Optimal Dosing of Lasmiditan in the Management of Acute Migraine Attack: A Systematic Review and Meta-analysis

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Abstract

Background: The current target of migraine treatment is focused on Triptans. Lasmiditan, a non-vasoconstrictive and highly selective $5HT_{1F}$ receptor agonist is a novel therapeutic discovery for migraine for patients with cardiovascular (CV) risk factors or stable cardiovascular diseases and who fail to respond to the existing treatment. **Objective:** To identify an optimal dosing of Lasmiditan 100 mg versus 200 mg for the treatment of acute migraine attacks in adult patients with cardiovascular risk factors. **Methods:** Systematic searches were run in databases such as Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Google scholar, and PUBMED. Out of 83 study records identified, two studies were included for quantitative analysis. **Results:** There was a significant headache pain freedom at 2 h [Odds Ratio (OR): 0.77; 95% Confidence interval (CI): 0.64–0.92] and sustained pain freedom at 24 h (OR): 0.75; 95% CI: 0.61–0.93] in patients taking Lasmiditan 200 mg compared to those taking Lasmiditan 100 mg. The results were statistically insignificant for parameters like most bothersome symptoms (MBS) free at 2 h, headache relief at 2 h, disability level at 2 h, and global impression of change at 2 h. A combined analysis of these parameters showed a remarkable difference between both the groups favoring Lasmiditan 200 mg [OR: 0.88; 95% CI: 0.81–0.95]. **Conclusion:** An oral dosing of Lasmiditan 200 mg is ideal for the treatment of acute migraine in adult patients with CV risk factors for attaining headache pain freedom at 2 h and sustained pain freedom at 24 compared to Lasmiditan 100 mg.

Keywords: Cardiovascular risk factors, Ditan, efficacy, lasmiditan, migraine, optimal dosing

Background

Migraine is the third most common disease in the world with a global age standardized prevalence of 14.4% in 2016.[1] Individuals with migraine headaches exhibit the symptoms of moderate to intense pain and are unique. Chronic migraine is defined as headache occurring on at least 15 days or more per month for more than 3 months.[2] The migraine disability assessment (MIDAS) questionnaire was developed to assess the disability in patients with headache and help in improving migraine care, which consists of five questions and scores the number of days in the past 3 months which had activity limitations because of migraine.[3,4]

During the late 1930s, Graham and Wolff have postulated that the headache of migraine attack is caused by the distention of cranial arteries and the constriction of these cranial arteries reduces the amplitude of their pulsations.[5] Few decades later, Moscowitz *et al*.[6] stated that the headache of migraine develops because of an abnormal interaction of large intracranial and extracranial blood vessels with trigeminal nerve's terminals.[6] Recent studies suggest that migraine is a neurovascular disorder. It is believed that migraine attacks are caused by the activation of trigeminovascular system. Vasodilation is assumed to be caused because of activation of nociceptive nerve fibers in meninges and release of inflammatory mediators. Vasodilation is thought to be mediated by the release of calcitonin gene-related peptide (CGRP).[7,8]

Triptans, ergotamine derivatives, NSAIDs, opioids, and combination medications are effective for acute treatment of migraine. Alkaloids, antiepileptic, phenazone, and dexamethasone have also been used for acute treatment of migraine attacks. In addition to the efficacy of drugs, safety aspect should also be considered before prescribing a drug for acute treatment of a migraine attack.[9-11] The triptans are currently considered as the drugs of choice to treat an ongoing migraine attack.[12,13]

The current objective of treatment is vasoconstriction and to reduce the levels of CGRP in the brain. It has been observed that agonism of serotonin can bring down the levels of CGRP, cause vasoconstriction, and interfere with nociceptive transduction and processing which leads to pain relief.[14]

Triptans target 5HT 1B/1D receptors, which are also present in coronary arteries. It leads to cardiac vasoconstriction, which

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makes this class of drugs contraindicated in patients with cardiovascular risk factors.[15-17]

To overcome this gap, a new class of drugs called "neurally acting anti-migraine agents (NAAMA)" or Ditans have been developed to act without vasoconstriction. Ditans are highly selective agonists for $5HT_{1F}$ receptors. Activation of 5 HT_{1F} receptors has shown advantage in animal studies. These results led to the hypothesis that migraine attacks can be aborted by selective agonism of $5HT_{1F}$ receptors.[18] Ditans have a better tolerability profile when compared to triptans because of their extremely low affinity to 5HT 1B/1D receptor subtypes which cause vasoconstriction.

Lasmiditan is the first and only drug in the class of Ditans to finish 2 phase III trials.[8,19] Due to low cardiovascular adverse effects, it can be used in patients having cardiovascular risk factors.[19] The adverse events caused by Lasmiditan are different from those caused by typical triptan side effects. The common side effects observed were mostly neurological. In phase III trials, Lasmiditan was well tolerated and no cardiovascular adverse effects were reported.[18]

As acknowledged earlier, Lasmiditan is the only drug from the Ditan class which makes it necessary to know its efficacy at the right dosing. This systematic review and meta-analysis aim to optimize the dosing of the drug, thus ruling out the contraindications in migraine patients with CV risk factors.

