

# Effectiveness of IV Therapy in the Headache Clinic for Refractory Migraines

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## ABSTRACT

The future of aggressive headache treatment is in the specialty clinic, a far more cost- and time-effective mode of treating intractable headaches, including refractory and chronic migraines. Compared with the emergency department, the headache clinic can offer a wider range of effective and definitive treatments and offer headache patients maximum degree of success for control of migraines. We have used IV treatment in the clinic since 1994 and presented initial data regarding its effectiveness in 1998. This study continues in documenting the degree of success of outpatient IV treatment of headaches.

Our total treated patients number over 1700. Of these, 874 were treated for refractory migraines or headaches; the rest were for pain flare-ups or a mixture of both.

We utilized the following treatments: IV magnesium sulfate, dexamethasone, valproate sodium, lidocaine, droperidol, dihydroergotamine, promethazine, propofol, tramadol, levetiracetam and ketamine.

Results are measured on the basis of successful resolution of symptoms, defined by at least a 50% decrease in severity of the presenting headache or migraine, or by return to work or regular activity. On this basis, 62 patients from the total pool, and 22 from the headache pool (22/874 [ 2.5%]) had unsuccessful treatment that required re-treatment in the clinic hospital ED or inpatient. This represents a 97.5% rate of effective treatment in the clinic setting.

We conclude that outpatient aggressive therapy of refractory headaches and migraines is highly successful with a very low need for re-treatment. It contributes to productivity, most importantly in the workplace and also at home and in personal life.

## RATIONALE

Some headache and pain practitioners have a sense (and the experience) that aggressive management of headache and pain flareups can be easily and effectively managed in an outpatient clinic setting, rather than in the traditional mode utilizing hospitalization or simply treatment in the emergency department (ED). Of course this is predicated upon having a clinic that can adequately perform the various treatments in the first place. Our belief is that this method of treatment is far more effective for the patient, far less costly and allows for a greater range of IV medications to be administered than would occur in the ED. This is based on our experience and out patients' satisfaction with treatment. Based on the results presented here, we urge headache and pain practitioners to incorporate these IV treatment techniques when they are seeing a patient with refractory headache or migraine.

## METHOD

This outpatient IV treatment approach requires nursing staff trained in IV therapy to start and monitor IV lines; pulse oximetry monitoring is desirable in many cases, and even necessary for some of the medications. A comfortable room or rooms where patients can be treated, hopefully where lights can be dimmed, would also be ideal. Many of my IV rooms are multi-use so that the psychologists or other clinicians can use them as well. We have a room that we use for cervical and lumbar traction, a fluoroscopy room and an EEG room that can be used for IV treatments. Some of these rooms already have easy chairs in them.

## LIST OF MEDICATION OPTIONS

We utilized the following treatments (listed alphabetically):

IV antinauseants, dexamethasone, lidocaine, dihydroergotamine, droperidol, ketamine, levetiracetam, magnesium sulfate, propofol, tramadol, steroids, and valproate sodium. (see Table 1). These treatment protocols, and their specifics, will be described in more detail individually.

### IV antinauseants (IV droperidol, metochlopramide, promethazine, prochlorperazine, and ondansetron)

Antinauseants have long been used along with opiate analgesia for headaches and for pain treatment, on the notion that use of both agents was somehow synergistic. Animal experiments seemed to support this idea, but human studies are not at all conclusive on this point. We've looked for evidence of this, but it is almost non-existent. Nevertheless, ED treatment of headache most often uses both opiates with antinauseants. In a very large study of ED treatment patterns in Canada and the US for headaches, analysis of 611,419 migraine treatments in 1998 showed that adjunct anti-emetics were most often given with opiates. Promethazine was used six times more often than dopamine antagonists like droperidol, prochlorperazine or metochlopramide. Our preference is to use metochlopramide, both IV and IM as a first-line antinauseant in the clinic. A very recent paper in Neurology, described an ED study showing superior effectiveness of IV metochlopramide, 20mg, against 6mg of SQ sumatriptan. Better decreased pain intensity scores and pain-free rates were found in this study.<sup>1</sup>

