

# The Timing of Gastric Stasis in an Acute Migraine Attack and its Impact on Treatment

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## OBJECTIVES

To review recent literature on existence, timing, importance and practical treatment implications of gastric stasis in migraineurs and acute migraine attacks. In addition, to propose a potential mechanism of gastric stasis.

## BACKGROUND

It is generally accepted that there is gastric stasis or some form of delayed emptying of the stomach during an acute migraine attack. The basis for this assumption comes from drug absorption studies conducted in the 1970s and 80s using aspirin, aspirin and metoclopramide, acetaminophen, and toltenamic acid [1-7]. These studies assumed that the rate-limiting step in the absorption of these drugs was the rate of emptying of the drug from the stomach, and the delay in absorption, as measured by  $T_{max}$  and  $AUC_{0-2 hrs}$ , was definitive evidence of gastric stasis. As this observed delay in absorption was only during the acute attack, it was concluded that gastric stasis is present only during an acute migraine attack. The same conclusion also was arrived at by a study using gastric impedance method [8]. However this study compared a group of migraineurs not having an acute attack with a different group of migraineurs during an acute attack. The drawbacks of this study also include inter-person variability and the use of a less reliable technique for measuring gastric motility.

More information about the timing and extent of gastric stasis during migraine would be helpful, since gastric stasis may have a significant impact on acute migraine therapy. Better understanding gastric stasis in migraineurs may help:

1. explain the wide variability in PK parameters, particularly  $T_{max}$ , of the orally administered triptans
2. explain the inconsistency of response to orally administered triptans
3. suggest better or alternative administration techniques to either overcome or bypass gastric stasis for better and more consistent response to therapy
4. settle the controversy related to the mechanism of higher response rates in early intervention studies with oral triptans

In this poster we review a body of emerging data which strongly suggest that, contrary to the general belief, gastric stasis is present in migraineurs both during and outside of a migraine attack. Based on these data, we also propose a potential mechanism for gastric stasis.

## METHODS

A literature search was carried out using Pub Med. The design and results from four studies on gastric stasis are presented, including published original work from the authors.

