International Journal of Research in Dermatology
Chattopadhyay PS et al. Int J Res Dermatol. 2026 Mar;12(2):xxx-xxx
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20260032

Original Research Article

Clinical study to evaluate efficacy and safety of topical balms for headache: a randomized trial

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Received: 15 December 2025
Revised: 07 January 2026
Accepted: 13 January 2026

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ABSTRACT

Background: Topical balms containing natural ingredients are commonly used in complementary therapies for headache. There is a need to evaluate the clinical efficacy and safety of these balms. Objectives were to assess the efficacy and safety of commercial balms in patients diagnosed with tension type headache as per the ICHD II criteria.
Methods: A randomised, single blind, multi-centre clinical trials were conducted for headache. Adult participants were enrolled at three sites in India (IND [n=31], [n=30] and [n=30]) to study the efficacy of three commercial balms (CT64, CT46 and CT17) by assessing percentage of subjects with meaningful headache relief and pain intensity after application on verbal rating scale (VRS). Effect on headache on a 100-point visual analog score (VAS), use of rescue medications, onset, intensity and duration of action of balm, quality of sleep, quality of pain relief, global assessment of overall effect by physician and patient and global assessment of tolerability of drug were also assessed.
Results: The CT64, CT46 and CT17 groups responded with 93.33%, 90.32% and 86.66% of total meaningful headache relief respectively. There is a significant decrease in headache intensity in CT64 followed by CT46 group on VAS scale. The VRS rating also demonstrated significant reduction in headache within two hours. The balms also demonstrated safe to use on the basis of adverse drug reaction study.
Conclusions: The commercial balms containing 10-15% menthol and 10-25% methyl salicylate can provide significant relief from headache and are safe to use.

Keywords: Balm, Headache, Clinical research, Safety

INTRODUCTION

A headache or cephalalgia is pain anywhere in the region of the head or neck. In India, headache disorders are prevalent i.e. 23% in general population in India, contributing significantly to disease burden.[1] Headache is a distressing sensory experience that can severely affect an individual's quality of life by disrupting work and overall well-being.[2] Common treatments include medication, massage and lifestyle changes.[3,4] Topical formulations often containing natural ingredients have long been used for pain relief,[5] due to their analgesic and anti-inflammatory properties.[6,7] The increasing demand for effective and safe topical pain relief options highlights a need for rigorous evaluation of commercial balms.

Menthol and camphor are two widely used active ingredients in topical pain relief products. It is a major component of Mentha species, offers cooling and analgesic effects by activating transient receptor potential (TRP) channels and Kappa opioid receptors (KOR).[8] However, high doses can cause sensory irritation by activating chemical nocisensors, specifically TRPA1 in humans.[9,10] While adverse reactions like asthma, gastrointestinal symptoms and cardiovascular toxicity have been reported, but they are generally considered anecdotal due to its long history of widespread use.[11,12] Camphor is another known agonist of TRP channels, providing long-term pain relief for muscle pain.[13] Nevertheless, accidental ingestion of camphor has led to regulatory measures due to its potential toxicity.[14,15] Flaman et al reported symptoms such as coughing and vomiting in children who accidentally ingested ointments containing camphor, menthol and eucalyptus oils.[16] In response to these concerns, the U. S. FDA has limited camphor concentration in topical products to 11%.[17]

Previous studies have explored the efficacy and safety of topical balms. Antonelli et al demonstrated the clinical efficacy and safety of a commercial balm with camphor (11%), menthol (9%), and other herbal ingredients for managing tension-type headache and enhancing leg blood flow when combined with massage. Kannan et al. conducted a randomized multicentre trial with 144 patients, assessing the safety and efficacy of four herbal pain balms for knee pain, low back pain and headaches, noting significant pain relief within 5, 10 and 30 minutes of application using VAS questionnaires.[18]

Despite the long-standing use and some existing research on topical pain balms, a comprehensive evaluation of commercial products containing natural ingredients, are still needed particularly concerning their clinical efficacy for headache and safe to use.

A randomized, multicentre clinical trials were conducted to evaluate their efficacy against headache, thereby addressing the need for robust scientific evidence supporting the use of these widely available products.

