



A Randomized, Multicentric, Open Label, Interventional Study to Evaluate the Efficacy and Tolerability of Four Types of Amrutanjan Pain Balms for Pain Relief in Patients with Primary Type of Headache and Body Pain Disorders

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Received 29 December 2020;

Accepted 22 January 2021;

Published 01 February 2021

Abstract

Introduction: Body pain disorders like knee pain, low back pain and primary headache disorders impose burdens that include substantial personal suffering, impaired quality of life, and financial cost. Repeated attacks, and often fear of future attacks, affects the family life, social life, and employment. **Objectives:** To evaluate the Safety, Efficacy and tolerability of four types of Amrutanjan Pain Balm preparations for rapid pain relief in patients with primary type of headache and body pain disorders. **Materials & Methods:** This study is a randomized, multicentric, open label, interventional study conducted at a secondary care centres in Chennai and Vellore. A total of 150 patients were screened and 144 patients were enrolled who were diagnosed with either body pain disorders like knee pain, low back pain or primary type of headache disorders like migraine, tension type headache and other primary head ache disorders. All the study participants were randomized to four arms of 36 each such that each arm comprised of 12 patients with knee pain, 12 patients with low back pain and 12 patients with primary headache disorder to receive four different formulations of Amrutanjan pain balms. Efficacy was evaluated by assessing pain reduction after treatment at various time points and duration of action. Visual analogue scale questionnaires were used post study to obtain feedback on overall status of improvement. **Results:** Patients enrolled with headache had 75 % tension-type, 17% migraine and 8% Cluster headache; those with knee joint Pain had osteoarthritis (80%) and reactive arthritis (20%) whereas patients with low back pain had lumbar strain and lumbar spondylosis. The onset of action was 55 seconds for patients with headache disorders, while it ranged between 95 to 115 seconds for joint pain and low back pain respectively. Highly significant improvement in the VAS score, was observed after 5, 10 and 30 minutes of test product application. **Conclusion:** All the four types of topical Amrutanjan pain balms and roll-on were found to be effective and safe for the treatment of primary headache and body pain disorders.

Keywords: *knee pain, low back pain, primary headache disorders, topical analgesics*

Introduction

Topical analgesic drugs are used to treat both acute pain (sprains, tendonitis, acute back pain, muscle aches) and chronic pain

(osteoarthritis of hand or knee, low back pain, and specific types of neuropathic pain) ^[1]. Body pain disorders like knee pain, low back pain and primary headache disorders impose burdens that include substantial personal suffering, impaired quality of life, and

financial cost. Knee joint pain due to Osteoarthritis is a degenerative joint disease that is a leading cause of physical disability and impaired quality of life in industrialized nations [2]. Non-specific low back pain is defined as pain between the lowest rib and the bottom of the buttocks that is not caused by serious, underlying problems such as rheumatoid arthritis, infection, fracture, cancer, or sciatica due to a ruptured disc or other pressure on nerves affecting up to 35% of the population in a given month [3]. The term "primary headache" refers to headache pain in the absence of another organic disorder known to cause headache. Tension type headache (TTH) is the most common primary headache worldwide, with prevalence in elderly adults of 35.8%. Migraine is the next most common headache disorder, with a prevalence of 5.7% in elderly adults [4]. Despite technological advances and thorough established treatments, pain in these disorders continues to defy health professionals, because it is a poorly controlled condition; partly because multiple aspects are involved in the pathogenesis of pain namely nociception (pain sensation and topography), emotion (fear and depression), and behavioural factors (catastrophism, vigilance, and somatic awareness). Pain management faces difficulties that restrict therapeutic success, such as the limited efficiency of analgesics, systemic effects, and cognitive impairment of drugs due to central effects [5].

Traditional medicinal plants are a promising alternative, with lower rate of adverse events and efficiency frequently comparable with that of conventional drugs. Nevertheless, their mechanism of action is in many cases elusive and/or uncertain. One such formulation namely Amrutanjan which is a blend of ten active ingredients is evaluated in this study as a treatment option for pain relief in patients with body pain disorders and primary headache disorders.