Methods

Objective

This study is intended to determine an optimal dosing of Lasmiditan in the treatment of acute migraine attacks in adult patients with CV risk factors by comparing the efficacy of Lasmiditan 100 mg and Lasmiditan 200 mg.

Criteria for study selection

Types of studies

Phase 3 randomized controlled trials [A **S**tudy of Two Doses of L**A**s**M**iditan {100 mg and 200 mg}] compared to placebo in the Ac**U**te Treatment of Mig**RAI**ne (SAMURAI) and A **S**tudy of three doses of Lasmiditan {50 mg, 100 mg and 200 mg} Compared to **P**lacebo in the **A**cute T**R**ea**T**ment of Migr**A**i**N**e (SPARTAN) which were implemented prospectively were included.[21,22] Common characteristics of the included trials were considered for our review.

Types of participants

Our search incorporated studies that were primarily conducted in adult patients with confirmed migraine attacks and CV risk factors. We included two studies that had recruited male or female patients ≥18 years of age with at least a 1 year history of debilitating migraine with or without aura (International Headache Society diagnostic criteria 1.1 or 1.2.1; a Migraine Disability Assessment (MIDAS) score ≥11; cardiovascular risk factors; previous episodes of three to eight migraine attacks per month; and an outset of migraine before 50 years of age. Participants with chronic migraine or other forms of primary or secondary headache disorder such as hemicrania continua, or headaches because of medication overuse with a frequency of >15 headache days per month within the past 12 months; start of or change in migraine preventative medication within 3 months before screening; and patients at serious risk of seizures were eliminated from the included trials.

The American College of Cardiology/American Heart Association guidelines was applied for identifying patients with cardiovascular risk factors.[20,21] They include age, systolic blood pressure (including treated or untreated), diabetes, current smoking status, and total and high-density lipoprotein.[20,21]

Types of interventions and control

The picked intervention was a one-time oral dosing of Lasmiditan 200 mg followed by an additional dosing between 2 h and 24 h in case migraine did not respond to the study drug. The comparison was made with an appropriate control the same as one-time oral dosing of Lasmiditan 100 mg followed by an additional dosing between 2 h and 24 h if unresponsive to the drug of interest.

Types of outcome measures

The primary efficacy outcome was to compare Lasmiditan 100 mg and Lasmiditan 200 mg on the proportion of patients who were headache pain free at 2 h after the first dose. However, comparison between Lasmiditan 100 mg and Lasmiditan 200 mg on the proportion of patients with sustained pain freedom at 24 h; the proportion of patients who were MBS (nausea, phonophobia, photophobia) free at 2 h; patient global impression of change at 2 h; the proportion of patients with headache pain relief at 2 h; and level of disability at 2 h were regarded as secondary outcomes.

Search methods

Electronic searches

Electronic search was conducted using the suitable keywords "Migraine, Acute migraine, Episodic migraine, Migraine preventive, Lasmiditan, Ditan, 5 HT1F agonist, Dose-ranging, Randomized controlled trial, Safety, Efficacy." The search for the relevant studies was conducted by authors between 20th November 2019 and 15th December 2019. The databases that were used to search are: Clinical trials registry, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, PubMed, and Scopus.

Searching other resources

All studies of interest including ongoing, published, and unpublished trials were considered and cross-indexing was done to scrutinize supplemental trials. Respective authors were contacted for additional details in case of missing or insufficient data. Search was also performed after the analysis to incorporate lately published studies on intervention of concern.

Data collection and analysis

Selection of studies

Chris Elizabeth Vinod (CEV), Shruthi Jaya Saju (SJS), and Bhavya Chebrolu (BC) performed the electronic search and obtained the full text version of all the relevant studies. Further, the literatures were transferred to Ryyan via Zotero and they were segregated based on our inclusion and exclusion criteria. The researchers were blinded during the eligibility screening of studies. In view of this, all the disputes were resolved by a fourth review author Roopa Satyanarayan Basutkar (RSB).

Data extraction and management

All the included studies were independently and manually inspected by all the three reviewers (CEV, SJS, and BC) using the pre-tested and modified data extraction form of Cochrane and the following details were retrieved: Aim of study, objectives, publication year, study population, total number randomized, recruitment of participants, informed consent obtained, baseline imbalances, primary and secondary outcomes, inclusion and exclusion criteria, time points measured and reported, intervention and control, duration of study, risk and bias assessment, imputation of missing data, and conflicts of interest. In accordance with the personalized data extraction form, an excel spreadsheet was prepared into which the data was entered. The retrieved data was cross verified by RSB and S Ponnusankar (SP). The respective study investigators would be contacted for clarification by the reviewers in case of any queries. The study characteristics are listed in Table 1.

Assessment of risk of bias in included studies

All the three reviewers (CEV, SJS, and BC) individually examined for the following realms using risk of bias tool: selection bias, allocation concealment, blinding (personnel and outcome assessors), attrition, and selective reporting. The above specified biases were labeled as "low" or "high" or "unclear" in a table with appropriate reasoning and judgment. Risk of bias was assessed using The Cochrane Collaboration's tool (Review Manager 5). All the disparities were resolved through unanimity by the review author RB and all the documented information was solely based on the study. In the studies conducted by Kuca *et al*. and Goadsby *et al*., the risk of assessment of bias was found to be low.