METHODS

Study design

The efficacy of three commercial balms (Table 1) CT64 (Zandu balm), CT46 (Zandu Ultra Power Balm) and CT17 (marketed sample) were evaluated by a randomized, single blind, multicentre, parallel, phase-II trial. Ninety-one subjects (age 18-65 years) diagnosed with headache according to international classification of headache disorders (ICHD II) criteria were participated. Participants were randomly assigned (computer-generated randomization) to one of the three balms after satisfying inclusion-exclusion criteria. Only the dermatologists had access to the random allocation sequence. The study was conducted during July 2015 to December 2015.

Table 1: Balm description.

CT64 (Zandu balm)	CT46 (Zandu ultra power balm)	CT17 (Marketed formula)
Mentha sp.	Mentha sp.	Ajowan ka phool
Gaultheria fragrantissima	*Gaultheria fragrantissima*	Pudina ka phool
Ointment Base QS	*Eucalyptus globulus*	Gandhapura tel
	Capsicum annuum	Turpentine ka tel
	Ointment base QS	Nilgiri ka tel
		Chaha ka tel
		Dalchini ka tal
		Pudina ka tel
		Ganjni ka tel
		Ointment base QS

Inclusion and exclusion criteria

The study inclusion criteria include male and female participants aged 18 to 65 who have been clinically diagnosed with tension type headache according to ICHD II guidelines. To qualify, individuals must have a headache history of 1 year, experiencing at least two days of headache per month with episodes lasting 4 hours if left untreated. Eligibility also extends to those who currently utilize local applications, such as oils or balms, for symptom relief and includes subjects with severe headaches requiring continuous medical management. All participants must provide written informed consent complying with the established study protocol requirements.

Conversely, the exclusion criteria rule out individuals whose headaches are attributed to migraine, sinusitis, cold, fever or other underlying disease. Participants are disqualified if they have a history of surgery involving the head, neck, eyes, ears or nose within the year prior to recruitment or if they regularly use analgesics or oral contraceptives. Medical exclusions also apply to those who have participated in other investigational drug trials within one month of randomization or those suffering from serious conditions such as uncontrolled diabetes mellitus, tuberculosis, HIV/ ischemic heart disease. Furthermore, study excludes individuals who are currently pregnant/ lactating, those with known hypersensitivity to similar trial drug compounds/anyone with significant pre-existing medical or surgical disease.

Study procedure

Participant's detailed medical history along with current medications (if any) were noted and their systematic examinations were done. A wash out period of three days was given. During wash out period and study period (viz. 3 days+4 weeks), they were advised to refrain from NSAID's or any other local or systematic analgesics

except paracetamol (up to 2.0 g/day) in case of severe headache. Participants were provided with clear, standardized instructions for applying the assigned balms. They were instructed to apply a thin, uniform layer (approximately 0.5 grams) to the affected area (forehead or temples) at the onset of a headache for 28 days. Participants were trained on the application technique during their initial visit with demonstrations. Primary outcomes i.e., changes in pain intensity on a VRS of 0-5. It is also assessed on a 100-point VAS at 1, 2 and 4 hours after each balm application and were recorded by participant in the diaries provided to them. Secondary outcomes i.e., comparative assessments of onset of action, duration of action, absorption, spreadability of balms, quality of sleep, quality of pain relief and safety by reporting adverse events were also recorded. Participants were followed up weekly for 28 days through subject diary. Investigators also performed the assessments at baseline and follow-up visits (Days 7, 14, 21, and 28) (Figure 1).

