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Original Research Article

Assessing the impact of a fixed dose combination of camylofin and mefenamic acid on the onset of pain relief in patients with moderate to severe dysmenorrhea

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ABSTRACT

Background: A fixed-dose combination (FDC) of camylofin 50 mg and mefenamic acid 250 mg was found to be effective and safe following 5 days of treatment in women with primary dysmenorrhea. Here, we assess the onset of analgesia FDC within 24 hours of administration of the FDC using two independent patient-reported outcome tools.
Method: In this prospective, single-center study, 140 women with moderate-to-severe primary dysmenorrhea received 3 tablets of the FDC over 24 hours. Primary endpoints were time to pain relief using the 11-point numerical rating scale (NRS-11) and the 100-mm visual analog scale (VAS) and proportion of patients with pain relief in the first 2 hours post-1st dose administration. Pain relief was defined as ≥1-point reduction in pain score on both scales. Secondary endpoints were change in pain intensity scores from baseline to 24 hours post-1st dose using both scales and incidence of adverse events (AEs).
Results: Median duration of onset of pain relief using NRS-11 and VAS was 50-and 20-minutes post-1st dose, respectively. Statistically significant reductions ($p<0.0001$) post 1st dose was observed from 40 minutes on the NRS-11 and at all post-baseline timepoints on the VAS. Only 3 patients (2.1%) reported treatment emergent AEs, all of which were related to the study drug, 'mild' in intensity, and resolved without sequalae.
Conclusions: The FDC of camylofin and mefenamic acid provided analgesia onset within 20 min on VAS and 50 min on NRS after administration of first dose and a good safety profile in women with primary dysmenorrhea.

Keywords: Camylofin, Mefenamic acid, Primary dysmenorrhea, 11-point numerical rating scale, Visual analog scale

INTRODUCTION

Dysmenorrhea is characterized by a painful and cramps in the lower abdomen often accompanied by other biological symptoms including dizziness, fatigue, sweating, backache, headache, nausea, vomiting, and diarrhea, occurring just before or during menstruation.[1] Depending on etiology, dysmenorrhea can be classified as primary i.e. painful menstruation in the absence of pelvic pathology,[2] or secondary, which is painful menses due to pelvic pathology or a recognized medical condition.[3]

Prevalence of dysmenorrhea varies between 28% and 71.7%,[4] whereas studies from India have reported a prevalence range between 50 and 87.8%.[5-9] Dysmenorrhea can affect up to 90% of women of childbearing age to varying degrees.[10] Menstrual pain restricts movement and usual activity pattern, thereby affecting quality of life.

Camylofin is a spasmolytic agent with a musculotropic and neurotropic mode of action. Camylofin causes direct antispasmodic action by inhibiting the enzyme phosphodiesterase 4, which results in increase in intracellular concentration of cyclic adenosine monophosphate, depletion of intracellular calcium levels, and relaxation of smooth muscle cells, thereby pain alleviation.[11] In addition, it has a mild atropine-like

anticholinergic effect, which is elicited by inhibiting the binding of acetylcholine with muscarinic receptors.[12]

Non-steroidal anti-inflammatory drugs (NSAIDs), which act by blocking prostaglandin production, have been widely used to manage painful cramps in dysmenorrhea.[13] Mefenamic acid is an NSAID with anti-inflammatory, antipyretic, and analgesic activities. It reduces formation of precursors of prostaglandins and thromboxanes. The resulting decrease in prostaglandin synthesis, by prostaglandin synthase, is responsible for the therapeutic effects of mefenamic acid.[14] However, efficacy is often accompanied by gastrointestinal effects (nausea, vomiting, and/or diarrhea) which, though tolerable are of concern.[15]

A FDC of camyolfin and mefenamic acid was found to have a good safety and tolerability profile and could effectively relieve pain in Indian women with primary dysmenorrhea following 3-5 days of treatment.[16] Here, we evaluated the onset of analgesia following treatment with the FDC of camyolfin and mefenamic acid in women with moderate to severe dysmenorrhea.

METHODS

Study design

This was a prospective, single-center, investigator-initiated study conducted at Shubham Sudbhawana super speciality hospital, Varanasi, Uttar Pradesh, India (CTRI/2020/12/030017). The clinical study protocol and other study related documents were reviewed by the institutional ethics committee of the study site. All patients provided written informed consent prior to participation in the study. Eligible patients were administered one anafortan MF 50 mg/250 mg tablet (camylofin 50 mg + mefenamic acid 250 mg) at the site after baseline assessments. Patients were given two additional tablets for self-administration, one each to be taken in the afternoon and at night after food. Dosing compliance was monitored through drug accountability records.

