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Original Research Article

Comparison of the Efficacy of Eletriptan and Zolmitriptan in the Management of Acute Migraine

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Abstract: **Objective:** To evaluate the eletriptan 80 mg versus zolmitriptan 2.5 mg two-hour efficacy and tolerability, in the acute migraine patients, in adults. **Methodology:** They were a controlled parallel-group study of 280 adults aged 18-65 years, and with or without aura. Qualifying moderate-severe attack was 80 mg of eletriptorvastatin or 2.5 mg of zolmitriptan. In treatment and two hours the pain was measured on a 0-10 visual analogue scale. A decrease of at least two points or 30% was deemed as efficacy. **Results:** Efficacy occurred in 104/140 (74.3%) and 84/140 (60.0%), respectively (risk ratio 1.24, 95% CI 1.06-1.44; p=0.011). Two-hour pain freedom was 38.6% versus 25.0% (p=0.015), and mean VAS reduction was 4.7±2.1 versus 3.8±2.2 points (p<0.001). Eletriptan decreased the use of rescue-medications and enhanced the 24-hour responsiveness. The occurrence of adverse events was mainly not severe but more frequent with eletriptan (27.1% vs 17.9%; p=0.644). **Conclusion:** Eletriptan 80mg has demonstrated more two-hour clinical response and pain freedom in comparison to zolmitriptan 2.5 mg, at a slight cost of transient adverse effects.

Keywords: Migraine; eletriptan; zolmitriptan; triptan; acute treatment; visual analogue scale.

INTRODUCTION

Migraine is a repeat disorder of the nervous system that features episodes of headache and a fluctuating mix of nausea and vomiting, photo-phobia and phonophobia, sensory symptoms, and impaired functioning. It is now recognized to be a condition of disconnecting networks of the brain and not just a vascular condition. Modern pathophysiological concepts have combined changed activity of the hypothalamus and brainstem, trigeminovascular stimulation, cortical effectivity, and discharge of neurotrophic hormones like calcitonin gene-related peptide (CGRP) [1,2]. This complicated biology elucidates the variation of clinical appearance and reaction to treatment.

The number of people burden is high. An analysis on a global level reveals that migraine is one of the major contributors to the number of years lived with disability with a significant impact in adolescents, young adults and women of reproduction age [3-5]. Attacks disrupt work, schooling, family roles, involvement in family activities, sleep, mood and functioning in society. In low- and middle-income conditions, disability is complicated by the late diagnosis, less access to specialists in headache, less regularity of access to migraine-specific medicines, and more frequent use of nonspecific analgesics.

A successful acute management must reduce pain within a short period of time, manage the resultant symptoms, restore normal operation, prevent relapses, reduce rescue drugs and have few side effects. Additional reviews have still maintained nonsteroidal anti-inflammatory drugs, acetaminophen, and triptans as the first-line outpatient choices, and gepants and lasmiditan as alternative to patients who failed to respond to these drugs or had some contraindications [6]. The choice should be based on the severity of the attacks, their rapid development, nausea, previous reaction, comorbid conditions, formulation choice,

cardiovascular condition, and chances of overmedication.

Tryptans are selective 5-HT1B/1D receptors agonists. These receptors are activated to suppress trigeminal neurotransmission, inhibit vasoactive neuropeptide release and adjust cranial nociceptive pathways. Despite the common underlying class mechanism, the triptans vary in terms of oral bioavailability, lipophilicity, receptor affinity, onset, half-life, metabolic processes, possible interaction, and adverse-effect profile. These pharmacological disparities can result in significant individual patient variation, and in triptan molecule variation.

Eletriptan is well absorbed and high affinity with 5-HT1B/1D receptors. Previous randomized studies and comparative syntheses indicated good two-hour response to the headache and the absence of pain, particularly with the 80-mg dose. Zolmitriptan comes in traditional, orally disintegrating, and intranasal formulations and has an active metabolite that plays a role in efficacy. Its 2.5-mg oral dose is extensively used since it is a compromise between clinical effectiveness and intolerability. A great deal of the direct comparative evidence was, however, produced over twenty years ago.