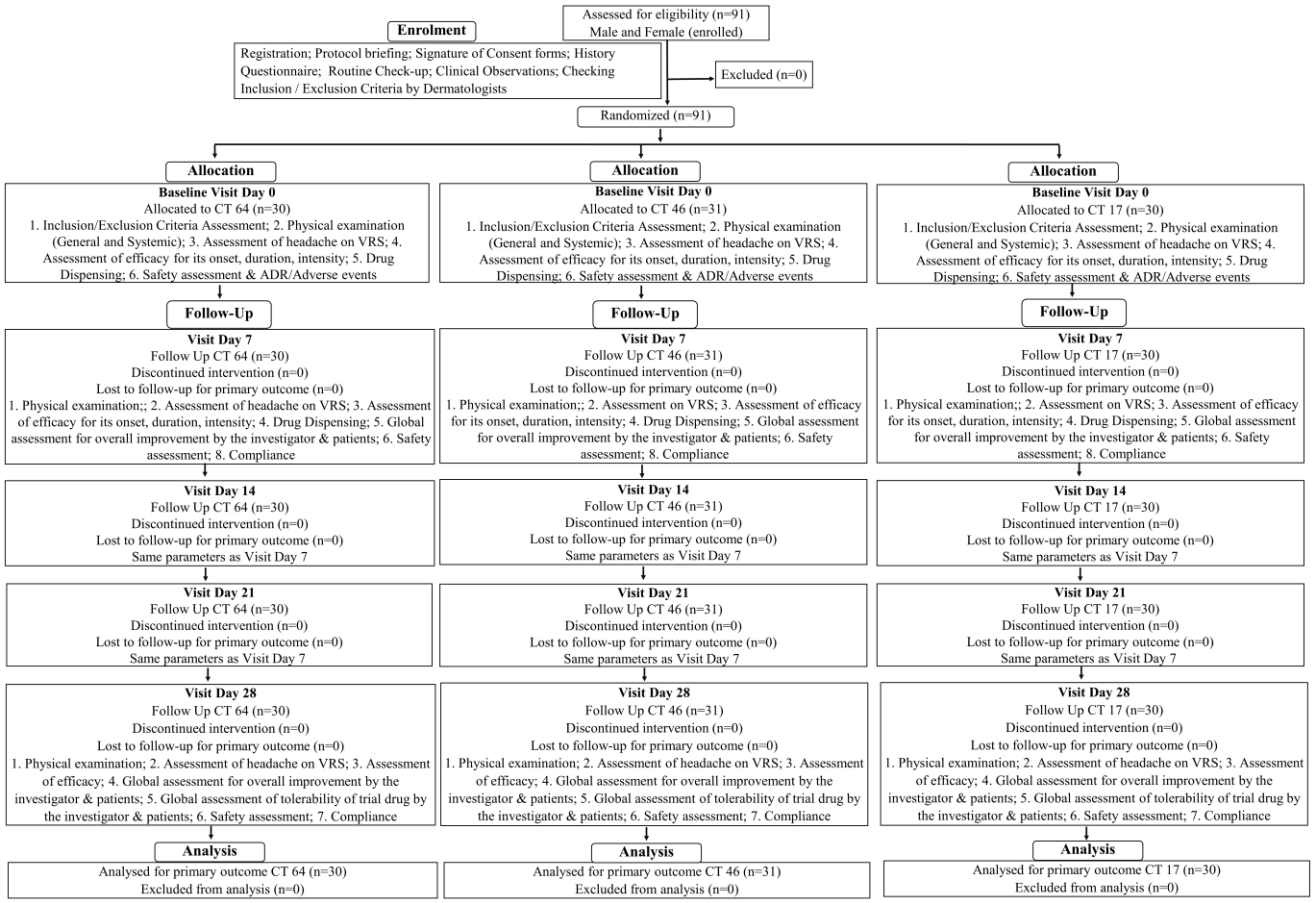

Figure 1: Study design for clinical trial on headache.

Centre and ethical considerations

The study protocol and related documents were reviewed and approved by the institutional ethics committee (IEC) in India at R. A. Podar Medical College and M. A. Podar Hospital, Worli, Mumbai; Ayurved Seva Sanga, Ayurved Mahavidyalaya, Nashik and Shri Gurudev Ayurved College, Amravati. The study was conducted in compliance with schedule Y of the drugs and cosmetics act, 1945 (India), as amended in 2005 and the ethical guidelines of the Indian council of medical research (ICMR) for biomedical research on human participants, which are derived from the world medical association's declaration of Helsinki.[19] The study was registered on clinical trial registry of India, under Ayurvedic study (CTRI/2017/06/008797) retrospectively.

Statistical methods and data analysis

The in-house statistician performed the analysis using available SPSS statistical software.

For the analysis of efficacy variables, data was analysed from the intent to treat population and per protocol population. The values of the last visit were considered for final analysis for subjects who were not completed the study schedule (Last observation carry forward) for intent to treat analysis. Safety analysis was done on all the subjects who have administered at least one dose of the treatment.

Data describing quantitative measures were expressed as median or mean±SD or standard error/mean with range. Qualitative variables presented as counts and percentage.