Eligibility criteria

Premenopausal women aged 18-45 years with primary dysmenorrhea on the 1st or 2nd day of their current menstrual cycle, who had a history of moderate to severe primary dysmenorrhea during four or more of the previous six menstrual cycles on the 11-point numeric rating scale (NRS), and who were willing to abstain from alcohol consumption throughout the 24-hour study period were included. Pregnant and lactating mothers, patients at risk for COVID-19, patients taking camylofin dihydrochloride 50 mg, mefenamic acid I.P. 250 mg or any other prescription-only and/or non-prescription analgesics, antispasmodics, antidepressants/ antipsychotic medication within the 4 weeks before study enrolment, patients with secondary dysmenorrhea (including the etiologies of leiomyomata [fibroids], pelvic inflammatory disease, tubo-ovarian abscess, ovarian torsion, and endometriosis), and patients with a history of irregular menstrual cycles in 6 months prior to enrolment were excluded.

Study endpoints

The primary endpoints were median duration required to obtain any relief in pain as assessed using the NRS-11 and visual analog scale (VAS) and percentage of patients achieving pain relief in the first 2 hours using the NRS-11. The secondary endpoints were change in pain intensity score from baseline to 24 hours using the NRS-11 and VAS and number and proportion of treatment emergent adverse events (TEAEs).

Study assessments

Patients' demographic data were collected along with their medical/surgical history, medication history and current medical conditions during screening. Patients were asked to rate their pain level using the NRS-11, wherein score 0=no pain, scores 1-3=mild pain (nagging, annoying, or interfering a little with activities of daily learning [ADLs]), scores 4-6=moderate pain (interfering significantly with ADLs), or scores 7-10=severe pain (disabling; unable to perform ADLs). Using VAS, patients were asked to rate their pain level between score 0 for no pain to score 100 for worst imaginable pain. A single point reduction in VAS and NRS 11 scores from baseline score was considered as onset pain relief. Pain assessments were recorded every 10 minutes for the first 2 hours and at 4, 8, 12 and 24 hours post 1st dose.

AEs and serious AEs occurring during the study period were monitored until satisfactory resolution or stabilization. An AE was defined as any untoward or unfavorable medical occurrence, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the study, regardless of being related to participation, including concurrent illnesses or injuries and exacerbation of pre-existing conditions.

Statistical analysis

Assuming that ~45% of the subjects would show at least 1 point improvement in pain within 2 hours after administration of the 1st dose and assuming that ~70% of the subjects would show at least 1-point improvement in pain based on historical data, a sample size of ~140 subjects was estimated to provide 5% level of significance and 80% power to estimate median time to pain reduction at two hours.

The intent-to-treat (ITT) set comprised all patients who received at least one dose of the study treatment and had at least one post-baseline assessment. The per protocol (PP) set comprised of all patients who received at least one dose of the study treatment and who did not have any major protocol deviations. Safety set comprised of all patients who received at least one dose of the study treatment. All

categorical variables were summarized as frequency and percentages. All continuous variables were summarized as n, mean, and standard deviation (SD). The Kaplan-Meier method was used to estimate median duration of onset of any pain relief and reported as point estimate and 95% confidence interval. Percentage change in pain intensity score from baseline to 24 hours post 1st dose on NRS 11 was assessed using repeated measures model and summarized descriptively. Paired *t* test at 5% level of significance was used for analyzing statistical significance of secondary endpoints. All statistical analyses were performed using the R software version 4.0.3.

RESULTS

Patient disposition

As per protocol, 140 women with moderate to severe primary dysmenorrhea were screened and enrolled and were treated in this study. All enrolled patients completed the study (Figure 1).