Registration

The review protocol was registered prospectively with PROSPERO [CRD42020166670].

Statistical analysis

As per the instructions given in the Cochrane handbook for systematic review and meta-analysis, this study was carried out. The efficacy of two oral dosages of Lasmiditan, that is, 100 mg and 200 mg were evaluated quantitatively. For data analysis, a minimum of two studies were required. Simultaneously, quantitative analysis was performed for all the common outcomes of interest in both included studies. The number of participants who experienced the event and the total number of participants under each study group was derived from the data and the mean difference was extracted by means of Review Manager 5.3. Furthermore, a forest plot was generated. The level of heterogeneity (I^2) was put up as the base for performing the random or fixed effect modeling.

Results

Description of studies

Results of the search

After the electronic search, a total of 83 articles were sorted out for the review of which three articles were secluded for eligibility screening. Two full text articles were identified and included for the review. The study flow chart is represented in Figure 1. The included studies were conducted in adult patients with acute migraine and CV risk factors. The primary outcome of our study was to compare the efficacy of Lasmiditan 100 mg and Lasmiditan 200 mg of the proportion of patients who were

Table 1: Characteristics of included studies

Source	Design	Duration	Participants	Mean age	Intervention and control	Outcome
Kuca *et al*.[19]	Randomized, double-blind, placebo controlled	17 months	*n*: 2,231	Intervention group Lasmiditan 100 mg - 42.2 Lasmiditan 200 mg - 41.4 Control group Placebo - 42.4	Intervention group Lasmiditan 100 mg, Lasmiditan 200 mg Control group Placebo	Primary Efficacy outcomes: Headache pain free at 2 h Secondary efficacy outcomes: MBS free at 2 h, 24 h and 48 h. Headache relief at 2 h. Safety outcomes: Treatment-emergent adverse events (TEAEs) after the first dose
Goadsby *et al*.[20]	Prospective, randomized, double-blind, placebo controlled, multi-Centre phase 3 study	14 months	*n*: 3005	Intervention group Lasmiditan 50 mg- 42.8 Lasmiditan 100 mg - 43.4 Lasmiditan 200 mg - 41.8 Control group Placebo - 42.6	Intervention group Lasmiditan 50 mg Lasmiditan 100 mg Lasmiditan 200 mg Control group Placebo	Primary efficacy outcomes: Headache pain free at 2 h, MBS free at 2 h Secondary efficacy outcomes: Sustained pain freedom at 24 h & 48 h and Headache relief at 2 h. Safety outcomes: Treatment-emergent adverse events (TEAEs) after the first dose