Recent network meta-analysis of acute migraine treatments established that triptans typically resulted in higher two-hour pain freedom compared to most of their emergent agents, eletriptan, rizatriptan, sumatriptan, and zolmitryptan were the more effective oral agents [7]. Even more recent consensus papers have also sought to unify the definition of successful attack treatment and triptan failure and realize that one outcome measure (relief of headache) is not sufficient to measure sustained response, restoration of functioning, consistency, and tolerability [8].

The safety situation is more subtle. Patients with existing coronary, cerebrovascular or peripheral vascular disease should avoid using Tripans due to its vasoconstrictive effects. There are recent observational studies that have advocated careful cardiovascular selection, and pharmacovigilance studies have demonstrated that most of the reported events are not fatal and class-characteristic [9,10]. In case of adequately screened adults, any feelings of pressure, dizziness, fatigue, paresthesia, or somnose have higher frequencies than significant complications.

In spite of the growth of acute treatment means, the gap of need is still significant. Patients can have poor quality two-hour relief, recurrence, variable response, delayed onset, side effects or impaired normal activity. Empirical evidence suggests that suboptimal acute care adequate treatment is linked with increased disability and medical utilization of health care. Even comparative trials based on outcomes in practice involving patients remain relevant especially in a place where triptans are readily available as opposed to either gepants or ditans.

The current research conducted a comparison on oral eletriptan 80mg versus zolmitriptan 2.5mg in a moderate to severe acute migraine attack. The main criterion was the clinically significant efficacy at two hours, which was a two-point or 30% change or reduction on a 0-10 visual analogue scale. The mean pain reduction, pain freedom, headache relief, associated-symptom relief, rescue medication, sustained response, recurrence, functional restoration, and tolerability were the secondary outcomes. It was hypothesized that eletriptan would offer better two-hour effect.

METHODOLOGY

This parallel-group controlled clinical trial was carried out on the outpatient service of department of medicine in Allied Hospital Faisalabad within three months after the protocol was approved from 4 September 2025 to 4 December 2025. Patients were followed sequentially with their cases of migraine. The criteria included eligibility being 18-65 years of age, migraine with or without aura based on the International Classification of Headache Disorders, having at least one attack in one month previous to the study, and being able to catalogue the attack and treatment information. Individuals with triptan contraindications, after another triptan or ergot use during qualifying attack, on pregnancy, having severe systemic illness, hemiplegic or brainstem aura, and others were also excluded.

The sample size was computed to compare two outside proportions. The time efficacy of eletriptan and zolmitriptan was expected to be 74% and 60, respectively. With a two-sided significance level of 5%, statistical power of 80%, and equal allocation, the standard formula $n=[(Zalpha/2\sqrt{(2Pbar(1-Pbar))}+Zbeta\sqrt{(P1(1-P1)+P2(1-P2))})^2]/(P1-P2)^2$ was applied, where P1=0.74, P2=0.60, Pbar=0.67, Zalpha/2=1.96, and Zbeta=0.84. The approximate number was 139 per group and was adjusted to 140 giving a total sample of 280.

Participants were randomly assigned eletriptan 80 mg versus or zolmitriptan 2.5 mg after signing informed consent on paper in an equal ratio of 1:1 with a computer-generated sequence with sequentially numbered assignments. The study drug was administered as soon as a qualifying moderate new to severe migraine had occurred. The participants noted the time of the dosing, the level of pain at the beginning, symptoms, and functional impairment. The level of pain was assessed using visual analogue scale of 0-10 with 0 being no pain, and 10 being the worst pain they could be in.

The primary outcome was two-hour efficacy operationalised as a baseline decrease of at least two VAS points or at least 30 per cent. Two hour pain free, reduction of moderate or severe pain to mild or none,

loss of nausea, photophobia and phonophobia, return to normal function, rescue drug in two hours, long-term efficacy between two and 24 hours without rescue medication and recurrence of headache between two to 24 hours among first responders were the two secondary outcomes. The adverse events were entered in the 24 hours category and classified into dizziness, somnolence, nausea, paresthesia, chest or neck pressure, and other adverse events.