There is a growing body of evidence that blockade of central dopamine receptor systems can enhance anti-nociception or reduce the migraine severity itself. One of the initial studies using IV droperidol<sup>10</sup> used quite high doses (mean = 5.6mg) and reported nearly all of their patients being sedated and over 50% with extrapyramidal symptoms 24 hours after treatment. We repeated a series of patients in our clinic using up to 1/15<sup>th</sup> the dose of IV droperidol with only 3% side effects and over 80% success rate in reducing or eliminating refractory migraines. A recent double-blind trial of intramuscular droperidol, again using high doses of the medication, showed efficacy; however, the placebo response rate was 57% vs 84% for droperidol. Once again, anxiety, akathisia and somnolence were rated as severe in 30% of patients, presumably due to the high doses employed. Thus, keeping doses quite low (around 2 mg total) can be very effective and we have quite a number of patients who use droperidol IM as rescue medication for their migraines, either with migraine-specific therapy or to avoid a trip to the emergency room. We begin with 0.625mg of IM droperidol, repeated after 20-30 minutes, and once again if needed.

### IV MgSO4

In the headache clinic, this treatment is a sort of "opening shot" for intractable headaches, both migraines and not. It can be given alone, or combined with antinauseants (IV metochlopramide, promethazine, prochlorperazine or droperidol) or with IV steroids.

There is a substantial literature on use of magnesium intravenously for migraines and cluster headaches. The original studies by Masukop and colleagues utilized ion-sensitive Mg<sup>2+</sup> electrodes to measure ionized magnesium, a technique not commonly available. Magnesium has primary effects as a physiologic antagonist to calcium. It also blocks NMDA-type glutamate excitatory amino acid activity, and nitric oxide synthesis and release, all of which are factors in migraine pathophysiology or maintenance. It augments serotonin which may be a direct means of blocking migraines. Multiple types of headaches, including migraines, migrainous headaches, tension-type headache and cluster headaches respond to intravenous magnesium therapy.

We have found that although 1-2 grams of IV Mg<sup>2+</sup> given over 30 minutes was very well tolerated and resulted in an almost 85% reduction of intractable migraine, we are sometimes prepared to increase the dose for a very refractory headache. In addition, Mg<sup>2+</sup> is the gold standard for muscle relaxation so it will relax muscle spasm in the neck area that accompanies refractory headache quite well. It also works very well to relax muscle spasm from any source, making it very useful for flareups of pain with muscle spasm and cramping. In all, this is a very easy IV to do or have done for your patient in the ED setting.

### IV steroids

There is very little published literature on the use of corticosteroids in migraines, although there is more data in the cluster headache field. Treatment of status migrainosus or analgesic rebound headaches. We use dexamethasone in the clinic fairly often for refractory migraines, for help in detoxification regimens and for pain flare-ups. This is not necessarily done by an oral taper. Most often, I give it along with IV MgSO<sub>4</sub>, as the both compatible in the same IV bag (unpublished observations). Other authors have published results from their own clinics, showing that dexamethasone was indeed effective in their migraine and status migrainosus. Other than very rare transient elevations in blood sugar and dency to be hungry and have more energy, I see very little in the way of negative effects from a single IV dose of dexamethasone in my headache clinic. Usually, 4 mg is the dose I use IV.

### IV Dihydroergotamine (DHE)

The gold standard for treating intractable migraines is dihydroergotamine (DHE), a compound similar to, but very different pharmacologically from, ergotamine. Many people forget that the pharmacologic profile of DHE is predominantly that of a vasoconstrictor (as well as an arterial constrictor), whereas ergotamine is a pure arterial vasoconstrictor. DHE can be given IV or IM and has a 10-14 half-life. The original IV DHE protocol to treat refractory migraine headaches was introduced in 1986 by Professor Raskin and it became the mainstay of inpatient and in-clinic treatments. Typically, it was given every 8 hours with IV metochlopramide, 10mg, for 2-3 days. In retrospect, metochlopramide probably also has a migraine blocking effect as discussed under the antinauseants. Comparisons of this protocol against "typical" treatment with meperidine and promethazine showed similar efficacy with significantly fewer side effects in the DHE/metochlopramide group, making it very useful for office-based treatment of migraines.