n: Total number of participants; MBS: Most Bothersome Symptoms

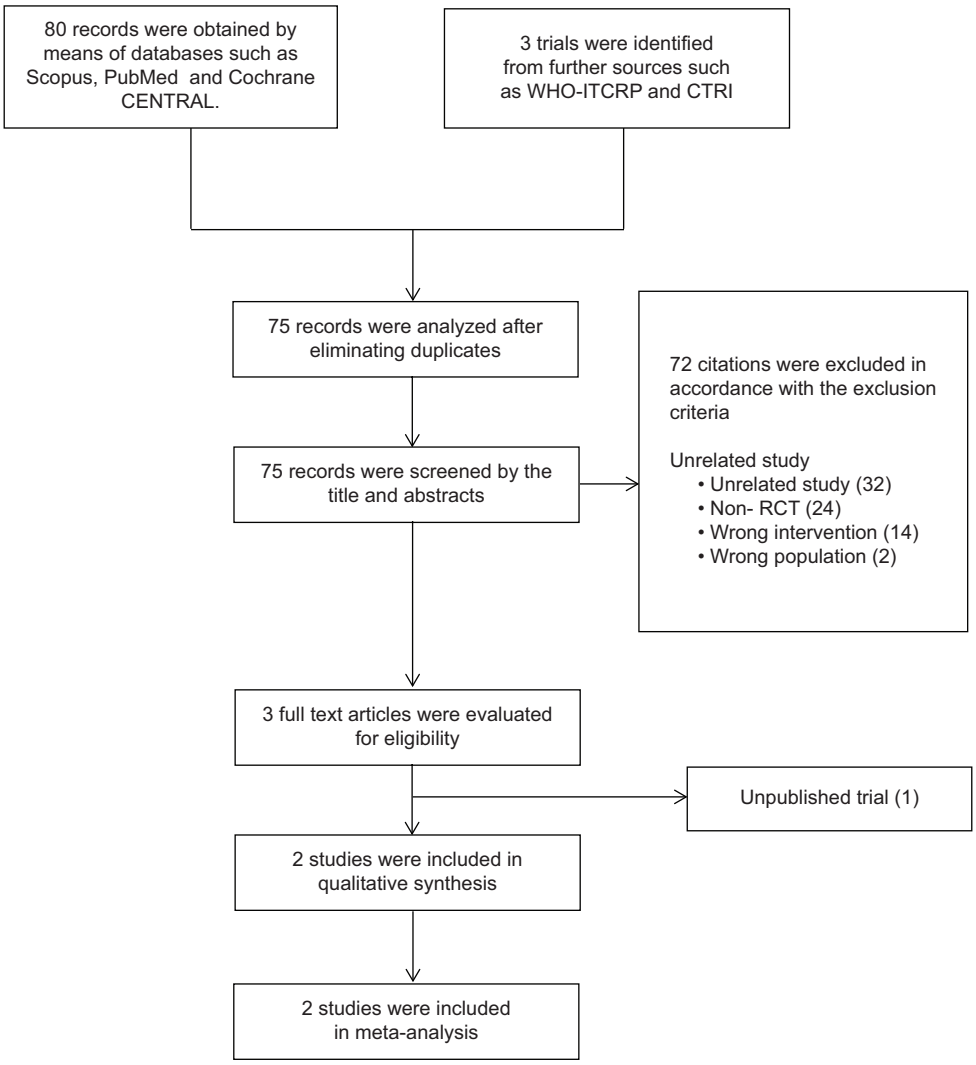

Figure 1: The flow diagram of the included studies in the review. *Notes.* WHO-ITCRP: World Health Organization – International Clinical Trials Registry Platform; CTRI: Clinical Trials Registry – India; RCT: Randomized Controlled Trial

headache pain free at 2 h after administration of the first dose of study medication. Secondary efficacy endpoints included comparison between Lasmiditan 100 mg and Lasmiditan 200 mg of the proportion of patients with sustained pain freedom at 2 h; the proportion of patients with MBS-free at 2 h; the proportion of patients with headache pain relief at 2 h; patient global impression of change at 2 h, and the level of disability at 2 h post dosing of the drug of interest. Headache severity at 2 h was recorded on a scale of 0–3 (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). The level of disability was assessed using the 4-point MIDAS scale based on the level of interference in regular activities because of migraine (not at all, mild, moderate, requires bed rest). Global impression of change was measured using a 7-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse). For our analysis, we chose the criteria "not at all" and "very much better" from the MIDAS scale and Global impression of change, respectively. Both the included studies (Kuca *et al*. and Goadsby *et al.*) were conducted for more than a period of 12 months (Kuca *et al*., 2018; Goadsby *et al*., 2019).

There were no significant imbalances identified in the methodological qualities of the incorporated studies. In Kuca *et al.* the method used for blinding of personnel and participants were not clearly stated; therefore, we concluded the risk of performance bias as "Unclear," whereas a "Low" risk of detection and reporting bias was considered as the participants, outcome assessors were blinded and all the outcomes were reported as listed (Kuca *et al*., 2018). In both the studies (Kuca *et al.* and Goadsby *et al.*), the randomization method and allocation concealment were clearly mentioned. Thus, the risk of selection bias was "Low" (Kuca *et al*., 2018; Goadsby *et al*., 2019). Similarly, there was a "Low" risk of performance, detection, and reporting bias with Goadsby *et al.* There was a "High" risk of attrition bias with Goadsby *et al.* since five serious adverse events were reported of which two were treatment related (Goadsby *et al*., 2019). No other potential causes of

bias were detected from the included trials. Risk of bias for the included studies is summarized in Figure 2.

Outcomes

The common efficacy outcomes in the two included trials (Kuca *et al.* and Goadsby *et al.*) were headache pain free at 2 h, MBS-free at 2 h, sustained pain freedom at 24 h, headache relief at 2 h, disability level at 2 h, and global impression of change at 2 h are depicted in the forest plot [Figure 3]. As there was low heterogeneity within the included studies, fixed effect modeling was performed. Combining both the included studies, headache pain free at 2 h was evaluated in 1,046 subjects in the control group and 1,035 subjects in the case group. Similarly, 969 and 964 subjects were analyzed for MBS- free at 2 h in the control and case group, respectively. Additional outcomes such as sustained pain freedom at 24 h, headache relief at 2 h, disability level at 2 h, and global impression of change at 2 h were measured in 1,133 subjects in the control group and 1,120 subjects in the case group. All the efficacy endpoints were assessed using entries made by the subjects in an electronic diary that was provided to each participant at the beginning of the study.

Headache pain free at 2 hours

The analysis of Kuca *et al*. and Goadsby *et al.* showed a significant result with a *P* value of 0.005 ($P < 0.05$) and no heterogeneity ($I^2 = 0\%$); 95% Confidence Interval (CI): 0.64–0.92. An odds ratio of 0.77 indicates that the combined treatment effect of headache pain freedom is on average of 77% higher when treated with Lasmiditan 200 mg compared to Lasmiditan 100 mg.

MBS- free at 2 h

An odds ratio of 0.92 suggests that the odds for the outcome to occur were 92% higher in the 200 mg group when compared to the 100 mg group. However, these results were insignificant with a *P* value of 0.34 ($P > 0.05$). Heterogeneity among the studies was low with $I^2 = 3\%$; 95% CI: 0.76–1.10.