Comparison of variables representing categorical data like improvement in clinical symptoms, overall global improvement assessed by subjects and investigators were performed using appropriate statistical methods.

Mean differences of continuous variables like reduction number of symptoms were examined by student t test. All p values were reported based on two-sided significance test and all the statistical tests were interpreted at 95% level of significance.

All adverse events data was listed per subject including severity grading, relationship with investigational product and relationship of the adverse event to other causality, action taken and outcome of the adverse event. Any clinically significant changes in laboratory parameters were reported.

Simultaneous estimation of components using gas chromatography

Cyclohexane and primary standards were sourced from Merck, India. Volumetric flasks (10, 25 and 100 mL), a 1 mL pipette was used for chromatographic analysis. The balms were obtained from the local market in Kolkata, India.

Accurately weighed 100 mg of each working standard (L-menthol, methyl salicylate, thymol) was transferred into a 100 mL volumetric flask. 60 mL of cyclohexane was added and shaked gently to dissolve, then made the volume with cyclohexane and mixed well. 1.0 mL of this mixed standard stock solution was transferred to a 10 mL volumetric flask, made volume with cyclohexane.

The 250 mg balm samples were accurately weighed, transferred to 25 mL volumetric flasks, added 25 mL of cyclohexane and sonicated with intermittent shaking for 1-2 minutes until dissolved. Then 1 mL of each sample stock solution was transferred to a 10 mL volumetric flask and made volume with cyclohexane.

All analyses were performed on an Agilent 6890 GC system (Wilmington, DE, USA) with a DB-1 capillary column (30×250 µm, 0.25 µm film thickness, Agilent Technologies), a split injector and a flame ionization detector (FID). Separations of the three active constituents were performed on the DB-1 capillary column with a temperature gradient: 80 ºC for 2 min, ramp at 5 ºC/min to 160 ºC, ramp at 10 ºC/min to 180 ºC, ramp at 15 ºC/min to 270 ºC for a total run time of 28 min. Inlet temperature was 260 ºC with a split ratio of 10:1. Samples were injected using the auto sampler with an injection volume of 1.0 µl.

FID temperature was set at 300 ºC. Hydrogen was used as the carrier gas at a flow rate of 1.0 mL/min in constant flow mode. The percent RSD of the response factor of 2 injections from 2 preparations of the standard or sample (n=4) is less than 2.

RESULTS

Demographics of the study participants

Ninety-one participants had completed the study. Comparative efficacy of all three balms in reducing headache was assessed by total or meaningful headache relief and pain intensity on VRS and VAS scale. Demographic characteristics of the participants are depicted in Table 2.

There was no significant difference in the age of the participants, average number of episodes of headaches and duration of headaches in the three groups.

GC analysis

The quantification of menthol, methyl salicylate and thymol was achieved with precision using the validated GC method. Detailed findings are summarized in Figure 2, highlighting the method's robustness and reliability for analysis. The chromatogram showed distinct and well-separated peaks, affirming the efficacy of the developed analytical approach. These results underscore the method's capability to accurately measure and distinguish target compounds within the tested samples.

Table 2: Baseline demography and clinical characteristics of participants.

Characteristics	CT64	CT46	CT17	Remarks
Male	12	12	12	Total male=36
Female	18	19	18	Total female=55
Total participants	30	31	30	Total participants=91
Mean age (in years)	39.61	37.70	45.39	p>0.05 between group analysis
Average episodes of headache (28 days study)	5.25	4.86	4.90	p>0.05
Average duration of headache in hours	10.25	9.12	9.58	p>0.05

Table 3: Percentage of meaningful headache relief.

Parameters	CT64	CT46	CT17	Remark
Total no. of subjects	30	31	30	Equal number in both groups
Percentage of subjects with meaningful headache relief	93.33	90.32	86.66	p>0.05