One of the authors [JCK] introduced the DHE45 protocol to Dallas in 1987. We have switched to an outpatient protocol where we give two or even three doses of IV or IM DHE/metochlopramide per day for up to three days. The third dose, if needed, can be given at home by the patient or a family member. This results in a tremendous cost and time savings for the patient and for the clinical staff. The patient can also continue a short protocol (3-5 days) of 2 IM doses at home each day to break a bad cycle of migraines. This is especially useful for peri-menstrual or seasonal migraine flareups.

### IV Valproate sodium

Sodium valproate (divalproex sodium as an enteric-coated preparation) was approved in 1994 for oral use in the prophylaxis of migraines in the United States. It was the first anticonvulsant molecule to be found useful in treating migraines in a prophylaxis manner. After a time, an IV version of the valproate sodium was developed and has been used for treatment of seizures. In our search for additional agents to use in the clinic intravenously for intractable migraines and other headaches, we turned to this compound and presented an initial open-label study in 2001.

Our IV study was a sample of 85 intractable migraineurs and the response to IV valproate sodium was a 98% reduction in severity of migraine, patient-rated on a 0-10 numeric rating scale. The average dose of valproate was 720 mg, given IV over about 50 minutes (100-200mg every 5-10 minutes).

We have recently gone back over our initial study data and extracted 23 cases of bona fide HIS-criteria status migrainosus from our initial published study sample treated with IV valproate sodium in the headache clinic. This very difficult-to-treat migraine population responded to IV valproate sodium as well as other headaches, but needed a higher dose of valproate sodium (1017mg) and a longer treatment time (73 minutes vs 50 minutes). 13 of the 23 patients rated their migraines as 0/10 in severity after treatment (57%)<sup>17</sup>.

### IV methocarbamol

Although methocarbamol is an older muscle relaxant preparation with an uncertain pharmacologic mechanism(s) of action, it is one of the very few available IV form and, for this reason, I sometimes utilize it in the clinic to treat migraines and other headaches especially if accompanied by a lot of neck spasm. We know of no published studies looking at effectiveness of this agent intravenously to treat headaches. All our information is anecdotal and rarely do we use it alone, it is often used after or with the above other agents. We have about 60 patients over the last 4-5 years for whom addition of methocarbamol is a positive element in their overall headache and muscle spasm relief.

### IV lidocaine

Lidocaine is an indiscriminate blocker of sodium (Na<sup>+</sup>) channels and blockade of this system has definite implications for reducing neuropathic pain disorders. Many of the so-called anti-convulsants (better termed neuronal stabilizing agents) have this mechanism of action, at least, in their pharmacology. We have used IV lidocaine, with pulse oximetry monitoring, in the clinic for years in the treatment of headache and pain flare-ups. The paradigm is to treat very slowly, so as to saturate the Na<sup>+</sup> channels and obtain the best possible blockade. Often, the response is short-lived (12-48 hours) and buys time for other treatments to be put in place. This is not a first-line choice for migraines, but IV lidocaine may be part of a regimen of daily or nearly-daily IV treatments to break a cycle of headache. IV lidocaine and Ca<sup>2+</sup> channel blockade (via IV MgSO<sub>4</sub>) can be particularly effective, along with IV dexamethasone.

### Combinations

It seems like virtually every combination of IV medications at our disposal has been tried or given in my clinic at one time or another for refractory migraines, headaches or a combination of these with a pain flareup. Of course, we make every effort to use one medication at a time and to document carefully the percentage reduction to that single agent. As you can imagine, agents that have worked successfully, perhaps many times before, might not work in the next particular situation and so we always have the next potential treatment "game plan". For example, one flareup may have much more nausea than the last 3 did. Or, there may be more accompanying muscle spasm, or burning pain. One must be flexible and individualized in each treatment paradigm.

## CONCLUSIONS:

1. Outpatient aggressive therapy of refractory headaches and migraines with IV therapies is highly efficacious with a very low need for re-treatment.
2. Our series successfully treated refractory migraine and other headaches 97.5% of the time [852 of 874 patients].
3. Treatment in this manner contributes tremendously to productivity, most importantly in the workplace, at home and in personal life for the migraine sufferer.
4. We would urge headache specialists and physicians interested in the acute management of headache disorders to explore these options in their practices.