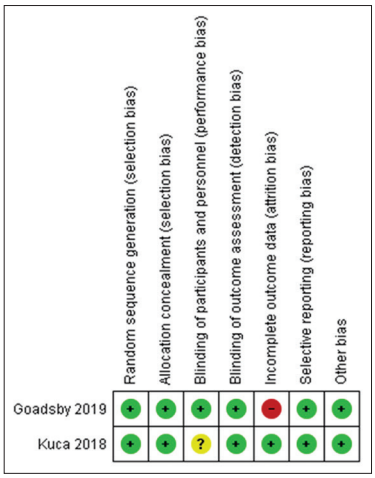

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Sustained pain freedom at 24 h

There was a significant difference in subjects' sustained pain freedom at 24 h in both Lasmiditan 100 mg and Lasmiditan 200 mg groups ($P = 0.009$; $I^2 = 0\%$; 95% CI: 0.61–0.93). The odds ratio was 0.75, which implies that the 200 mg group had 75% higher odds for the outcome to occur when compared to the 100 mg group.

Headache relief at 2 h

The analysis of relief of headache at 2 h showed no significant difference between both the groups ($P = 0.96$; $I^2 = 0\%$; 95% CI: 0.84–1.18). An odds ratio of 1 indicates that there is no association between the event and the doses.

Disability level at 2 h (Not at all)

The results of disability level at 2 h showed an insignificant difference between both the groups ($P = 0.39$; $I^2 = 0\%$; 95% CI: 0.78–1.10). An odds ratio of 0.93 suggests 93% reduced odds of disability level in Lasmiditan 200 mg group compared to Lasmiditan 100 mg group.

3.2.6. Global impression of change at 2 h (Very much better)

Global impression of change at 2 h demonstrated an insignificant difference between both the groups ($P = 0.41$; $I^2 = 0\%$; 95% CI: 0.70–1.16). Odds ratio of 0.90 indicates 90% higher odds for the outcome to occur when treated with Lasmiditan 200 mg compared to Lasmiditan 100 mg.

On compiling the data from all the efficacy endpoints from both the studies with a confidence interval of 95%, the results revealed a significant difference between Lasmiditan 100 mg and Lasmiditan 200 mg groups ($P = 0.001$; $I^2 = 0\%$; 95% CI: 0.81–0.95). Odds ratio of the pooled data was 0.88 which implies that the odds of Lasmiditan having higher efficacy was 88% greater in Lasmiditan 200 mg compared to Lasmiditan 100 mg group.

Safety profile of Lasmiditan

Triptans gained popularity over the past decade owing to its migraine specific pain relief.[22] Concerns in terms of its safety predominantly in patients with CV risk factors are still under debate because of its vasoconstrictive action on cardiac endothelial cells, thereby inducing consequential ischemic events.[22,23] However, the recent introduction of Lasmiditan for the treatment of migraine has shown promising effects regarding safety in patients with confirmed CV related diseases and risk factors because of its non-vasoconstrictive activity. Trials such as Kuca *et al.* and Goadsby *et al.* had reported nervous system related TEAEs (Treatment-emergent adverse events) such as dizziness, somnolence, and paresthesia majority of which were mild to moderate in intensity. No severe TEAEs related to Lasmiditan were reported in Kuca *et al.,* whereas five major adverse events were reported in Goadsby *et al.* of which two were treatment related (Presyncope 200 mg; dystonic reaction 100 mg). All the recorded TEAEs were dose-related, the higher the dose the more proportion of patients experienced the TEAEs. Meanwhile, the incidence of cardiovascular