## RESULTS AND DISCUSSION

### A. Studies measuring actual gastric emptying

#### STUDY 1: IN INDUCED MIGRAINES (9)

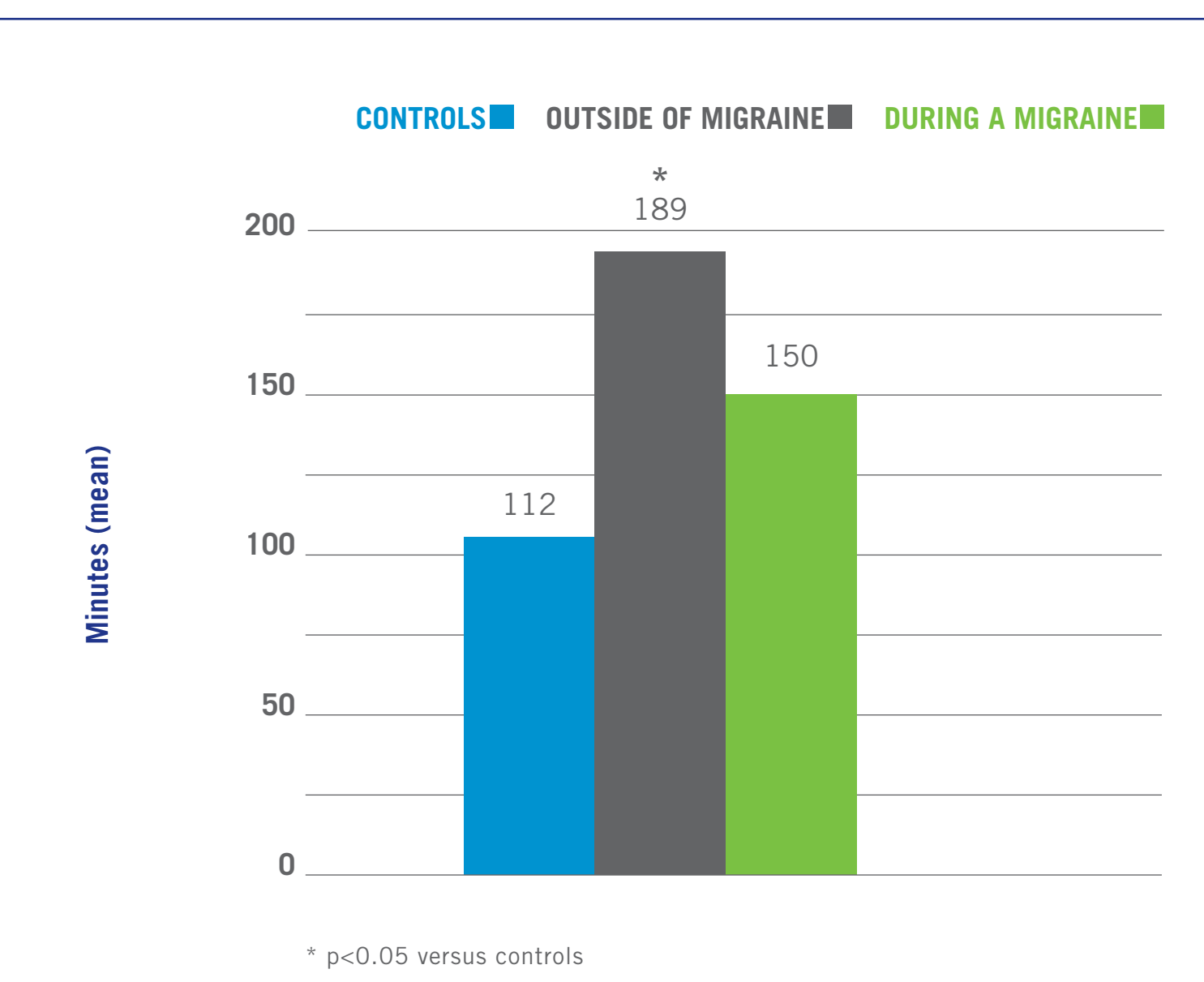
##### Overview

Utilizing gastric scintigraphy, a well accepted, validated and widely used technique for measuring gastric motility, we studied gastric motility in 10 migraineurs and 10 non-migraineurs, as measured by slowing of gastric emptying and an increase in tracer retained in the stomach [9]. These techniques were used for the first time to study the motility both during (ictally) and outside of (interictally) a migraine attack.

##### Results

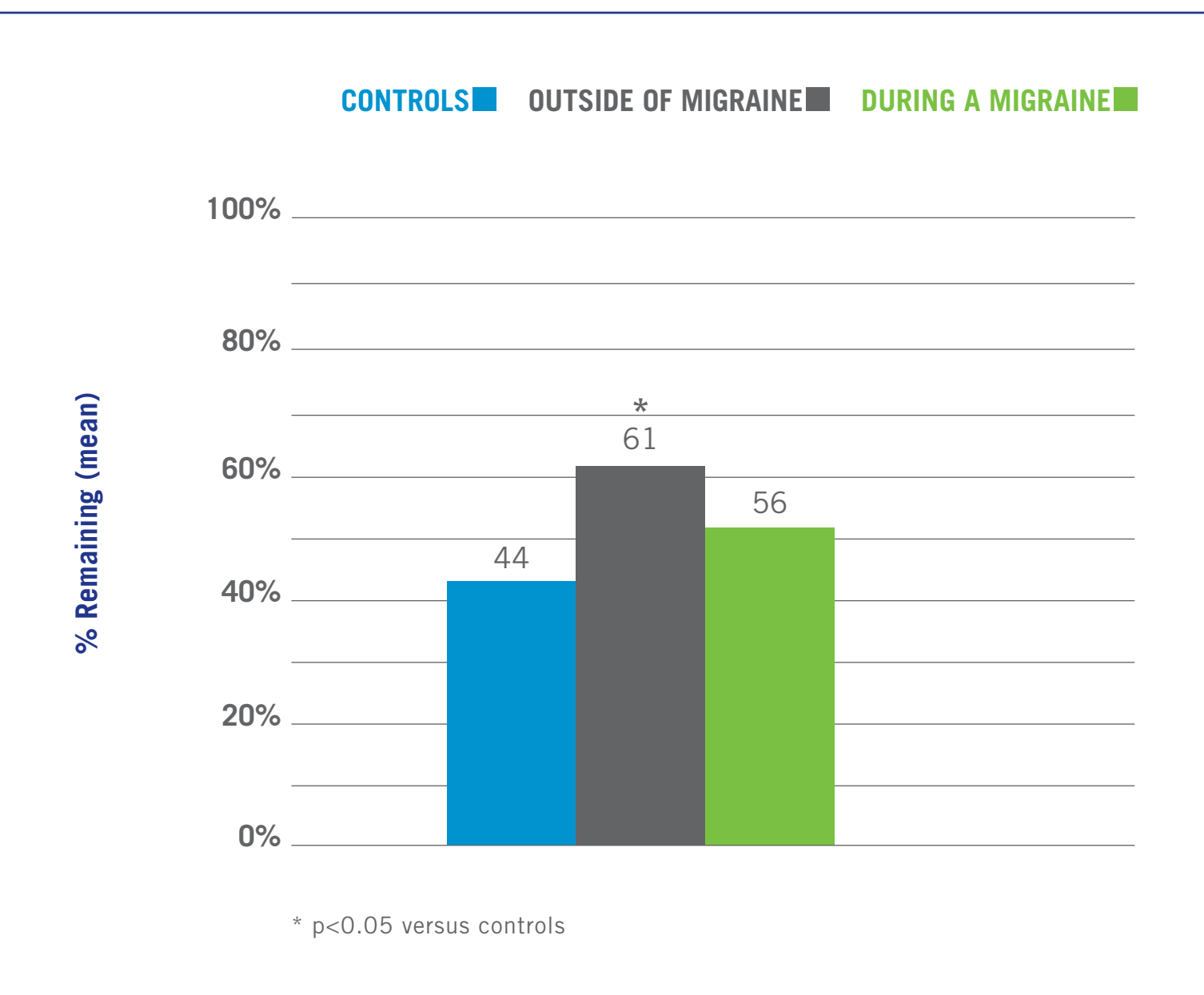
The mean time to emptying of half the gastric content ( $T_{1/2}$ ) was slightly longer interictally (188.8 minutes) compared to ictally (149.9 minutes) but not statistically significant. The median  $T_{1/2}$  for migraineurs was also slightly longer interictally (164.5 minutes) compared to ictally (105.0 minutes), but not statistically significant. When comparing migraineurs to controls without migraine, the mean  $T_{1/2}$  was longer in migraineurs (both ictally and interictally) compared to controls. Specifically, the mean  $T_{1/2}$  for migraineurs interictally took over an hour longer than non-migrainous controls (188.8 vs 111.8 minutes;  $p < 0.05$ ). Although the mean  $T_{1/2}$  for migraineurs ictally was longer, it was not statistically significant from non-migrainous controls (149.9 vs. 111.8 minutes;  $p > 0.05$ ). The median  $T_{1/2}$  comparisons showed similar results: interictally, but not ictally, migraineurs had a significant delay in emptying from the stomach compared to non-migrainous controls.