Amrutanjan Pain Balm has grown to become a household brand across all social cultures of India. It is one of the most trusted brand in India since 1893. Amrutanjan Pain Balm is the classic headache & cold remedy for over 125 years and has been kicking out stress induced headaches for over 4 generations. It has ten active ingredients which provide relief from headaches and cold related body pains. It has a soothing aroma which acts as a relaxant for the day to day stress. Four new preparations are available now namely New Amrutanjan Pain Balm Extra Power (NAPBEP), Amrutanjan Strong Pain Balm (ASPB), Amrutanjan New Maha Strong Pain Balm (ANMSPB) and New Amrutanjan Headache Faster Relaxation Roll-on (NAFRR).

The active components of this preparation include *Cinnamomum camphora*, *Carum copticum*, *Mentha arvensis*, *Gaultheria fragrantissima*, *Eugenia caryophyllus*, *Turpentine ka tel*, *Cymbopogon citratus*, *Dalchini ka tel*, *Mentha piperita*, and *Eucalyptus globulus*. The active principles of this Amrutanjan formulation possess multiple properties like analgesic, anti-inflammatory, antitussive, antipyretic, antirheumatic, rubefacient, counter irritant and local anesthetic properties [6]. Ayurvedic preparations for pain relief has been studied for its safety and efficacy and looked for the symptomatic relief without harmful side effects [7]. Therefore, this study was in search for evidence for the new preparations as effective alternatives for pain therapy.

Materials and Methods

This study is a randomized, multicentric, open label, interventional study conducted at secondary care centres in Chennai and Vellore.

A total of 150 patients were screened and 144 patients were enrolled based on the study criteria. Sample size was calculated using Sample Size Calculator Pro. Version 1.0. considering the hypothetical proportion before treatment as 90% and proportion after treatment as 20%. With alpha error 0.05 and beta error 0.2. The required minimum sample size was calculated to be 12 per treatment. Hence considering 4 different formulations and 3 indications. The sample size per arm was calculated to be 36 and the total sample size was 144 [8,9].

Inclusion criteria

1. Patients of either sex aged above 18 years and are able to understand written and/or verbal instructions and are ready to comply with all study requirements with a willingness to participate and give written informed consent voluntarily.
2. Patients who had been diagnosed with body pain disorders like knee pain, low back pain and primary type of headache disorders like migraine, tension type headache and other primary headache disorders.

Exclusion criteria

Subjects presenting with any of the following were not included in the trial.

1. Women of child bearing potential who are either unwilling or unable to use an acceptable method of birth control [such as oral contraceptives, other hormonal contraceptives (implants or injectable products, vaginal products, skin patches), or IUDs, barrier methods] to avoid pregnancy during the study period.
2. Secondary type of headache disorders.
3. Known allergy to compounds of investigational product.
4. Subjects who had a diagnosis of chronic migraine, basilar or hemiplegic migraine and who are on medications for the same.
5. Subjects suffering from medical or psychiatric conditions that would increase the risk of adverse events or interfere with study assessments.
6. Participation in an investigational drug trial in the 30 days prior to the screening visit.
7. Immuno-compromised (history) individuals like known HIV positive Subjects or Subjects who are on treatment with steroids or immunomodulators.
8. Subjects of vulnerable group (children, lactating mother, elderly >80 years, handicapped, seriously ill, mentally challenged).
9. History of drug or alcohol abuse during the last 6 months.

The study was commenced only after getting approval from 'Ki3 Ethics Committee for AYUSH' and proper informed consent from the study participants. All the study participants were randomly assigned using random number generator (STAT TREK software) to four arms of 36 each such that each arm comprised of 12 patients with knee pain, 12 patients with low back pain and 12 patients with primary headache disorder to receive four different formulations of Amrutanjan pain balms as mentioned below. (Figure 1)