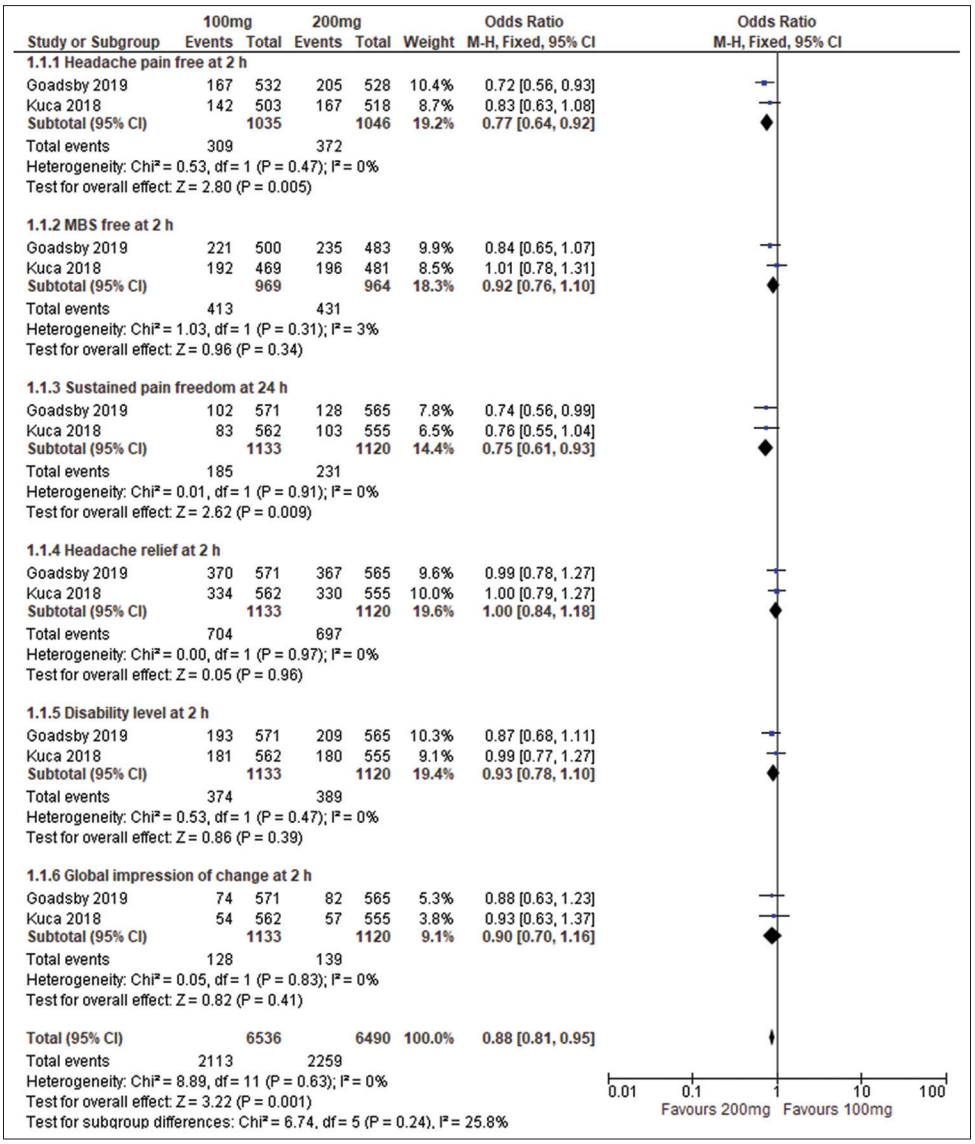

Figure 3: Forest Plot of primary and secondary efficacy outcomes for Lasmiditan 100 mg and Lasmiditan 200 mg. *Notes.* M-H: Mantel – Haenszel; CI: Confidence interval; I^2: Heterogeneity; MBS: Most Bothersome Symptoms; df: Degree of freedom; P: Probability

TEAEs (palpitations, bradycardia, and tachycardia) with the study drug were low. No clinically substantial differences were observed in blood chemistry, hematology, vital signs, urine analysis, ECGs, or physical examinations across the treatment groups. Overall, treatment with Lasmiditan is safe and well-tolerated (Kuca *et al*., 2018; Goadsby *et al*., 2019).

The quality of evidence was assessed using the GradePro software. Summary of findings (SOF) was prepared for the endpoints relating to the comparison between Lasmiditan 100 mg and Lasmiditan 200 mg groups in adult patients with acute migraine and CV risk factors. By considering the odds ratio, primary efficacy outcome headache pain free at 2 h has 77% higher chance to occur when treated with Lasmiditan 200 mg compared to Lasmiditan 100 mg. In a similar manner, relatively higher chances for secondary efficacy outcomes (MBS free at 2 h, disability level at 2 h, global impression of change at 2 h, and sustained pain freedom at 24 h) to occur were observed with Lasmiditan 200 mg group but the results were insignificant as mentioned earlier. The level of evidence was high for all the outcomes as there were no considerable variations in the included studies. Summary of findings table is tabulated in Table 2.

Discussion

The treatment guidelines for migraine are quite well established, nevertheless there are still aspects that must be dealt with. One among them is the threats encountered in migraine patients with CV risk factors because of the intake of Triptans making them clueless regarding the treatment options. Besides, migraine itself is an influential target factor for CV related diseases and events. Figuring out a convenient treatment option that does not aggravate these risks could reinforce the safety over current treatment strategies such as Triptans which are otherwise inadvisable in patients with CV history or risk.

Table 2: Summary of findings- Lasmiditan 200 mg is compared to Lasmiditan 100 mg in adult patients with migraine and cardiovascular risk factors

Outcomes	Groups		Effects		Number of participants (Studies)	Certainty of the evidence (Grade)
	Lasmiditan 200 mg	Lasmiditan 100 mg	Relative (95% CI)	Absolute (95% CI)		
Headache pain free at 2 h	77% higher	23% lower	OR 0.77 (0.64-0.92)	52 fewer per 1,000 (from 84 fewer to 17 fewer)	2,081 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]
MBS free at 2 h	92% higher	8% lower	OR 0.92 (0.76-1.10)	20 fewer per 1,000 (from 65 fewer to 23 more)	1,933 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]
Sustained pain freedom at 24 h	75% higher	25% lower	OR 0.75 (0.61-0.93)	36 fewer per 1,000 (from 57 fewer to 10 fewer)	2,253 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]
Headache relief at 2 h	No significant association between dose and event	No significant association between dose and event	OR 1.00 (0.84-1.18)	0 fewer per 1,000 (from 42 fewer to 38 more)	2,253 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]
Disability level at 2 h (Not at all)	93% higher	7% lower	OR 0.93 (0.78-1.10)	16 fewer per 1,000 (from 52 fewer to 21 more)	2,253 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]
Global Impression of change at 2 h (Very much better)	90% higher	10% lower	OR 0.90 (0.70-1.1.6)	10 fewer per 1,000 (from 31 fewer to 16 more	2,253 (2 RCTs)[19,20]	⊕⊕⊕⊕ HIGH[a]

