medical care due to headaches, it is our opinion that guidelines are essential to guide the medical staff regarding the aspects of patient care, evaluation and the most appropriate therapy for each case.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Two major groups divide headaches: primary and secondary. Primary headaches are not detected by clinical examination, laboratory or imaging exams. Neurochemical disorders involving an imbalance among neurotransmitters are associated with genetic and environmental factors making individuals susceptible to developing the disease. (6)

The definition of secondary headache according with the third version of the International Classification of Headache is:

“When a new headache occurs for the first time in close temporal relation to another disorder that is known to cause headache, or fulfills other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder” (7)

Diagnostic criteria are based on the third version of the International Classification of Headache (ICDH-3 Beta).

WARNING SIGNS

Although primary headaches constitute the vast majority of painful cranial disorders, with studies demonstrating prevalence higher than 95%, the possibility of a headache secondary to a severe disorder makes many doctors to request indiscriminately complementary exams in order to exclude a life-threatening condition. (5,8).

According to the International Society of Headache some criteria define the indication of ancillary investigation in the investigation of a possible secondary headache (Table 1).

INVESTIGATION

Suspicion of a secondary headache should be directed in accordance with the diagnostic hypothesis after a careful clinical assessment (medical history and physical/neurological examination).

Computed tomography (CT), magnetic resonance imaging (MRI), cerebral arteriography, CSF examination and blood tests (complete blood count, CRP, ESR, electrolytes, glucose, etc.) are the main resources. (5,8,9)

TREATMENT

After diagnosis during evaluation, treatment can be planned accordingly. People who seek emergency care unit usually present with migraine and cluster headache. In spite of this, a small percentage of patients with tension-type headache can be seen in an ED. (10)

In a didactic way, primary headaches guidelines for EDs can be split according to the primary condition.

Table 1 - Headache Alert Signs

- Changes in neurological examination
- Change in level of consciousness
- Worst headache of life
- Sudden Onset, explosive
- Change the characteristic of the headache (intensity, frequency, location, character)
- Headache new after 50 years of age
- Headache associated with fever or other signs of systemic diseases
- Signs of meningeal irritation
- Beginning of headache after physical exertion, sexual activity or cough
- Post-traumatic headache
- Headache recently in a patient with Acquired Immunodeficiency Syndrome or cancer
MIGRAINE

Patients admitted to an ED due to migrainous attack usually present with nausea and/or history of vomiting. Thus, in case of dehydration signs it is essential to perform volume replacement (isotonic saline solution). Patients who present with photo and phonophobia require a room devoid of light and/or noise.\(^{\text{11-13}}\)

Treatment for migrainous headaches can be done with several classes of drugs, mainly directed to pathophysiological issues, which can be used for the acute treatment: opioid and non-opioid analgesics, nonsteroidal anti-inflammatory drugs, corticosteroids, antidopaminergic agents, serotonergic agonists and propofol.\(^{\text{12-18}}\)

Triptans

Triptans inhibit the release of vasoactive peptides, promoting vasoconstriction and blocking pain pathways in the brainstem. As a result the transmission in the trigeminal nuclei (nucleus caudalis) is inhibited, blocking the afferent pathways to second-order neurons; this effect is probably mediated by a reduction in the levels of calcitonin gene related peptide (CGRP).\(^{\text{19}}\)

Sumatriptan has shown a better profile in some studies with triptans usage in EDs (Table 2), due to the possibility of parenteral administration (subcutaneous or intranasal) and due to its good therapeutical response in migraine. Tfelt-Hansen, De Vries and Saxena showed better effectiveness for subcutaneous than intranasal sumatriptan.\(^{\text{19}}\)

Currently, the Brazilian health care institutions do not refund a hospital for the use of this medication in emergency services.