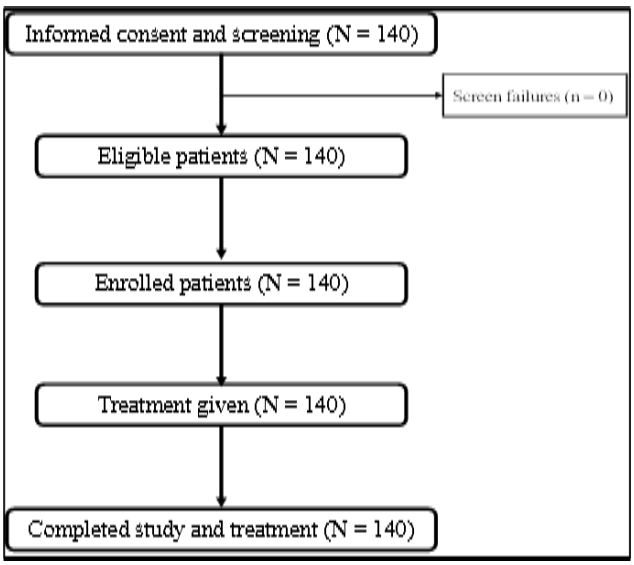

Figure 1: Patient disposition.

Mean (SD) age of patients was 24.2 (4.57) years. The patients' mean (SD) height was 1.6 (0.04) m and the mean (SD) weight was 55.3 (6.34) kg. The mean (SD) BMI was 22.0 (2.32) kg/m^2 (Table 1).

Table 1: Patient demographics, (n=140).

Baseline characteristic, mean (SD)	Overall
Age (Years)	24.2 (4.57)
Weight (kg)	55.3 (6.34)
Height (m)	1.59 (0.04)
BMI (kg/m^2)	22.0 (2.32)
VAS score	86.10 (8.85)
NRS-11 score	7.79 (0.89)

BMI-body mass index; NRS-11, 11-point numerical rating scale; SD-standard deviation; VAS-visual analog scale.

None of the patients showed any major protocol deviation, and all 140 patients completed the study. Hence, all patients were included in the analysis. Since the PP and the ITT populations were the same, no separate analysis was done for the PP population.

Onset of analgesia

Median duration of onset of at least 1-point reduction in pain using NRS-11 was found to be 50 minutes post 1st dose, i.e., as per the Kaplan-Meier time-to-event curve, approximately 50% of patients showed pain relief in 50 minutes post 1st dose (Figure 2A). In all, 0.7% patients achieved at least 1-point reduction in pain on the NRS-11 by 10 minutes post-1st dose, whereas all 140 patients were observed to have pain relief by 100 minutes post 1st-dose.

Median duration of onset of at least 1-point reduction in pain using the VAS was observed to be 20 minutes post 1st dose, i.e., approximately 50% of total patients showed pain relief in 20 minutes post 1st dose based (Figure 2B).

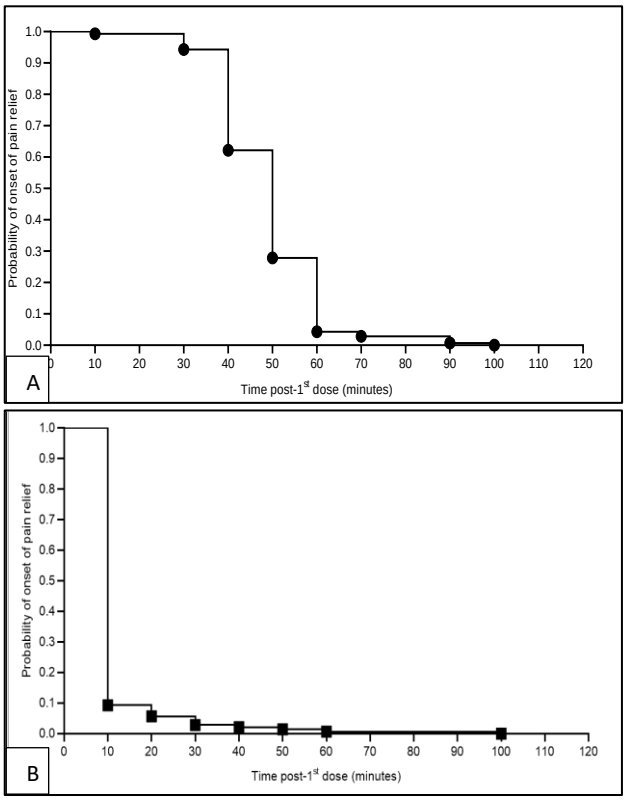

Figure 2 (A and B): Kaplan-Meier curve for duration of onset of pain relief based on NRS-11, Kaplan-Meier curve for duration of onset of pain relief based on VAS.

Improvement in pain intensity

Mean (SD) pain intensity decreased from 10 min to 24 hours post-1st dose on both NRS-11 (Figure 3A) and VAS (Figure 3 B). Mean (SD) NRS 11 score at baseline was 7.79 (0.89) reduced to 2.63 (1.85) at 24 hours post 1st dose.