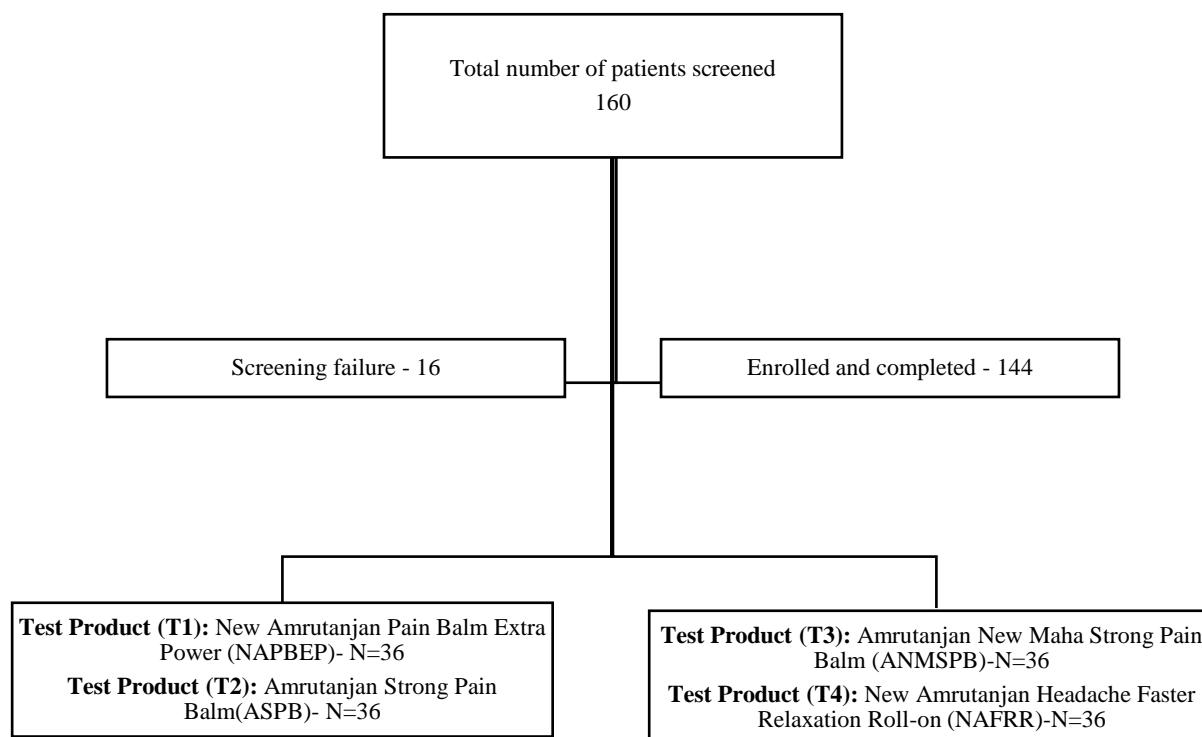


Figure 1: Study design. Flowchart of study participants enrolment.

Test product 1: New Amrutanjan Pain Balm Extra Power (NAPBEP): 36 subjects

Test product 2: Amrutanjan Strong Pain Balm (ASPB): 36 subjects

Test product 3: Amrutanjan New Maha Strong Pain Balm (ANMSPB): 36 subjects

Test product 4: New Amrutanjan Headache Faster Relaxation Roll-on (NAFRR): 36

Amrutanjan preparations were supplied by Amrutanjan Health Care Limited, Tamil Nadu, India. The study protocol was reviewed and approved by ‘Ethics Committee for AYUSH products’. The study was registered in CTRI website and the registration number is CTRI/2020/06/026013.

Study participants were requested to apply pea-sized amount of approximately 0.25g of the pain balm in thin layer to the pain area below and abutting the base of the skull (frontal & temporal bone region) to the base of the neck as well as behind and between the ears within 2 hours of the onset of Headache – in case of headache. b) lower back region in case of low back pain. c) knee joint region – in case of knee pain. In case of roll-on, patients were asked to gently apply 4 rolls (equivalent to 0.25g) on the pain area as mentioned above. If they had no relief after 2 h of product application, they were permitted to use their own rescue Medication. The patients were requested to visit for only one follow up on the subsequent day.