Dipyrone

Dipyrone or metamizole (Table 3) is a pyrazolone derivative from the family of non-opioid analgesics with mechanism of action at the level of the peripheral nervous system and central nervous system.\(^{\text{21}}\) Bigal et al. compared the use of dipyrone (1 g) versus placebo in the acute treatment of migraine patients with and without aura and tension-type headache.\(^{\text{21}}\)

The authors found a significant improvement in pain and associated symptoms intensity in the dipyrone group. A randomized, double-blind, placebo-controlled trial was carried out in the following year, but only with patients in migraine attack (with and without aura) aiming to compare the efficacy of dipyrone against placebo. Statistically significant improvement of pain was seen in patients from dipyrone group, as well as the associated symptoms, when compared to the control group.\(^{\text{22}}\)

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**Table 2 - Sumatriptan pharmacological data**

<table>
<thead>
<tr>
<th>Route</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>6 mg; repeat if necessary ≥ 1 hour after the initial dose (maximum: two injections of 6 mg per 24-hour period)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Paresthesia, dizziness, flushing, chest pain, nausea and vomiting</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnancy, coronary artery disease, cerebrovascular disease, peripheral vascular disease, basilar or hemiplegic migraine, uncontrolled hypertension, previous adverse reaction, use of other ergotamine or triptan derivative in the previous 24h. Use of MAOI in the last 2 weeks, caution with use SSRI because of the risk of serotoninergic syndrome</td>
</tr>
</tbody>
</table>

MAOI: Monoamine oxidase inhibitors; SSRI: Selective serotonin reuptake inhibitors.

**Table 3 - Dipyrone Pharmacological Data**

<table>
<thead>
<tr>
<th>Route</th>
<th>Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1 g</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Urticaria, rash, hypotension, agranulocytosis</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Known hypersensitivity to dipyrone; porphyria acute liver; congenital deficiency of glucose-6-phosphate dehydrogenase; dysfunction of insufficient bone marrow or diseases of the hematopoietic system</td>
</tr>
</tbody>
</table>
Nonsteroidal anti-inflammatory drugs (NSAIDs)

Cyclooxygenase, an enzyme that catalyzes the synthesis of the cyclic endoperoxidases from arachidonic acid and forms prostaglandins, is inhibited by the six main classes of all NSAIDs. NSAIDs are widely known and indicated for the treatment of acute migraine. Among them, ketorolac (Table 4) presents more studies demonstrating effectiveness, particularly with parenteral route in EDs. In 2013, a systematic review showed its effectiveness in the treatment of migraine attack in comparison with sumatriptan (subcutaneous - SC), chlorpromazine (intramuscular - IM), and dihydroergotamine combined with metoclopramide (intravenous - IV).

No studies comparing different NSAIDs' effectiveness were found, however if one is not effective, other drugs might be tested.

Magnesium sulfate

Episodic or chronic migraine patients are known to have lower of magnesium serum levels than the rest of the population. Based on this information, magnesium sulphate (Table 5) was used in both preventive and abortive treatment of migraine attack. Bigal et al. compared the effect of magnesium sulphate (1g) in patients with migraine "with and without aura" versus "placebo". They noticed that in the group of "migraine with aura" there was significant improvement of pain, nausea, photo- and phonophobia as compared to the placebo group. Unlike the "migraineurs with aura", the "migraine without aura" group showed significant reduction only in photo- and phonophobia. This data suggests that intravenous magnesium sulfate is effective for "migraine with aura" attacks but should be used only as an add-on therapy for "migraine without aura" attacks.

Dermikaya et al. evaluated the effectiveness of magnesium sulfate in moderate to strong migraine attacks comparing it to placebo. Most of the patients who used the medication reported that headache relieved as well as the accompanying symptoms. Patients who did not show improvement with placebo received magnesium sulfate in the same dose of the active group, obtaining a satisfactory answer both to the headache and to the accompanying symptoms.

Antidopaminergic agents

Antidopaminergic agents may be used as monotherapy for migraine attack through IV (metoclopramide, and chlorpromazine) or IM (chlorpromazine) route. These drugs are effective, acting as dopamine receptors antagonists, i.e., in the pathophysiology of the disease. These agents benefit has been demonstrated in placebo-controlled trials. Intravenous Diphenhydramine (12.5-20 mg every hour for two hours) can be eventually associated with an antiemetic to prevent akathisia and acute dystonic reactions, which are the main side effects of this class of drugs.