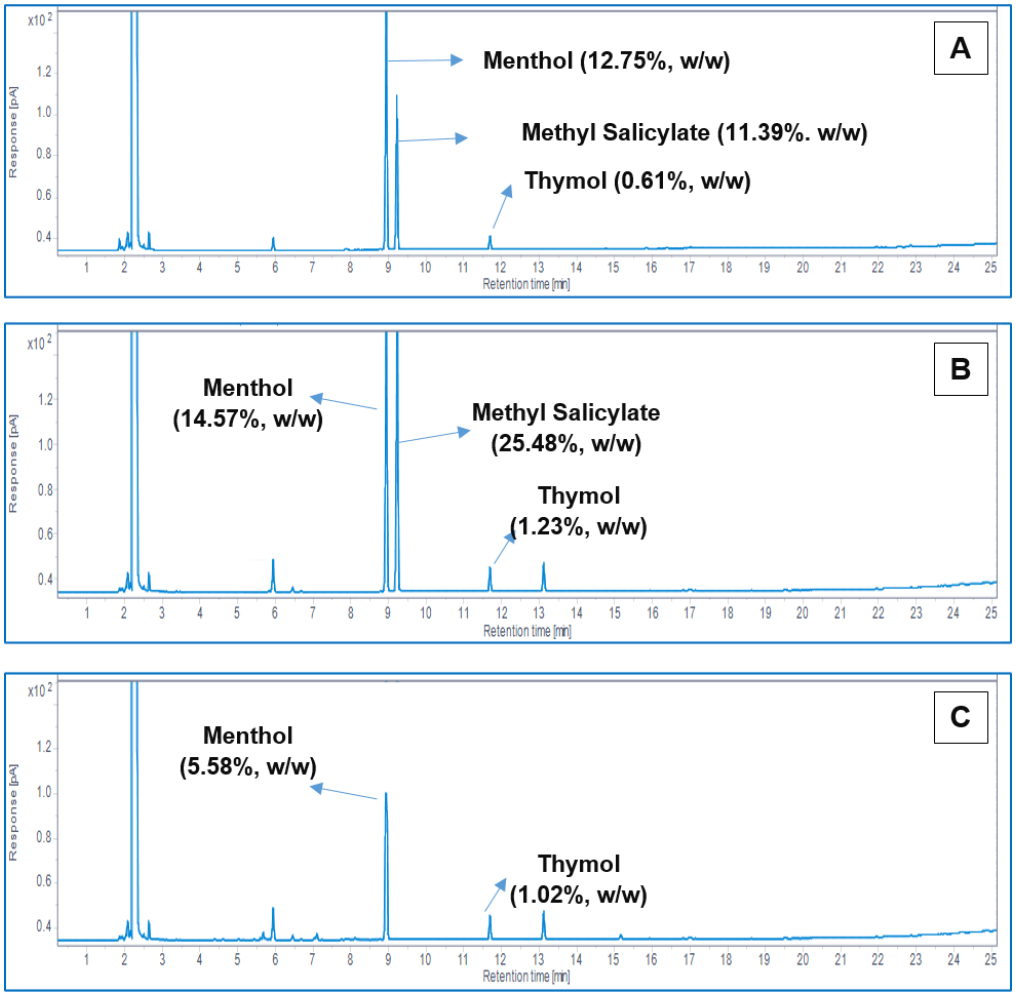

Figure 2 (A-C): GLC chromatogram and actives content of A) Zandu balm (CT64); B) Zandu ultra power balm (CT46), marketed sample (CT17).

Total or meaningful headache relief

There was a meaningful relief from headache (Table 3) in 28 participants of a total 30 participants studied in CT64 group (93.33%), 28 participants of a total of 31 participants in CT46 group (90.32%). The CT17 group reported a meaningful relief of 26 participants of a total of 30 (86.66%).

Headache intensity assessment

The headache intensity was measured by VAS scale (0-100 points) in the three groups (Table 4). Zero signifies no headache and hundred signifies severe headache. The mean intensity of headache was observed in three study groups before application. The intensity of headache was recorded at baseline as well as at intervals of 1 hr, 2 hrs, 4 hrs, 8 hrs and 24 hrs.

The intensity was also measured on VRS (0-5 points) by participants in all three groups. The mean intensity of headache before application of balm and after different time intervals were compared among three study groups (Table 5).

Comparative global assessment for efficacy balms

Using a structured assessment parameter, participants' perception of the balms was assessed. In all the balm formulation, the most of the participants found to have a faster action and longer duration compared to their usual balms. Assessment of use of rescue medication, sleep quality, quality of pain relief, absorption of balm, spreadability of balm were done through subject diary and by examination during follow up visits (Table 6).