The primary efficacy endpoints were:

- i. assessment of onset of pain reduction after treatment at 30 seconds, 1 min, 2 min, 5 min, 10 min, 30 min and 60 min.(using visual analog scale)
- ii. assessment of duration of action (i.e need for second application) of the test product for pain relief.(time frame : 0-24 hours)

Visual analog scale (VAS) questionnaires were filled in by the Subjects and scores were given, ranging from 0 to 5 (based on the severity of happy face sad face pain scale). For statistical analysis,

ordinal conversion of pain levels was assigned as 0–no pain up to 10-severe pain.

The secondary safety end points included monitoring of other side effects like skin rashes, redness, photophobia, phonophobia and any serious adverse events during the study period.

The total study duration was one month. For each subject the duration in the study was 24 hours. Subjects were asked to visit clinical facility/institution for follow up visit on day 2.

Statistical analysis: Descriptive statistics were performed for baseline characteristics like age, sex and also any adverse events and tolerability profiles. All the results of VAS scores were evaluated and compared within the groups using two way ANOVA followed by Bonferroni test, by SPSS software version 21.0.P value < 0.05 was considered as statistically significant (denoted with *) and P value < 0.001 was considered as statistically highly significant (denoted with **)

Results

In this study 160 Subjects were screened and 144 were enrolled after fulfilling the inclusion criteria and getting proper signed informed consent. The Subjects were allotted equally to 4 different test groups as per computer generated randomization. The mean age group of the subjects involved in the study was 43.25. Out of the 144 Subjects enrolled, there was 94 female and 50 male Subjects.

The patients enrolled in the study with headache had 75 % tension-type, 17% Mild to moderate migraine and 8% Cluster headache. Patients with knee joint Pain had Osteoarthritis (80%)

and reactive arthritis (20%) whereas patients with low back pain had lumbar strain and lumbar spondylosis.

The onset of action was less than a minute (55 seconds) for headache disorders, while it ranged between 95 to 115 seconds for joint pain and low back pain respectively. Complete relief of pain was achieved in 10-20 minutes for headache, joint pain and low back pain. While the duration of action ranged from 4 to 23 hours of duration.

All the results were evaluated and compared within the groups using 2 way ANOVA followed by Bonferroni posttest. (The baseline VAS scores at time zero second was compared with that of 30 seconds, 1 minute, 2 minute, 5 minute, 10 minute and 30 minute respectively) There was a statistically significant improvement in the VAS scores from 2 minutes of application of test products, in case of headache disorders. However, in case of joint pain and low back ache disorders, the improvement showed

after 5 minutes of test product application. Highly significant improvement in the VAS score, was observed after 5, 10 and 30 minutes of test product application.

There were no documented serious adverse events during the trial period. The most common other side effect encountered during the study period was mild Erythema at the site of application of the test product, which subsided on its own without any medical intervention.

On analyzing the overall percentage of the subjective response in improvement of pain from the time of application of test products, it was found out that 80-90% of subjects reported good on overall status of improvement in headache disorders in all four types of pain balm and 60-70% of subjects reported good overall status of improvement in Joint pain and low back pain disorders.

Table 1: Demographic details of study participants

Test group	Condition	Mean age + SD	Male (n)	Female (n)
NAPBEP(T1)(n=36)	Headache	35.1 + 6.3	5	7
	Joint Pain	48.7+ 6.7	3	9
	Low Back Pain	45.5+ 7.3	3	9
ASPB(T2) (n=36)	Headache	34.0 + 7.0	6	6
	Joint Pain	46.0 + 8.4	5	7
	Low Back Pain	43.3 + 11.5	5	7
ANMSPB(T3) (n=36)	Headache	42.0+ 9.3	3	9
	Joint Pain	51.3+ 7.4	5	7
	Low Back Pain	43.3 + 11.5	5	7
NAFRR(T4) (n=36)	Headache	37.1+ 11.4	6	6
	Joint Pain	48.0+ 10.7	0	12
	Low Back Pain	42.4+ 8.8	4	8