<table>
<thead>
<tr>
<th>Table 4 - Ketorolac pharmacological data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketorolac</strong></td>
</tr>
<tr>
<td>Route</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>Contraindications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5 - Magnesium sulfate pharmacological data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnesium sulfate</strong></td>
</tr>
<tr>
<td>Route</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>Contraindications</td>
</tr>
</tbody>
</table>
As monotherapy, intravenous Metoclopramide (Table 6) is effective for the treatment of acute migraine, as demonstrated in systematic reviews and meta-analysis.\(^{(29)}\)

Studies revealed that metoclopramide is more effective than placebo, as effective as sumatriptan SC and less effective than intravenous chlorpromazine (NNT 4 vs NNT 2).\(^{(30,31)}\)

**Table 6 - Metoclopramide pharmacological data**

<table>
<thead>
<tr>
<th>Route</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>10 mg or 20 mg IV every 30 minutes, up to four times</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Water Retention, reduction of seizure threshold, hypertension, flushing (after high doses IV), dystonic reactions, akathisia, confusion, parkinsonism, tardive dyskinesia.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to Metoclopramide or any component of the formulation; gastrointestinal obstruction, perforation or hemorrhage; pheochromocytoma; history of convulsions or concomitant use of other agents capable of increasing extrapyramidal reactions</td>
</tr>
</tbody>
</table>

Intravenous Chlorpromazine (Table 7) has been associated with significant improvement in pain, nausea, photophobia, phonophobia and less need of rescue medication in 60 minutes when compared with placebo. This benefit was seen both in the treatment of migraine with and without aura. In addition, patients treated with chlorpromazine showed a significantly reduced 24-hour recurrence rate in relation to placebo.\(^{(32)}\)

**Table 7 - Chlorpromazine pharmacological data**

<table>
<thead>
<tr>
<th>Route</th>
<th>Intravenous or intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.1 mg/kg.</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Orthostatic hypotension, somnolence, dizziness, QT changes, dystonia, akathisia, parkinsonism, tardive dyskinesia, neuroleptic malignant syndrome.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to Chlorpromazine or any component of the formulation (cross-reactivity between phenothiazines can occur); severe depression of the CNS; coma.</td>
</tr>
</tbody>
</table>

**Corticosteroids**

Many patients do not present complete pain relief when they are discharged from EDs, in addition, they can experience headache with significant intensity in the following 24 hours.\(^{(16)}\) Therefore, health care providers in EDs should offer treatment of acute headache, and also for the prevention of relapse in the following days.

Aiming this goal several studies have reported the effectiveness of the action of intravenous dexamethasone in reducing the recurrence of pain in 24 to 72 hours following the migraine attack.\(^{(13,16,33)}\)

Dexamethasone also should not be administered for acute treatment of migraine, except in cases of migraine status, when attack duration is greater than 72 hours.\(^{(34)}\)

**Table 8 - Dexamethasone pharmacological data**

<table>
<thead>
<tr>
<th>Route</th>
<th>Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>10 to 24 mg, for 10 minutes</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Dizziness, nausea, flushing, hypertension, hyperglycemia</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections</td>
</tr>
</tbody>
</table>

**Opioid**

Opiates are substances with analgesic properties containing synthetic or semi-synthetic drugs derivatives of opium poppy. Mu, delta, and kappa are three types of opioid receptors, which are widely distributed in the nervous system, with a higher concentration in the periaqueductal gray matter, posterior horn of the spinal cord and locus ceruleus.\(^{(35)}\)

Mainly used opioids in ED are meperidine, tramadol, and nalbuphine. Meperidine is the opioid most studied for ER headache treatment, despite this, tramadol presents better tolerability. Tramadol weakly binds the mu opioid receptor and also inhibits serotonin and norepinephrine re-uptake. Therefore presents a lower rate of side effects in cardiorespiratory and gastrointestinal systems.\(^{(16,35)}\)
Related to craniofacial pain, it is known that opioids can modify the input of nociceptive information in the core level of spinal trigeminal nucleus, but does not interfere in the pathophysiology of migrainous pain, which is neurovascular.\textsuperscript{(16,35)} In addition, there are a number of negative aspects that the authors enumerate to substantiate the restricted use of opioids in the treatment of headaches.\textsuperscript{(14,16,35-37)}

- Extensive list of adverse effects: sedation, respiratory depression, bradycardia and hypotension, etc.;
- High risk of tolerance, dependence and addiction: when used in long-term;
- Propensity for headache development by abusive intake of medication;
- Risk of chronicity;
- Opioid-induced hyperalgesia;
- Increased frequency of visits to ED’s;
- Existence of better alternatives for the treatment of primary headache.