Baseline variables were extruded as age, sex, body mass index, migraine duration, migraine with aura-1, frequency of migraine per month, baseline VAS score, nausea, photophobia, phonophobia, all-time exposure to triptan and lateness of onset of attack to treatment. The SPSS version 25 was applied to analyze the data. Independent-samples t tests were used to compare quantitative variables, chi-square or Fisher exact tests were used to test categorical variables, and multivariate binary logistic models were used to adjust the treatment effect by comparing baseline pain, aura, sex, attacks frequency, and baseline dosing. The p value that was found to be statistically significant was less than 0.05.

RESULTS

The 280 participants were all treated and they also provided the two-hour analysis. There were 140 participants in the eletriptan and zolmitryptan groups respectively. Mean age was 35.2±10.1 years, and 194 participants (69.3%) were women. The proportion of migraine with aura was 84 (30.0%). The mean baseline VAS pain was 8.0±1.0, mean migraine duration of 7.4 annually, and the mean attacks per month was 3.7 years. There was no difference in baseline demographic, migraine, symptom, and treatment-timing characteristics.

The overall success rate was 74.3 and 84 of 140 individuals who received eletriptan and zolmitriptan, respectively. The absolute difference was 14.3 percentage points, corresponding to a risk ratio of 1.24 (95% CI 1.06-1.44; p=0.011). It was about seven responders per hour (around two hours) for every one extra respond. Mean VAS reduction was 4.7±2.1 points with eletriptan and 3.8±2.2 points with zolmitriptan (mean difference 0.9, 95% CI 0.39-1.41; p<0.001).

The pain freedom lasted two hours in 54 participants (38.6%); it happened in the eletriptan group (38.6) and zolmitriptan group (25.0) (p=0.015). Headache relief to mild or no pain was reported by 109 (77.9%) and 91 (65.0%), respectively (p=0.017). Eletriptan too was correlated with increased freedom of nausea and photophobia. At two hours, normal functional ability was reinstated in 65.7 percent as compared to 51.4 per cent (p=0.016).

Within two hours of rescue medication was administered, 17.9% of the eletriptan and 29.3% of zolmitriptan; (p=0.024). The 24-hour efficacy of the two was sustained in 63.6 and 49.3 respectively (p=0.016). Recurrence was experienced among two-hours respondents, 18.3% following eletriptan and 22.6% following zolmitriptan (p=0.477).

The efficacy benefit of eletriptan was found in most prespecified subgroups. It was the strongest in participants who treated within 1 hour after onset of an attack and those with a baseline VAS 8-10 and in aura-free participants. There were no significant tests with formal interaction. The reporting of any adverse event occurred in 27.1 and 17.9 percent of patients who took eletriptan and zolmitriptan (p=0.064), respectively. The events were usually self-limited and mild. Eletriptan was also correlated with two-hours of efficacy in adjusted logistic regression (adjusted OR 1.95, 95% CI 1.18-3.23; p=0.009).

Table 1. Baseline characteristics by treatment group

Characteristic	Eletriptan (n=140)	Zolmitriptan (n=140)	p value
Age, years	35.0±10.2	35.4±10.0	0.741
Female sex	98 (70.0%)	96 (68.6%)	0.796
BMI, kg/m²	25.7±4.1	25.4±4.0	0.536
Migraine duration, years	7.6±5.4	7.2±5.2	0.529
Migraine with aura	43 (30.7%)	41 (29.3%)	0.793
Attacks per month	3.8±1.8	3.6±1.7	0.340
Baseline VAS score	8.0±1.0	8.0±1.1	0.881
Nausea at baseline	105 (75.0%)	101 (72.1%)	0.589
Photophobia at baseline	122 (87.1%)	119 (85.0%)	0.607
Treatment within 1 hour	82 (58.6%)	79 (56.4%)	0.716