Evaluation of AE/SAE (Safety evaluation)

Safety evaluation was done on the basis of occurrence of adverse drug reaction. It was observed that 3 subjects developed mild rashes in CT46 group, 4 subjects developed mild rashes on the head in CT64 group while 4 subjects developed mild rashes and burning sensation in the CT17 group. These symptoms subsided in 2-3 days and the study medication was allowed to be stopped during this period. These events were recorded as mild ADR. None of the other AE recorded in the study were related either of the study balms.

Table 4: Intensity of headache on VAS at different intervals in three groups.

Time interval	VAS scale (0-100 points)			
	CT-64	CT-46	CT-17	P value between group analysis
Intensity at the start of headache before application of balm	50.85±20.28	52.50±0.25	51.29±19.25	p>0.05
Intensity of headache after 1 hour	9.25±2.75 p<0.01	10.05±2.85 p<0.01	10.29±2.56 p<0.01	p>0.05
Intensity of headache after 2 hours	3.85±0.65 p<0.01	4.87±0.56 p<0.01	4.21±0.56 p<0.01	p>0.05
Intensity of hHeadache after 4 hours	0 p<0.01	0 p<0.01	0 p<0.01	p>0.05
Intensity of headache after 8 hours	0 p<0.01	0 p<0.01	0 p<0.01	p>0.05
Intensity of headache after 24 hours	0 p<0.01	0 p<0.01	0 p<0.01	p>0.05

Table 5: Intensity of headache on VRS scale at different intervals in three groups.

Time interval	VRS scale (0-5 points)			
	CT-64	CT-46	CT-17	P value between group analysis
Intensity at the start of headache before application of balm	2.40±1.35	2.65±1.40	2.55±1.28	p>0.05
Intensity of headache after 1 hour	0.48±0.06	0.45±0.09	0.52±0.08	p>0.05
Intensity of headache after 2 hours	0.08±0.02	0.15±0.01	0.08±0.02	p>0.05
Intensity of headache after 4 hours	0	0	0	p>0.05
Intensity of headache after 8 hours	0	0	0	p>0.05
Intensity of headache after 24 hours	0	0	0	p>0.05

Table 6: Global assessment for efficacy of balms.

Parameters	CT-64	CT-46	CT-17	Remarks
Use of rescue medications (%)	33.33	25.80	26.66	p>0.05, among group analysis
Faster onset action	50.00	80.00	43.33	% of subjects agreed and strongly agreed as compared to other balms
Onset of pain relief	56.66	77.40	56.66	
Duration of action (Long lasting effect)	86.66	87.09	70.00	
Intensity (Stronger) of action	60.00	70.96	49.99	
Quality of sleep	66.66	77.41	63.33	% of subjects with sound sleep
Average quality of pain relief	60.00	70.96	49.99	Ability to get back to normal in subjects (%)
Global assessment for overall relief in headache by the subject at the end of 28 days of the study	90.00	90.31	86.66	% of subjects good and very good as compared to other balms
Global assessment for overall improvement by the investigator at the end of study	53.32	54.82	59.99	
Absorption (better) of balm compared to other balms.	83.33	90.31	73.33	% of subjects agreed and strongly agreed as compared to other balms
Spreadability (better) of balm compared to other balms	86.66	83.86	66.66	

*Rating scale 1-strongly disagree; 2-disagree; 3-neutral; 4-agree; 5-strongly agree

DISCUSSION

The present study evaluated the efficacy and safety of three commercial balm formulations (CT46, CT64 and CT17) containing menthol, methyl salicylate and thymol. The chemical analysis revealed menthol, methyl salicylate and thymol contents were 12-15%, 11-26% and 0.0-1.5% in w/w respectively. These concentrations are consistent with established therapeutic properties for

topical counter-irritants. Menthol acts as a TRPM8 receptor agonist, inducing a cooling sensation and providing local analgesic effects, while methyl salicylate serves as a topical NSAID that inhibits prostaglandin synthesis.

From the Table 3, it is observed that both the CT46 and CT64 group formulations provided rapid relief within the first hour and sustained efficacy, with no headaches reported after 4 hours.