Although opioids are still widely prescribed in ED, the current guidelines restrict its use as a second- or third-line therapy, useful for a well-selected minority of patients whose headache is incapacitating, having contraindications to other medications and the gold standard was not successful.\textsuperscript{(14,16,35-37)}

Propofol

Propofol (Table 10) is a rapid and short-acting intravenous anesthetic agent with an agonist effect on gamma-aminobutyric acid (GABA) receptors, afferent sympathetic activity inhibition, reduction of cardiac baroreceptor reflex and stimulation of nitric oxide production, with consequent vasodilation.\textsuperscript{[38]} In general, this anesthetic is used for induction and maintenance of general anesthesia, sedation for mechanical ventilation and other invasive or semi-invasive procedures.\textsuperscript{[39]}

Krusz et al. made the first report on the use of propofol for treatment of intractable headache, migrainous or non-migrainous. Seventy-seven patients refractory to conventional pharmacological therapy were submitted to subanesthetic doses of propofol, resulting in 95\% of reduction of headache after 20 to 30 minutes with 81.8\% of the patients reporting complete resolution of head pain. Ever since several similar studies have been published with similar results.\textsuperscript{[40]}

Propofol bolus dose is 1\% (10 mg/1mL-10 mL) as slow infusion (with a rate of 1 mL in 10 seconds), every 5 to 10 minutes until appropriate therapeutic effect and/or the maximum dose of 110 mg.\textsuperscript{[38,40]}

Mosier et al. demonstrated that the use of propofol reduced the amount of hours the patient stayed in the Emergency Care Unit due to headache, 6.5 h (± 3.76) to 3.1 h (± 1.2 h).\textsuperscript{[41]} Several authors reported an almost complete relief of pain (> 95\%) after 20 to 30 minutes of administration of Propofol.\textsuperscript{[38,40]}

Studies with subanesthetic doses for the treatment of refractory headache have proven that propofol could be considered a safe drug. However, due to the potential side effects (lowered level of consciousness, hypopnea, hypotension and bradycardia), patients who receive this treatment should be supervised with cardiac monitor and pulse oximetry, supplementary oxygen through nasal cannula and a member of nursing team should be available during sedation.\textsuperscript{[41]}

Cumulative effect of sedation must be monitored if patient requires chlorpromazine followed by propofol, since this can lead to respiratory depression.

TENSION-TYPE HEADACHE

Mild to moderate intensity is the innate characteristic of tension-type headache (TTH), and these patients present low demand in emergency services. Usually their crises are alleviated by orally administered ordinary analgesics (dipyrone, acetaminophen and nonsteroidal anti-inflammatory).\textsuperscript{[1,2,7,42]}

A systematic review was performed by Weinman et al. to evaluate the efficacy of parenteral drugs in the treatment
of acute TTH in emergency units.\(^{(42)}\) In this study, the results were presented using the number needed to treat (NNT) with a confidence index (CI) of 95%. Medications showed greater efficacy than placebo (NNT; 95% CI) were Dipyrrone 1g EV (4; 2-26), Chlorpromazine 0.1mg/kg IV (4; 2-26), and Metoclopramide 10 mg IV (2; 1-3). Metoclopramide 20 mg EV + Diphenhydramine 25 mg EV association was superior to Ketorolac 30 mg EV (4; 2-8). Additionally, this review showed that other medications were not more effective than the placebo, such as: mepivacaine, meperidine associated with promethazine and sumatriptan.

**CLUSTER HEADACHE**

Cluster Headache is a more painful primary headache, including reports of suicide and attempts of suicide to avoid the episode recurrence.\(^{(46)}\) Therefore, early diagnosis and appropriate treatment are essential for the relief of the patient's suffering.