Figure 1. Mean time to half emptying in stomach at 2 hours



- Both ictal and interictal emptying times were abnormal (>120 mnts) compared to normal controls (<120 mnts)
- There was no statistical difference between ictal and interictal gastric emptying times

Figure 2. Mean radiolabel tracer remaining at 2 hours



- Both ictal and interictal tracer retentions were abnormal (>50%) compared to normal controls (<50%)
- There was no statistical difference between ictal and interictal tracer retention

##### Conclusions

This study not only demonstrated for the first time objective evidence for gastric stasis in migraine, but surprisingly demonstrated the presence of gastric stasis both during a migraine attack and also during the interictal period.

#### STUDY 2: IN SPONTANEOUS MIGRAINES (10)

##### Overview

Because of the unexpected results of the above study and to make sure that the results were not an anomaly of the induced migraine included in that study, we opted to repeat the study in patients during their spontaneous migraines [10]. Nine additional studies were performed as a follow-up to ascertain if there is a similar delay during spontaneous migraine. Gastric scintigraphy using a standard meal was performed in three subjects during spontaneous migraine, induced migraine and in the interictal period.

##### Results

The time to half emptying was delayed during spontaneous migraine (130 minutes), during induced migraine (152 minutes) and during the interictal period migraine (176 minutes) compared to normative values established at the center (112 minutes). Similar gastric slowing was seen in all three groups when a percentage of nuclear material remaining in the stomach measured at two hours was used as the end point.

##### Conclusions

This study confirmed the presence of gastric stasis in migraineurs both during and in between attacks and also during a spontaneous migraine and induced migraine.

### B. Studies measuring anti-migraine drug absorption

#### STUDY 3: RIZATRIPTAN (11)

##### Overview

In a study, part of a larger trial, conducted to examine the pharmacokinetics of rizatriptan tablets during and between migraine attacks the results were similar to ours [11]. Participating patients met the criteria for migraine with or without aura of the International Classification of the Headache Disorders (second edition) and suffered between one and eight migraines per month for the previous 6 months. In part 1 of the study, 21 patients were randomized to receive a single 5-mg tablet of rizatriptan or placebo in the migraine-free state. In part 2, the same patients were treated during migraine with rizatriptan 5-mg tablets (n=18) or placebo (n=3). Blood samples were obtained before dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after dosing.

##### Results

The plasma concentration profile (ie,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $T_{max}$ ) of rizatriptan 5-mg tablets administered during and between migraine attacks were comparable.

##### Conclusions

Results from this study confirm that, at least as measured by the absorption kinetics of a triptan, there is no difference in gastric motility during or outside of a migraine attack. If there is gastric stasis, it is present both during and outside of an acute attack, and not just during an acute attack as previously thought.