The significant decrease in VAS and VRS scores across all groups, particularly CT46 and CT64, indicates potent analgesic activity. The observation of statistically significant relief within one hour aligns with the findings of Haghighi et al who demonstrated that 10% menthol solution significantly reduced headache intensity within 90 minutes compared to placebo.[20] The sustained efficacy-with no headaches reported after 4 hours-suggests that the synergistic combination of menthol and methyl salicylate in these balms provides a more prolonged effect than only l-menthol as topicals. The results of Barkin who noted that multi-ingredient topical analgesics often provide superior pain management through multiple pathways of action.[21]

The results from the Table 4 and 5 indicate that the balms, especially CT64 and CT46 are effective in reducing headache intensity, as demonstrated by the significant decrease in VAS and VRS scores as these balms contain higher amounts of menthol and methyl salicylate. From the above table it is observed that there was a statistically significant relief from headache within one hour after application in all the three study groups as seen on VRS scale (0-5 points). There was no headache recorded after 4 hours of application of the test products.

It is observed that 8 subjects (25.8%) in CT46 group, 10 subjects (33.33%) in CT64 group and 8 subjects (26.66%) in CT17 group required rescue medication (Paracetamol) at least once in the entire study period (Table 6), but the majority of the cohort achieved total relief through topical application alone. This is a favourable outcome compared to studies by et al where topical applications were found to significantly reduce the need for oral analgesics in migraine patients.[20] The higher efficacy noted in CT46 and CT64 can be attributed to the higher concentrations of active ingredients.

In CT46 group, 80.63% and 87.09% of subjects reported faster onset of action and longer duration of action of the balm respectively with either strongly agreed or agreed option. Similar trend was observed in the CT64 group, with 50.00% and 86.66% of participants reporting faster onset and longer duration, respectively compared to other regular balms. This subjective strength is likely due to the high concentration of methyl salicylate, which enhances skin penetration. Both groups also perceived the test products as stronger than regular balms with 70.96% and 60.00% in the CT46 and CT64 groups, respectively. In CT17 group 43.33% of subjects had a faster onset of action of the balm.

The CT46 group reported 77.40% of faster onset of pain relief action followed by 56.66% in CT64 group. It is observed that 87.09% and 86.66% of subjects had agreed or strongly agreed for long lasting action of the balms.

Sleep quality after balm application was generally good in all groups which is a critical secondary outcome, with significant differences between CT46 (77.41% good sleep), CT64 (66.66% good sleep) and CT17 (63.33% good sleep). As established by Whiting et al effective pain management is directly correlated with the reduction of sleep disturbances.[22] For better quality of pain relief, 70.96% of subjects in CT46 had agreed or strongly agreed.

No major adverse events were observed in any patients of all the groups during the study period. All the balms were well tolerated by patients. The assessment of safety and tolerability were also recorded in case record forms (CRFs). This safety profile is consistent with the systemic review by Derry et al which concluded that topical salicylates and menthol have a significantly lower risk of gastrointestinal and systemic side effects compared to oral NSAIDs, making them a safer alternative for acute pain management.[23]

Despite the positive findings, this study has several limitations. First, the sample size per group was relatively small, which may limit the generalizability of the results to a broader population. Second, the study relied heavily on self-reported scales (VAS and VRS) and subjective perceptions, which are susceptible to individual bias and the placebo effect.

CONCLUSION

The present study successfully evaluated the chemical composition, safety and clinical efficacy of commercial balms. GC analysis confirmed CT46 and CT64 balms contain menthol, methyl salicylate, thymol within acceptable limit and absence of camphor, ensuring their quality and safety. In randomized, phase-II trials, the CT64 and CT46 formulations showed significant reductions from headaches, providing rapid pain relief as compared to CT17 group. There were significant reductions in pain intensity on both VAS and VRS scale, with minimal use of rescue medications. CT46 consistently showed a trend towards faster onset, longer duration and greater improvement in pain. The study indicates that all the balm samples are safe for topical application in healthy individuals, as supported by no record of major adverse events. The investigators' global assessments align with the participants' experiences, confirming the balms have comparable effectiveness against headache. In future, potential synergistic effects will be explored of combining the balms with other

therapeutic options to enhance faster and better pain relief.

Funding: Emami Limited, Kolkata, India
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee clinical trial registry of India, under Ayurvedic study (CTRI/2017/06/008797)

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Cite this article as: Chattopadhyay PS, Rewadkar M, Agiwal S, Nagpure SS, Ganguly P, Bothra A, et al. Clinical study to evaluate efficacy and safety of topical balms for headache: a randomized trial. Int J Res Dermatol 2026;12:xxx-xx.