The percentage change in NRS-11 score of 0.29% at 10 minutes post 1st dose improved by 65.71% at 24 hours post 1st dose. A statistically significant reduction in NRS-11 pain score was observed from 40 minutes post dose till the end of treatment at 24 hours post 1st dose Table 2.

Table 2: Pain intensity from baseline to 24 hours post-1st dose as assessed by NRS-11, (n=140).

Time point post 1st dose	Absolute score	Change in pain intensity score		
	Mean (SD)	Mean (SD)	% mean (SD)	P value
Baseline	7.79 (0.89)	-	-	-
10 min	7.81 (0.90)	0.02 (0.22)	0.29 (3.03)	0.2583
40 min	7.40 (1.01)	-0.39 (0.56)	-5.04 (7.18)	<0.0001
4 hours	4.62 (1.06)	-3.17 (1.06)	-40.59 (12.64)	<0.0001
8 hours	4.05 (1.17)	-3.74 (1.33)	-47.7 (15.32)	<0.0001
12 hours	3.35 (1.37)	-4.44 (1.58)	-56.59 (18.3)	<0.0001
24 hours	2.63 (1.85)	-5.16 (2.09)	-65.71 (24.67)	<0.0001

P values by paired t test, NRS-11, 11-point numerical rating scale; SD-standard deviation.

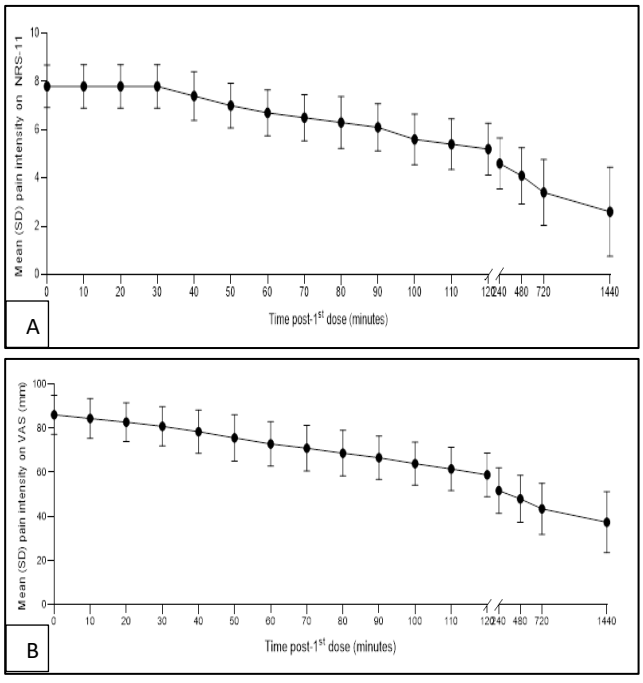

Figure 3 (A and B): Change in pain intensity score from baseline to 24 hours on NRS 11. Change in pain intensity score from baseline to 24 hours on VAS.

Mean (SD) change in NRS score of 0.02 (0.22) at 10 minutes post 1st dose decreased by 5.16 (2.09) at 24 hours post 1st dose. At 100 minutes post dose, mean (SD) change in NRS score was 5.55 (1.05). At 12 hours post dose, mean (SD) change in NRS score was 3.35 (1.37), which further reduced to 2.63 (1.85) at 24 hours post 1st dose (Table 2). Statistically significant reduction (p<0.0001) in NRS 11 pain score was observed at 40 minutes post 1st dose till the end of treatment, i.e., 24 hours post 1st dose (Table 2).

Mean (SD) VAS score of 86.10 (8.85) at baseline reduced to 37.41 (13.85) at 24 hours post 1st dose (Table 3).

Mean (SD) percentage change in VAS score of −1.88% (5.36) at 10 minutes post 1st dose improved to -55.76% (24.67) at 24 hours post 1st dose. Statistically significant reduction in VAS score was observed from 10 minutes till the end of treatment at 24 hours post 1st dose.

Mean (SD) change in VAS score of -1.71 (4.75) at 10 minutes post 1st dose further reduced to -48.69 (17.56) at 24 hours post 1st dose. At 24 hours post dose, 3 patients had a VAS score of 0. Statistically significant reduction (p<0.0001) in VAS score was observed in comparison with the baseline score, throughout the post treatment study period (Table 3).