Inhaled oxygen and subcutaneous sumatriptan are examples of first-line medications. Other drugs have been used as second-line for acute treatment with reasonable efficiency: intranasal lidocaine and ergot derivatives - oral and parenteral.\(^{(13,43-49)}\)

**Oxygen**

After the discovering and being described by Horton in 1956, oxygen has been the first treatment administered to the patient with cluster headache. Pure oxygen (100%) is inhaled through a face mask, with minimum flow of 10 to 15 liters/minute, the patient seated and the trunk bending forward, for 10 to 15 minutes. Therapy is safe, without contraindications or side effects, except in patients with chronic obstructive pulmonary disease who present the risk of developing severe hypercapnia and narcosis by carbon dioxide. Near 60 to 78% of patients get improvement of headache within 15 minutes.\(^{(13,43-49)}\) (Table 11)

<table>
<thead>
<tr>
<th>Route</th>
<th>Inhalation (Venturi mask)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow</td>
<td>10-15 l/min for 15 minutes</td>
</tr>
<tr>
<td>Position</td>
<td>Seated and trunk bending over</td>
</tr>
<tr>
<td>Duration</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>None</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>

**Triptans**

Serotonin receptor agonists, also known as 5-HT\(^{1b/1d}\) or triptans, are part of the first-line treatment for cluster headache attacks. Sumatriptan (subcutaneous and intranasal) and Zolmitriptan (intranasal) present more studies showing their effectiveness.\(^{(13,43-47,49)}\)

Sumatriptan 6mg subcutaneous (Table 2) has shown a high efficacy in significant reduction of pain, near 80%, in the first 15 minutes, and in this same interval showed the ability to annihilate the pain around in a scale of 50%. Comparing to sumatriptan 12 mg, no statistically significant difference between the two doses was found, and the latter caused more adverse effects than the first.\(^{(13,43-47,49)}\)

Intranasal sumatriptan (20 mg) also proved to be effective in reducing pain as compared to placebo (57% vs 26%). After intra-nasal sumatriptan patients were pain-free in the first 30 minutes (47% vs. 18%). In a comparative study subcutaneous sumatriptan (6 mg) proved to be more effective and with an earlier therapeutic effect than intranasal sumatriptan (20 mg).\(^{(13,43-47,49)}\)

Intranasal Zolmitriptan proved efficacy in the treatment of cluster headache at doses of 5 or 10 mg with similar results, without significant adverse effects at the highest dose. Although there is no comparative face-to-face studies comparing zolmitriptan with sumatriptan, their respective studies show similar efficacy, and one or another can be administered in cluster headaches.\(^{(1,43-47,49)}\) In Brazil, only the oral presentation of Zolmitriptan is available.

**Lidocaine (Lignocaine)**

Intranasal lidocaine (Table 2) (1 ml at a concentration of 4 to 10%) can be used in the nostril ipsilateral to the side of symptoms. Studies have shown it to lead to a moderate response in pain relief. Administration of lidocaine should be done with the patient's head extended to 45 degrees and rotated 30-40 degrees to the affected side obtaining a moderate response in pain relief. Still, it is considered a second-line drug, being recommended in the acute treatment of cluster headache way as adjuvant.\(^{(13,43,44,46,47,49)}\)

<table>
<thead>
<tr>
<th>Route</th>
<th>Intranasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1 mL at a concentration of 4-10%</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Anxiety, dizziness, confusion, tachycardia, flushing, local irritation</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to lidocaine or to any component of the formulation; hypersensitivity to other local anesthetics of the amide type</td>
</tr>
</tbody>
</table>
**UNDIFFERENTIATED PRIMARY HEADACHES**

Primary or benign headaches are those not secondary to other pathological process, such as: meningitis, sinusitis, traumatic brain injury, vascular disorders, etc. Although the existence of an international effort (International Classification of Headache) to establish diagnostic criteria for the variety of headaches, the majority of patients presenting to an Emergency Department due to this complaint leaves it with the diagnose of an undifferentiated headache.\(^{(50,51)}\)

Even in the absence of a specific diagnosis (migraine, tension-type headache, cluster headache, etc.), but as part of a defined diagnostic group (primary headaches), some researchers have dedicated themselves to the study of therapeutic options for acute headache management.