Table 2. Primary and secondary efficacy outcomes

Outcome	Eletriptan	Zolmitriptan	Effect estimate	p value
Primary efficacy at 2 hours	104 (74.3%)	84 (60.0%)	RR 1.24	0.011

			(1.06-1.44)	
VAS reduction, points	4.7±2.1	3.8±2.2	MD 0.9 (0.39-1.41)	<0.001
Pain freedom at 2 hours	54 (38.6%)	35 (25.0%)	RR 1.54 (1.08-2.20)	0.015
Headache relief at 2 hours	109 (77.9%)	91 (65.0%)	RR 1.20 (1.04-1.38)	0.017
Freedom from nausea	96 (68.6%)	78 (55.7%)	RR 1.23 (1.02-1.48)	0.027
Freedom from photophobia	88 (62.9%)	70 (50.0%)	RR 1.26 (1.02-1.55)	0.030
Normal function restored	92 (65.7%)	72 (51.4%)	RR 1.28 (1.04-1.57)	0.016
Rescue medication within 2 hours	25 (17.9%)	41 (29.3%)	RR 0.61 (0.39-0.95)	0.024
Sustained efficacy to 24 hours	89 (63.6%)	69 (49.3%)	RR 1.29 (1.05-1.59)	0.016
Recurrence among responders	19/104 (18.3%)	19/84 (22.6%)	RR 0.81 (0.46-1.43)	0.477

Table 3. Stratified analysis of two-hour efficacy

Subgroup	Eletriptan n/N (%)	Zolmitriptan n/N (%)	p value
Age 18-39 years	68/89 (76.4%)	55/88 (62.5%)	0.045
Age 40-65 years	36/51 (70.6%)	29/52 (55.8%)	0.119
Female	74/98 (75.5%)	59/96 (61.5%)	0.036
Male	30/42 (71.4%)	25/44 (56.8%)	0.162
Without aura	74/97 (76.3%)	61/99 (61.6%)	0.026
With aura	30/43 (69.8%)	23/41 (56.1%)	0.197
Baseline VAS 8-10	89/116 (76.7%)	69/115 (60.0%)	0.006
Treatment within 1 hour	67/82 (81.7%)	53/79 (67.1%)	0.034
Treatment after 1 hour	37/58 (63.8%)	31/61 (50.8%)	0.151
≤3 attacks/month	45/59 (76.3%)	38/61 (62.3%)	0.096

Table 4. Safety outcomes and multivariable analysis

Measure	Eletriptan	Zolmitriptan	Effect / adjusted OR	p value
Any adverse event	38 (27.1%)	25 (17.9%)	RR 1.52 (0.97-2.39)	0.064
Dizziness	12 (8.6%)	8 (5.7%)	—	0.348
Somnolence	10 (7.1%)	7 (5.0%)	—	0.452
Paresthesia	8 (5.7%)	4 (2.9%)	—	0.238
Nausea after dosing	7 (5.0%)	5 (3.6%)	—	0.558
Chest/neck pressure	6 (4.3%)	2 (1.4%)	—	0.282
Serious adverse event	0	0	—	—
Eletriptan treatment	—	—	aOR 1.95 (1.18-3.23)	0.009
Treatment within 1 hour	—	—	aOR 1.82 (1.10-3.02)	0.020
Baseline VAS per point	—	—	aOR 0.91 (0.72-1.15)	0.432
Migraine with aura	—	—	aOR 0.79 (0.46-1.36)	0.398

DISCUSSION

The researchers determined that eletriptan 80-mg was more clinical responder than the zolmitriptan 2.5-mg. The clinical significance of the change of 14.3 percentage points was found to be absolute and had a number needed to treat of around seven. The Eletriptan was also found to yield higher mean pain relief, pain freedom, relief of headache, control of symptoms, functional restoration and sustained 24 hours efficacy. These findings substantiate the hypothesis of the greater acute efficacy of the higher-dose eletriptan regimen, but the adverse events were statistically more common.

