

## A randomized open-label study of sodium valproate vs sumatriptan and metoclopramide for prolonged migraine headache

### BACKGROUND:

- Migraine is a common neurological disorder debilitating 10% of patients.
- Some patients cannot use the first line treatment for migraines, the triptans, due to safety concerns and lack of efficacy.
- Valproic acid has been effective in treating migraines, but no studies have compared the safety and efficacy of intravenous valproic acid with triptans for the treatment of acute, prolonged migraine.

### OBJECTIVE:

- To assess the safety and efficacy of intravenous valproic acid (iVPA) vs. subcutaneous sumatriptan + intramuscular metoclopramide in treating acute, prolonged, moderate to severe migraines

### METHODS

- **Design:** prospective, open-label, randomized, controlled, parallel-group study
- **Duration:** June 2010 – March 2011 (9 months)
- **Inclusion Criteria:** Patients diagnosed with moderate to severe migraine (International Headache Society 1.1) whose migraine began >4 hours and <72 hours before the start of treatment
- **Exclusion Criteria:** pregnancy; history of allergy to valproate, sumatriptan, or metoclopramide; use of valproate for migraine prophylaxis; administration of another antimigraine medication (i.e. triptans, ergot compounds) or valproate within 24 hours before enrollment
- **# patients enrolled:** 60 (30 per group)
- **Drug regimens/dosages used:**
  - iVPA 400 mg IV diluted in 100mL d5W, infused over 10-15 minutes
  - OR
  - Metoclopramide 10 mg IM, followed by sumatriptan 6 mg SQ
- **Primary Outcome Measure:** Between-treatment group comparison of pain relief based on mean Visual Analog Scale (VAS) in a period of 24 hours after starting treatment
- **Secondary Outcome Measures:** mean reduction in VAS between the 2 arms at different time points; trend of VAS pain score improvement between the 2 groups
- **Power:** 80%
- **Data handling method used:** Intent-to-treat

### RESULTS

- 52/60 patients completed the study (26 in each group)
- **Primary Outcome Measure:** At 1 hour, 53.3% of patients in the iVPA group obtained pain relief compared to 23.3% of patients in the sumatriptan-metoclopramide group ( $p = .033$ ). At 2 hours, 60% of patients in the iVPA group had moderate to severe headache compared to 30% of patients in the sumatriptan-metoclopramide group ( $p=.037$ ). There were no significant differences in headache relief between groups at other time points. There were no significant differences between groups for alleviation of nausea, photophobia, and phonophobia.
- **Secondary Outcome Measures:** The mean reduction in VAS score was significant over time in both groups with linear trend ( $P<.001$ ,  $F = 90.26$ ). The mean reduction in VAS in the iVPA group was significantly greater than the sumatriptan-metoclopramide group, with a mean difference of 0.91 ( $p = 0.48$ ; 95% CI: 0.009-1.81). There was significantly faster pain relief in the iVPA group compared to the control group within 24 hours ( $p = .003$ ,  $F = 5.42$ ).

- **Authors' conclusions:** Intravenous iVPA is a safe, efficacious treatment with a rapid onset of action for acute, prolonged migraines, and it is more effective when compared to sumatriptan beyond the first few hours of migraine.

#### STRENGTHS

- There were no reported conflicts of interest.
- Data handling method was appropriate to maintain an acceptable level of power
- The primary endpoint, pain relief, was appropriate to determine the efficacy of iVPA.

#### LIMITATIONS

- No blinding, therefore subject to bias
- No placebo
- Referral bias
- Study only analyzed one migraine attack per subject
- No baseline data on history of migraines
- Rescue medication could have interfered with results after the 1-hour time point
- Results of study can only be applied to specifically defined population of patients reporting to the ED 4-72 hours after the onset of moderate to severe migraine

#### CONCLUSIONS

- This study has many limitations that restrict its clinical applicability. An open-label study can significantly affect the results, especially one that uses subjective visual analog scales. A placebo comparison is necessary in this study to determine the actual effects of the treatment and active control.
- The study weaknesses are sufficient to invalidate its findings. If further research is done using a better study design which yields the same results, iVPA may be useful in patients who present to the ED with an acute, prolonged migraine.
- Further research is necessary. A larger study sample may reveal statistically significant differences among the 2 treatment groups at different time points. Patients in the sumatriptan group should be allowed to take a second dose if needed to determine sumatriptan's efficacy compared to iVPA. Future studies should be double-blind to reduce the chance of bias. A placebo group should be used to compare to iVPA. Since the study only involved patients living in Iran, and the efficacy of triptans has not been established in that population, trials evaluating iVPA are necessary in other populations as well. Studies should also examine drug efficacy based on more than 1 migraine attack in each patient.

#### Reference:

Bakhshayesh B, Seyed Saadat SM, Rezanian K, Hatamian H, Hossieninezhad M. A randomized open-label study of sodium valproate vs sumatriptan and metoclopramide for prolonged migraine headache. *Am J Emerg Med.* 2013 Mar;31(3):540-4.

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