Kuca *et al*. and Goadsby *et al*. showed no serious study limitations and in Kuca *et al*. blinding of participants and personnel were unclear. MBS: Most Bothersome Symptoms; CI: Confidence interval; OR: Odds ratio; RCT: Randomized Controlled Trial

The medical practice guidelines and consensus statements of FDA endorses health care practitioners to prescribe Triptans with caution in patients with CV risk factors.[24] Additionally, FDA recommends cardiac assessment in those with several CV risk factors.[24] The beneficial impact of Lasmiditan in patients with CV risks is currently under discussion. As the only drug in the "Ditan" class, it is fundamental to know the efficacy of Lasmiditan at the appropriate dosing. Our study is based on the integrated evaluation of two uniformly designed Phase 3 trials, SAMURAI and SPARTAN with the exception that SPARTAN enrolled patients with uncontrolled hypertension, clinically significant arrhythmia, or known coronary artery disease and an additional interventional group, that is, Lasmiditan 50 mg.[20,21] The current meta-analysis emphasizes on an ideal dosing of Lasmiditan for the treatment of acute migraine in adult patients with CV risk factors by evaluating two oral doses of Lasmiditan (100 g and 200 mg). No similar studies were conducted in the past.

The results of the pooled analysis suggest that the primary efficacy outcome, headache pain free at 2 h, and the secondary efficacy outcome, sustained pain freedom at 24 h favoured an oral dose of Lasmiditan 200 mg over Lasmiditan 100 mg with a statistically significant difference. Whereas the additional efficacy end points such as MBS- free at 2 h, disability level at 2 h, and global impression of change at 2 h indicated positive effects for Lasmiditan 200 mg but the results turned out to be non-significant. No relation was established between the event headache relief at 2 h and the doses. Results were insignificant for the same as well. On an average, an oral dosing of Lasmiditan 200 mg was shown to be 88% more efficacious compared to 10 0 mg.

The favorable benefits of an oral dosing of Lasmiditan 200 mg on acute migraine attacks were established by higher proportion of patients who were headache pain free at 2 h and with sustained pain freedom at 24 h. These results were consistent with the findings of Kuca *et al.* and Goadsby *et al.* Shapiro *et al.* showed that Lasmiditan 200 mg demonstrated efficacy across headache pain freedom.[25] Similarly,[26] Knievel *et al.* presented that greater number of patients achieved headache pain free when treated with Lasmiditan 200 mg (Knievel *et al*., 2020). Of clinical interest, a higher dose of Lasmiditan is associated with headache pain free at 2 h. In contrary to Kuca *et al.* and Goadsby *et al*., no significant differences were observed between the two groups for the outcomes such as MBS- free at 2 h, headache relief at 2 h, disability level at 2 h, and global impression of change at 2 h. Our results were based solely on data from SAMURAI and SPARTAN studies and hence there was not ample evidence to establish statistical significance.

This is the first study to determine an optimal dosing of Lasmiditan for the treatment of acute migraine in adult patients with CV risk factors by comparing the efficacy of two oral doses. To better understand the implications of our results, further research with longer follow-up is needed.

Limitations of our review include confined data which was inadequate to confirm the results of our analysis. As Lasmiditan is a brand-new medicine, studies on our sphere of interest were far less. Second, because the objective of this study was to identify an ideal dosing of Lasmiditan by comparing the efficacy of two of its doses, we did not emphasize much on the safety information regarding the same. Despite these limitations, this study could be a primary cornerstone for upcoming findings.

Conclusion

Being the first and only molecule representing the "Ditan" class which is developed for the advanced treatment of

acute migraine in adult patients with CV risk factors, it is a requisite to know the efficacy of Lasmiditan at proper dosing. Our study data noted that there was a significant difference in efficacy end points such as headache pain free at 2 h and sustained pain freedom at 24 h between the two groups favoring Lasmiditan 200 mg. Secondary outcomes such as MBS- free at 2 h, headache relief at 2 h, disability level at 2 h, and global impression of change at 2 h demonstrated an insignificant difference primarily attributing to the lack of sufficient evidence to support statistical significance. Overall, Lasmiditan dosed at 200 mg was 88% more effective compared to Lasmiditan 100 mg. With reference to our results, a conclusion is drawn that an oral dosing of Lasmiditan 200 mg is optimal in the treatment of acute migraine in adult patients with CV risk for achieving headache pain free at 2 h and sustained pain freedom at 24 h compared to its counterpart.

Contribution of authors

S Ponnusankar (SP), Roopa Satyanarayan Basutkar (RSB), Chris Elizabeth Vinod (CEV) and Shruthi Jaya Saju (SJS) were involved in designing the protocol. CEV, SJS, and Bhavya Chebrolu (BC) had performed the search, data collection, and bias appraisal. All discords were negotiated and substantiated by RB. SJS and CEV had transcribed the data into Review Manager 5.3 and conducted the analyses. The summary of findings table was prepared by CEV, SJS, and BC. The final document was prepared by SJS, CEV, BC, and RB. The drafted document was validated by SP and all other review authors to approve the final version for publication.