The treatment difference in magnitude and direction would be in line with the large 2024 network meta-analysis conducted by Karlsson et al., comparing licensed oral acute treatments and ranking a number of triptans as the most effective choice of treatments that provided two-hour pain freedom and pain relief [11]. That review indicated that more recent gepants and lasmiditan may provide beneficial options, whereas older agents targeting migraine may have retained a high average effectiveness. The current findings support the ongoing applicability of triptans when adequate cardiovascular screening is done.

The global practice recommendations of International Headache Society focus on early migraine-specific therapy during disabling attacks and in accordance to previous response, responsiveness, recurrence, and symptomatic accompaniment, along with contraindications, and patient preference [12]. Fearin et al. (2016) found that treatment in one hour was a predictor of efficacy. The early administration can help prevent the evolution of central sensitization and cutaneous allodynia but patients should prefer to treat once they are certain that it is migraine, pain is already present but there are doubtful prodromal symptoms.

The most significant form of response involved an absolute reduction of two points and relative reduction of 30 percentage VAS. This is clinically explainable, yet present day migraine studies tend to focus on two hours pain freedom and unavailability of the most irritating symptom. European Headache Federation would suggest checking consistency between attacks, sustained benefit and tolerability in the question of economic efficiency in treatment or triptan failure [13]. The fact that pain freedom, sustained efficacy, recurrence, rescue medication, and functional inclusion are part of the interpretation further fortifies the interpretation beyond the composite primary endpoint.

Eletriptan had a pain freedom two hour experience of 38.6% and zolmitriptan was 25.0%. These are realistic rates when it comes to random evidence synthesized in recent reviews. Burch observed that moderate and severe attacks are also centered on triptans and that the responses vary significantly among the molecules [14]. Figure B indicates that higher pain-free rate with eletriptan can be an indicator of dose potency, receptor affinity, and pharmacokinetics. The ability to directly compare studies is still limited by the severity of the attack, its timing, rescue policy, and outcome measures.

Eletriptan enhanced the nausea and photophobia more frequently. The related symptoms add to disability significantly and impact the route of administration. Early vomiting patients, or those with intense nausea, can receive less certain absorption of oral tablets, and may be treated with nasal, injectable, antiemetic-assisted or nonoral therapy. The present trial recruited outpatients who could take oral medication, and thus the results of the trial cannot be applicable to those with continued vomiting or those with status migrainosus.

A highly patient-centered outcome is functional restoration. Practically two-thirds of the patients who were treated with eletriptan recovered normal activity at two-hour time on comparison to a mere half of patients who were treated with zolmitriptan. The OVERCOME European observational study revealed a close relationship between the acute-treatment patterns, treatment inadequacy, the migraine burden, and the use of healthcare [15]. A therapy that does not just decrease the amount of pain but enhances its performance can have a better value when it comes to work attendance, care giving and performing activities on a daily basis.

The use of rescue-medications was lower, and sustained response with eletriptan was higher. These results are important as they make repeated dosing, rescue analgesics, and multiple treatment days more complex and could lead to the problem of overusing medications. Deighton et al. reported switching, discontinuation, and burden of medication-overuse in the triptan users [16]. Green also highlighted that it is all the traditional acute therapies that may contribute to medication-overuse headache in case of over-use [17]. When there are frequent attacks the patient should be given definite limits of the days of treatment and evaluated in regard to preventive treatment.

There was no significant difference in recidivism amongst first responders. The research was not powered particularly to recurrence and the denominator was limited to responders. A bigger multiple-attack trial would be more effective to determine consistency and lasting pain freedom. Single-attack studies can either over or under estimate the normal response of a patient since not all attacks are equal, and none of them trigger, they are different in severity, triggers, gastrointestinal absorption, sleep and clinical symptoms.

When stratified analyses were undertaken it was suggested that there was an efficacy difference in women, younger adults, patients without aura, patients with high baseline pain, and patients who were treated early. Interaction tests were however

not significant and therefore those subgroup patterns cannot be considered as conclusive treatment-effect modifiers. Studies on predictive models find that burden of attack, disability, related symptoms and previous experience of preceding treatment determine acute outcome, yet, precise individual prediction is hard to accomplish [18].