### IV propofol

Sometimes, interesting results are found serendipitously, as occurred in the case of the pre-anesthetic agent, propofol. We use this agent routinely in the clinic as a mild sedative prior to epidural steroid and other nerve blocks in a conscious sedation manner. We noted that some patients who had migraines at the time of their blocks would comment on betterment of the migraine before the block was performed but after propofol was given in conscious sedation doses. After researching the literature, we found no other mention of this agent in treating migraines and undertook a formal open-label study in the headache clinic to treat refractory migraines unresponsive to usual abortive approaches.

We treated a cohort of 77 patients and the results were nothing short of spectacular. Propofol was the most effective IV agent that we had ever employed, with a 95.4% success rate in reducing ongoing migraine headaches. The total dose was only 120mg, given slowly by IV push 20mg at a time. The most fascinating element in this study was the specific pharmacologic effect of propofol, which has dose effects on subtypes of the GABA<sub>A</sub> receptor. It had me speculating as to the role that this receptor system might play in the maintenance of migraine headaches. Indeed, topiramate has been approved for migraine prophylaxis last year and one of its mechanisms of action is on GABA<sub>A</sub> receptors.

### IV levetiracetam (Keppra)

Our data with the oral form of this neuronal stabilizing agent was the first available anywhere in the treatment of refractory migraine headaches, and this agent has a unique mechanism of action that blocks high-voltage calcium channels, another major activity of many neuronal stabilizing agents.

Subsequently, we developed an IV form of the same agent with a compounding pharmacy and evaluated levetiracetam IV in the treatment of refractory migraines. More recently, cluster headache flare-ups and trigeminal neuralgia have also been treated in the clinic. Call it somewhat proprietary for now, but this is a powerful, non-toxic form of treatment for many difficult pain and headache flare-ups. The manufacturer is working on an IV preparation for commercial use to treat seizure disorders.

### IV tramadol

Tramadol has been available in the US for a number of years and has been used in Europe for over 30 years. 0.5 billion people worldwide have been treated for pain with this agent, whose pharmacologic activity includes opiate-like effects on the mu receptor, as well as weak presynaptic reuptake inhibition of norepinephrine and serotonin (like venlafaxine or duloxetine).

IV tramadol has been available in Europe but not the US. We decided to formulate a sterile IV preparation to treat headaches. An IV form is available in Europe and has a fairly extensive literature in treating pain. The IV preparation of tramadol turned out to be very efficacious, very well-tolerated and treated refractory migraines and mixed headaches with pain flareups. We use 50mg IV every 5-15 minutes given in the clinic. If it has efficacy, we place the patient on oral tramadol.

### IV ketamine

Some headache and pain physicians tend to think that neuropathic pain, chronic daily headaches and migraines are quite similar in their biochemical mechanisms or underpinnings. The fields of pain and headache management have become more confluent and utilize common terminologies to describe these convergences: nociceptive pain, peripheral and central sensitization, wind-up, long-term potentiation and neuroplasticity are concepts basic to the pathophysiology, expression and maintenance of these disorders.

On the treatment side of things, why is it that medications with completely different structures and similar mechanisms of action (ie, propofol and topiramate, each of which act on GABA<sub>A</sub> receptors) can both reduce migraines and other headaches and pain as well?

One antagonist of NMDA-type glutamate receptors shown to decrease migraine attacks when given subcutaneously is ketamine. This anesthetic agent has been little studied thus far but may have theoretical implications for preventing chronic migraines. A recent study administered ketamine intranasally to migraine patients who had pronounced and disabling aura, but less than 50% had successful resolution with ketamine.

TABLE 1 – Medications for Use in the headache clinic

Medication	availability	pulse ox monitoring	Cost Factor	IM use
MgSO <sub>4</sub>	Very good	Not required	inexpensive	No
Antinauseants	Very good	Not required	inexpensive	Yes
Steroids	Very good	Not required	inexpensive	Yes
DHE45	Very good	Not required	moderate	Yes
Depacon	Very good	Not required	moderate	No
propofol	Very good	Required*	moderate	No
lidocaine	Very good	Required*	inexpensive	Yes
levetiracetam	Special compounding	Required	expensive	No
tramadol	Available in Europe	Required	moderate	No
ketamine	poor	Required*	moderate	Yes
methocarbamol	Very good	Not required	inexpensive	No

\*ACLS trained staff and crash cart is recommended on the premises