Abbreviations

5-HT, 5- Hydroxy tryptamine; NAAMA, Neurally acting anti-migraine agents; CGRP, Calcitonin gene-related peptide; CV, Cardiovascular; SAMURAI, A Study of Two Doses of LAsMiditan (100 mg and 200 mg) Compared to Placebo in the AcUte Treatment of MigRAIne; SPARTAN, A Study of three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute TReaTment of MigrAiNe; TEAEs, Treatment-emergent adverse events; MBS, Most bothersome symptoms; MIDAS, Migraine Disability Assessment scale; OR, Odds Ratio; CI, Confidence Interval; SOF, Summary of findings; CEV, Chris Elizabeth Vinod; SJS, Shruthi Jaya Saju; BC, Bhavya Chebrolu; RSB, Roopa Satyanarayan Basutkar; SP, S Ponnusankar.

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Ethical statement

This article does not contain any studies with human participants performed by any of the authors.

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Conflicts of interest

There are no conflicts of interest.

References

1. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, *et al*. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:954–76.
2. Olesen J, Bes A, Kunkel R, Lance JW, Nappi G, Pfaffenrath V, *et al*. The international classification of headache disorders, 3rd ed.ition (beta version). Cephalalgia 2013;33:629–808.
3. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology 2001;56:S20–8.
4. Stewart WF, Lipton R, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population- based sample of headache sufferers. Cephalalgia 1999;19:107–14.
5. Graham JR, Wollf H. Mechanism of migraine headache and action of ergotamine tartrate. A relation of headache to the effect of ergotamine tartrate on certain branches of the external carotid artery. After the observa experiments injection ergotamine by. Arch Neurol Psychiatry 1938;169:737–63.
6. Moskowitz MA, Romero J, Reinhard JF, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: Is there a relation to the headache phase of migraine? Lancet 1979;314:883–5.
7. Edvinsson, L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br J Clin Pharmacol 2015;80:193–9.
8. Rubio-Beltrán E, Labastida-Ramírez A, Villalón CM, MaassenVanDenBrink A. Is selective 5-HT1F receptor agonism an entity apart from that of the triptans in antimigraine therapy? Pharmacol Ther 2018;186:88–97.
9. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The american headache society evidence assessment of migraine pharmacotherapies. Headache 2015;55:3–20.
10. Becker WJ. Acute Migraine Treatment. Continuum (Minneap Minn). 2015;21:953-72.
11. Orr SL, Aubé M, Becker WJ, Davenport WJ, Dilli E, Dodick D, *et al*. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia 2015;35:271–84.
12. Bigal ME, Krymchantowski AV, Hargreaves R. The triptans. Expert Rev Neurother 2009;9:649–59.
13. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, *et al*. Triptans in the acute treatment of migraine: A systematic review and network meta-analysis. Headache 2015;55:221–35.
14. Aggarwal M, Puri V, Puri S. Serotonin and CGRP in migraine. Ann Neurosci 2012;19:88–94.
15. Tepper SJ, Millson D. Safety profile of the triptans. Expert Opin Drug Saf 2003;2:123–32.
16. Dodick D, Lipton RB, Martin V, Papademetriou V, Rosamond W, VanDenBrink AM, *et al*. Consensus statement: Cardiovascular safety profile of triptans (5-HT 1B/1D agonists) in the acute treatment of migraine. Headache 2004;44:414–25.
17. Lipton RB, Bigal ME, Amatniek JC, Stewart F. Tools for diagnosing migraine and measuring its severity. Headache 2004;44:387–98.
18. Raffaelli B, Israel H, Neeb L, Reuter U. The safety and efficacy of the 5-HT 1F receptor agonist lasmiditan in the acute treatment of migraine. Expert Opin Pharmacother 2017;18:1409–15.
19. Curto M, Cipolla F, Cisale GY, Capi M, Spuntarelli V, Guglielmetti M, *et al*. Profiling lasmiditan as a treatment option for migraine. Expert Opin Pharmacother 2020;21:147–53.
20. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine. Neurology 2018;91:e2222–32.
21. Goadsby PJ, Wietecha LA, Dennehy EB, Kuca B, Case MG, Aurora SK, *et al*. Double-blind study of lasmiditan for acute treatment of migraine. Brain 2019;142:1894–904.
22. Jamieson DG. The safety of triptans in the treatment of patients with migraine. Am J Med 2002;112:135–40.
23. Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R, *et al*. Adverse cardiovascular events associated with triptans and

ergotamines for treatment of migraine: Systematic review of observational studies. Cephalalgia 2015;35:118–31.
24. Alwhaibi M, Deb A, Sambamoorthi U. Triptans use for migraine headache among nonelderly adults with cardiovascular risk. Pain Res Treat 2016;2016:8538101. doi: 10.1155/2016/8538101.
25. Shapiro RE, Hochstetler HM, Dennehy EB, Khanna R, Doty EG, Berg PH, *et al*. Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: Post-hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials. J Headache Pain 2019;20:90.
26. Knievel K, Buchanan AS, Lombard L, Baygani S, Raskin J, Krege JH, *et al*. Lasmiditan for the acute treatment of migraine: Subgroup analyses by prior response to triptans. Cephalalgia 2020;40:19–27.