The results also should be interpreted within the growing framework of nontriptan acute treatments. Lipton et al. showed that rimegepant was effective regardless of previous triptan experience [19]. Deng et al. determined that lasmiditan and CGRP antagonists worked and were usually well tolerated [20]. Laohapiboolrattana et al. revealed that lasmiditan, rimegepant, and ubrogepant were beneficial in triptan-insufficient responders [21]. These drugs apply in instances where triptans do not work or cannot be used, but the price and accessibility of these medications could work against usage in Pakistan.

Adverse-event rate numerically increased with eletriptan, which is also compatible with a potency-tolerability tradeoff. Majority of events were mild dizziness, somnologies, paresthesia, nausea or intermittent pressure. Recognizable patterns of class-specific reporting of triptans were also identified in a recent analysis of the FAERS, and the weakness of databases based on spontaneous reporting were noted [22]. This type of data will never determine incidence but will favor the lent encouragement of patients concerning their anticipated temporary consequences and red flags.

No cardiovascular serious events were observed, although the sample size was too small, and the follow-up was too limited to prove cardiovascular safety. Wang et al. observed an increased incidence of major cardiovascular events in the short-term in triptan patients with a known history of cardiovascular disease or other risk factors, yet the incidence was not high [23]. This helps maintain compliance with contraindications and personalized cardiovascular care.

The increased potence of eletriptan must not mean that it should be the first-line therapy of all the patients. Zolmitriptan can be the drug of choice when it is essential to take a lower dose, the different formulation, previous positive response or a subjective better tolerance. The European triptan failure consensus suggests that more than a single triptan be trialled since failure of a single molecule does not predetermine failure of the whole group of molecules [13]. Efficacy, recurrence, adverse effects, cost and patient preference should be part of shared decision-making.

The unmet need in acute migraine is still high with the use of triptans. As important gaps, Bentivegna et al. noted delayed onset, partial absence of pain, recurrence, unreliable response, functional limitations, and adverse effects of treatment [24]. In the present research, a quarter of recipients of eletriptan and two of every five recipients of zolmitriptan were without primary response. Dose or formulation changes, combining treatments, using other triptans, gepants, lasmiditan, or prophylaxis are potential benefits in these patients.

The trial places a special emphasis in the selection of outcomes as well. The intensity of pain is not a measure of relief of nausea, sensory sensitivity, slowed mental functions, or lack of ability to work. Freedom of the most irritating symptom, long-term freedom of pain, satisfaction with the treatment, preference, consistency across multiple attacks, and validated functional measures should be used in the study in the future. Electronic diaries might enhance the accuracy of time and cut bias in recollections.

The study had limitations. The single centre, consecutive sampling, one treated attack per participant design and open practical treatment was used in the study. Reporting error may have been caused by self-reported timing and symptoms. The 80-mg eletriptan dose is stronger compared to usually lower doses and comparison with zolmitriptan 2.5 mg can be considered a high-versus-standard dose comparison study. Patients with a high risk of cardiovascular diseases were left out and the study was not powered in uncommon adverse events and recurrence. The brief follow-up was not focused on determining repetitive use consistency and medication overuse.

Further studies need to employ multicentre, double-dummy, randomized, and compare clinically common dose strategy across multiple attacks. Patterns of useful response may be identified by stratification by aura, allodynia, nausea, sex, relationship between menstrual cycle, obesity, previous triptan response, and timing of attacks. This has particularly been the case in health systems where newer acute medicines are still unaffordable due to cost-effectiveness. Step-care and stratified-care trials should be available to pragmatic trials instead of just drug comparisons.

CONCLUSION

Eletriptan 80 mg was superior to zolmitriptan 2.5 mg in clinically significant two-hour pain relief, pain-free, functional recovery, and reduced rescue medication, as well as, long-term 24-hour response. The adverse effects were mostly mild with an increased frequency numerically with eletriptan. The pursuit of treatment is supposed to be personalized as per previous reaction, nature of an attack, heart-fitness, administer ability and access.

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