#### STUDY 4: SUMATRIPTAN (12)

##### Overview

Another study compared the pharmacokinetics of sumatriptan after oral (100 mg) and subcutaneous (6 mg) administration in two age- and gender-matched groups: ten subjects (group A) with satisfactory response and ten (group B) with unsatisfactory response to oral sumatriptan [12]. Patients were studied during headache-free intervals. Blood samples were taken serially from baseline to 360 min after oral administration and from baseline to 180 min after subcutaneous injection. Sumatriptan plasma concentrations were determined by high-performance liquid chromatography (HPLC) with an electrochemical detector.

##### Results

Following oral dosing, patients in group A absorbed sumatriptan significantly faster and achieved early plasma levels significantly higher than patients in group B. The systemic exposure to sumatriptan during the first 2 hours, which are the most important for rapid onset of action and for antimigraine efficacy, was significantly greater in group A than in group B ( $p < 0.001$ , Student's t test for independent data). On the other hand, after subcutaneous injection of sumatriptan, the profile of the curves was similar in all patients, and there were no differences in pharmacokinetics between group A and group B.

#### STUDY 4: SUMATRIPTAN (12) CONT.

##### Conclusions

The differences in the oral absorption kinetics between group A and B is most likely due to gastric stasis as the same differences were not seen with parenteral administration. Considering that the study was done outside of an acute migraine attack, this study not only confirms the finding that gastric stasis exists outside of a migraine attack but also points out that gastric stasis can reduce the efficacy of oral triptans.

To date we could not find any published study that has systematically looked at gastric motility both inside and outside of a migraine attack and found absence of gastric stasis in the interictal period.

#### PROPOSED POTENTIAL MECHANISM OF GASTRIC STASIS

Gastric motility is regulated at multiple levels. The myenteric and Auerbach's plexuses in the gut, enterochromaffin cells, and local sympathetic innervation are all major peripheral players in the maintenance of GI motility.  $5HT_2$  and  $5HT_4$  receptors predominantly and  $5HT_{1A}$ ,  $5HT_{2A}$  and  $5HT_6$  receptors to some degree are involved [13,14]. More recent data suggest that sumatriptan can induce gastric stasis through its action on  $5HT_{1p}$  receptors [15]. The central control of GI motility appears to be primarily through the autonomic nervous system. There are several reports of demyelinating lesions in the brainstem that have resulted in gastric stasis, presumably due to interruption of autonomic fibers passing through the brainstem [16-18]. In one series treatment of the lesion with steroids resulted in improvement in both the lesion and the gastric stasis [16].

Chronic sufferers of migraine with frequent migraine attacks are reported to have deposition of iron in the brainstem [19]. Recently a large series of 138 migraineurs compared to 75 normal controls found MRI evidence of iron deposition in the brainstem of migraineurs [20]. This study also suggested that the deposition of iron may be correlated to the frequency of migraine attacks. Another study has suggested that there are white matter lesions in the posterior fossa in migraineurs, and the number of these lesions correlate with the type and frequency of the migraine attacks [21].

We postulate here that the gastric stasis commonly seen in migraineurs is not related to individual migraine attacks, but rather may be a function of the degree of autonomic dysfunction one develops, which in turn is related to the number and frequency of migraines one has suffered and the amount of iron deposition or white matter lesions that have developed in the brainstem as a result of these migraine attacks. Further studies are needed to clearly define the incidence of gastric stasis, relation to duration/frequency of migraine attacks and relation to type of migraines (aura versus no aura).

## CONCLUSIONS AND PRACTICAL IMPLICATIONS

The evidence suggests that at least a subset of migraineurs have gastric stasis both during and outside of a migraine attack. It is possible that the longer the history and frequency of migraine, the more likely one will have gastric stasis. If confirmed, this has many practical implications not only for acute treatment of a migraine attack, but also for administration of any oral drugs for this group of patients. A non-oral route of administration like intravenous, subcutaneous or oral inhalation, or co-administration of a prokinetic along with the oral tablet should be considered if an oral therapy provides lower efficacy than expected, or patients report inconsistent response.

Triptans have been shown to provide a much higher efficacy when administered early in the migraine attack and when the pain is mild in severity. One potential explanation for this observation is the development of Central Sensitization in later stage of a migraine cycle. A second explanation hypothesized is that early triptan administration may avoid the gastric stasis, which traditionally was believed to be present only during later stages of an acute attack. Our observations, and the literature review presented here suggests that gastric stasis is present throughout tends to make this later hypothesis less likely and favors the Central Sensitization hypothesis.

The review also highlights the gaps in our understanding of gastric stasis. Further studies are needed to correlate the presence and severity of gastric stasis to type and frequency of migraine attacks, other autonomic dysfunctions, degree of changes in the brainstem, and effect of treatment.

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