Table 3: Pain intensity baseline to 24 hours post-1st dose as assessed by VAS, (n=140).

Time point post 1st dose	Absolute score	Change in pain intensity score		
VAS score in mm	Mean (SD)	Mean (SD)	% mean (SD)	P value
Baseline	86.10 (8.85)	-	-	-
10 min	84.39 (9.10)	-1.71 (4.75)	-1.88 (5.36)	<0.0001
40 min	78.44 (9.86)	-7.66 (6.03)	-8.88 (6.94)	<0.0001
4 hours	51.67 (10.36)	-34.43 (11.84)	-39.61 (12.47	<0.0001
8 hours	47.98 (10.67)	-38.12 (13.15)	-43.75 (13.58)	<0.0001
12 hours	43.46 (11.60)	-42.64 (14.90)	-48.86 (15.17)	<0.0001
24 hours	37.41 (13.85)	-48.69 (17.56)	-55.76 (24.67)	<0.0001

P values by paired t test, SD-standard deviation; VAS-visual analog scale.

Safety outcomes of the FDC

A total 3 AEs occurred during the study. All AEs were 'mild' in intensity, related to the study drug, and resolved without sequalae. No serious AE occurred during study.

DISCUSSION

In the current study, median onset of analgesic effect of the FDC was 50 minutes on NRS 11 and 20 minutes on VAS,

with all 140 patients were achieving 1-point reduction on NRS 11 by 100 minutes post 1st dose. Percentage change in pain intensity score and mean change in pain intensity reduced significantly ($p<0.0001$) at 40 minutes post 1st dose till the end of treatment on NRS-11 and at all timepoints post 1st dose on VAS.

Pain is a subjective sensation that is important to quantify in a clinical setting.[17,18] Pain score thus becomes crucial in defining diagnosis and eventually administration of treatment. NRS-11 and VAS are among the few validated scales that are used to assess the pain.[19,20] Use of both these scales to assess effectiveness outcomes in the current study ensured robustness of findings by 2 independent measures.

In a randomized, open-label study evaluating the efficacy and tolerability of an FDC of camylofin 50 mg and mefenamic acid 250 mg (test group) versus dicyclomine 10 mg and mefenamic acid 250 mg (control group) in 50 women with primary dysmenorrhea, numerically higher reduction in VAS scores were observed for the test group versus control group following 3 and 5 days of treatment.[20] In a single-arm study, the same FDC of camylofin 50 mg and mefenamic acid 250 mg showed significant reduction in VAS score from baseline to days 3 and day 5 of treatment.[16] Our study results further corroborate findings from these previous studies regarding the effectiveness of the FDC of camylofin and mefenamic acid in the management of pain associated with primary dysmenorrhea. Moreover, onset of significant pain relief within 2 hours of administration of the 1st dose of the FDC further indicated early and sustained action of the FDC in these patients.

Single unit reduction in pain was considered as a pain relief for all patients on both NRS 11 and VAS. VAS is a magnified, more detailed, and finer scale as compared to NRS 11. Hence, single unit reduction on VAS is significantly smaller as compared to that on NRS 11. Due to this, a very small reduction in pain in a shorter period was recorded on VAS and not on the other scale, which led to the difference in median duration of onset of pain relief in our study (50 minutes on NRS 11 vs 20 minutes on VAS).

Only 3 patients (2.1% of total patients) reported one AE each in our study, and all AEs while being related to the study drug, were resolved without sequalae. This low rate of AEs is consistent with the single-arm study by Pandey et al where only 0.7% of treatment emergent AEs were found to be related to the FDC and were resolved without sequalae by the end of treatment at 5 days.[16]

The main strengths of the study were the use of two independent and validated scales to assess onset of analgesia with the FDC of camylofin and mefenamic acid in the real-world setting nevertheless, the single-center setting limits the generalizability of the study findings. Further, use of an additional questionnaire like menstrual symptom questionnaire or structured questionnaire consisting of domains such as dietary habits, pain reliever history, and menstrual history, would have further corroborated the positive results of this study.

CONCLUSION

In conclusion, a FDC of camylofin 50 mg and mefenamic acid 250 mg provided onset of analgesia within 20 min on the VAS scale and 50 min on the NRS scale after administration of the first dose and a good safety profile in women with moderate to severe primary dysmenorrhea. However, further multicenter studies are warranted to substantiate the early analgesic effect.

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