Miner et al.\(^{(51)}\) studied the efficacy of subcutaneous sumatriptan in the treatment of primary undifferentiated headache in the emergency unit care. A sample of 147 individuals with primary headache, excluding secondary causes, was submitted to treatment with sumatriptan. A trained researcher applied the diagnostic criteria according to the International Classification of Headache. Population was comprised of migraine, probable migraine and tension-type headache. The authors showed that pain relief response was attained for all headache types in a similar way.

Friedman et al.\(^{(50)}\) compared the effectiveness of intravenous Ketoroloc, and the association of intravenous Metoclopramide and Diphenhydramine infusions in the treatment of tension-type headache and all nonmigraine, noncluster recurrent headaches. The sample consisted of 120 adult individuals, equally randomized to anti-inflammatory drugs or to an antiemetic drug. Patients who received Metoclopramide (20 mg) + Diphenhydramine (25 mg) showed higher pain relief and remained pain-free for a longer period of time than those in the Ketorolac group (30 mg). The authors thus concluded that Metoclopramide plus Diphenhydramine promotes higher level of relief of tension-type headache, nonmigraine, and noncluster recurrent headaches than Ketorolac.

**OTHER TREATMENTS FOR PRIMARY HEADACHES**

**Valproate**

Sodium valproate is a well established medication in prophylactic treatment of headache. Intravenous sodium valproate has been used in the acute management of migraine.\(^{(52-55)}\) Regarding the control of head pain and associated symptoms (photophobia, phonophobia, nausea and vomiting) intravenous sodium valproate has comparable effectiveness to other standard treatment such as Dexamethasone, Sumatriptan, Dihydroergotamine.\(^{(52-54)}\)

Improvement was seen not only in migraineurs without aura but even in subjects with migraine with aura seems.\(^{(53)}\) Besides, valproate can be used in the acute treatment of other headaches such as chronic tension-type headache, cluster headache, unspecified chronic migraine, and transformed migraine.\(^{(56)}\)

**Table 13 - Valproate pharmacological data**

<table>
<thead>
<tr>
<th>Valproate</th>
<th>Route</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intravenous</td>
<td>100 mg/ml in 5 ml, flowing for 15 minutes</td>
<td>Nausea, headache, thrombocytopenia, somnolence, dizziness, tinnitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity to valproate or to any component of the formulation: liver disease, migraine prevention in women intending to get pregnant</td>
</tr>
</tbody>
</table>

**Oxygen**

Benefits of high-flow oxygen in (Table 11) are known in the acute treatment of cluster headache, as described. However, little was known of this treatment in other types of headache. Ozkurt et al.\(^{(57)}\) performed a prospective, controlled, randomized double-blind trial comparing high-flow oxygen and room air in patients with primary headaches in the emergency care unit. Diagnostics were tension-type headache, migraine, cluster headache and undifferentiated headache. It was noticed that the oxygen group showed significant improvement in all pain scores evaluated and a lesser need of additional analgesics as compared to placebo. Thus, high-flow oxygen proved to be an option as an adjunctive treatment of primary headache in the emergency care unit.

**CONCLUSION**

Primary headaches are responsible for increased demand on the emergency care, especially migraine and cluster headache. Diagnostic criteria based on ICHD-beta 3 should be applied, and, then, to direct the treatment according to the guidelines proposed in this review (Flowchart 1, Flowchart 2, Flowchart 3, and Flowchart 4).

It is important to stress that proper treatment can bring a significant relief to the headache patient and reduce the high morbidity caused by the disease.


UNDIFFERENTIATED PRIMARY HEADACHE

Ketorolac 30 mg/ml (1 ml) 1 amp + Saline 0.9% 10 ml, IV

Metoclopramide 5 mg/ml (2 ml) 1 amp + Saline 0.9% 10 ml, IV

Propofol 10 mg/ml (20 ml) 1 amp, IV: 1 ml (10 mg) every 5-10 min Slow Infusion


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