Table 2: Distribution of Subjects recruited

Test group	Distribution of patients based on clinical diagnosis N (%)						
	Headache			Joint pain		Low back pain	
	Tension headache	Migraine	Cluster headache	Osteoarthritis	Reactive arthritis	Lumbar strain	Lumbar spondylosis
NAPBEP	8 (67%)	3 (25%)	1 (8%)	9 (75%)	3 (25%)	9 (75%)	3 (25%)
ASPB	9 (75%)	2 (17 %)	1 (8%)	10 (83%)	2 (17%)	10(83%)	2 (17%)
ANMSPB	9 (75%)	2 (17 %)	1 (8%)	10 (83%)	2 (17%)	10(83%)	2 (17%)
NAFRR	8 (67%)	3 (25%)	1 (8%)	9 (75%)	3 (25%)	9 (75%)	3 (25%)

Table 3: Onset and duration of action of New Amrutanjan Pain Balm Extra Power and Amrutanjan Strong Pain Balm

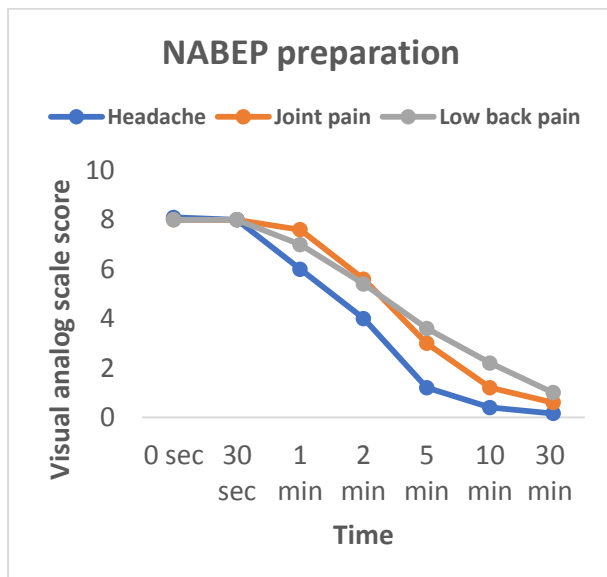
CONDITION	NAPBEP (T1) Mean Values			ASPB(T2) Mean Values		
	Onset of action (seconds)	Complete Relief (Min. sec)	Duration of action (hrs. min)	Onset of action (seconds)	Complete Relief (Min. sec)	Duration of action (hrs. min)
Headache	55.00	9.10	10.29	60.00	8.20	8.02
Joint Pain	110.00	22.55	4.45	95.00	22.30	4.15
Low Back Pain	115.00	39.10	3.19	125.00	30.50	3.44

Table 4: Onset and duration of action of Amrutanjan New Maha Strong Pain Balm and New Amrutanjan Headache Faster Relaxation Roll-on

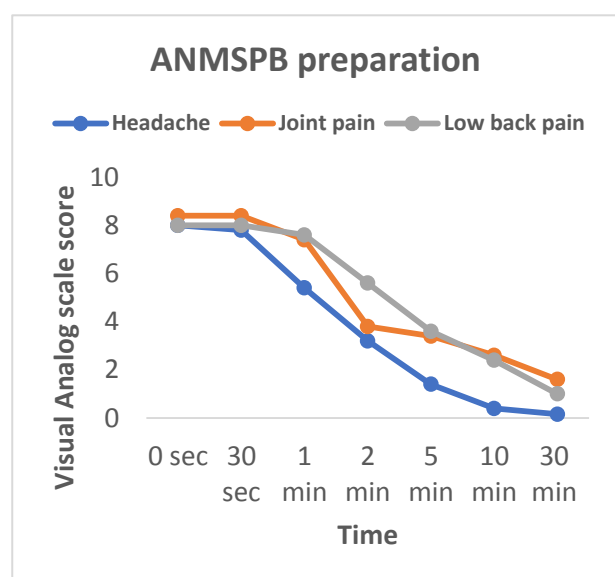
CONDITION	ANMSPB (T3) Mean Values			NAFRR (T4) Mean Values		
	Onset of action (seconds)	Complete Relief (Min. sec)	Duration of action (hrs. min)	Onset of action (seconds)	Complete Relief (Min. sec)	Duration of action (hrs. min)
Headache	99.00	8.35	23.18	80.00	7.57	20.26
Joint Pain	108.00	20.40	20.29	220.00	23.25	18.17
Low Back Pain	120.00	10.30	18.33	127.00	16.08	20.50

Table 5: Comparison of VAS scores at various time points of different test products:

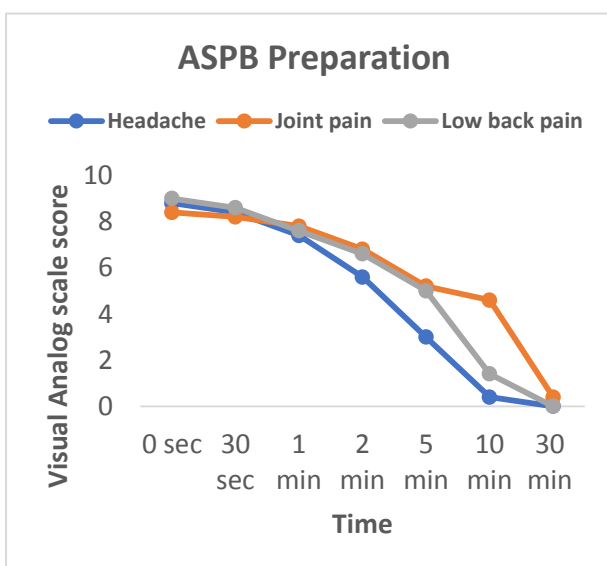
Test Product	Condition	Visual Analog Scale (score 0-10) [mean ± SD]						
		0 sec	30 sec	1 min	2 min	5 min	10 min	30 min
NAPBEP (T1)	Headache (N=12)	8.1 ± 0.6	8.0 ± 0.4	6.0 ± 0.8*	4.0 ± 1.4 **	1.2 ± 1.4 **	0.4 ± 0.6 **	0.16 ± 0.4**
	Joint Pain (N=12)	8.0 ± 0.8	8.0 ± 0.8	7.6 ± 0.6	5.6 ± 1.0*	3.0 ± 1.4 **	1.2 ± 1.4 **	0.6 ± 1.2 **
	Low Back Pain (N=12)	8.0 ± 0.0	8.0 ± 0.0	7.0 ± 1.0	5.4 ± 1.2*	3.6 ± 1.4 **	2.2 ± 1.2 **	1.0 ± 1.2 **
ASPB (T2)	Headache (N=12)	8.0 ± 0.8	7.8 ± 1.0	5.4 ± 1.2*	3.2 ± 1.2 **	1.4 ± 1.2 **	0.4 ± 0.6 **	0.16 ± 0.4 **
	Joint Pain (N=12)	8.4 ± 0.6	8.4 ± 0.6	7.4 ± 1.2	3.4 ± 1.4	3.8 ± 2.6 **	2.6 ± 2.0 **	1.6 ± 2.2 **
	Low Back Pain (N=12)	8.0 ± 0.0	8.0 ± 0.0	7.6 ± 0.6	5.6 ± 1.0 *	3.6 ± 1.0 **	2.4 ± 1.4 **	1.0 ± 1.4 **
ANMSPB (T3)	Headache (N=12)	8.8 ± 0.6	8.4 ± 1.2	7.4 ± 2.2	5.6 ± 3.0 *	3.0 ± 3.0 *	0.4 ± 0.8 **	0.0 ± 0.0 **
	Joint Pain (N=12)	8.4 ± 0.0	8.2 ± 0.4	7.8 ± 1.2	6.8 ± 2.6	5.2 ± 3.2 *	4.6 ± 2.8 *	0.4 ± 0.8 **
	Low Back Pain (N=12)	9.0 ± 0.0	8.6 ± 1.2	7.6 ± 1.6	6.6 ± 2.4 *	5.0 ± 2.6 **	1.4 ± 1.4 **	0.0 ± 0.0 **
NAFRR (T4)	Headache (N=12)	9.0 ± 0.6	8.2 ± 1.2	7.4 ± 2.0	6.0 ± 2.8 *	3.0 ± 2.6 **	0.4 ± 1.0 **	0.0 ± 0.0 **
	Joint Pain (N=12)	8.2 ± 0.0	8.2 ± 0.4	7.6 ± 1.4	6.8 ± 2.2	5.8 ± 3.8 *	4.8 ± 3.8 *	3.4 ± 2.8 **
	Low Back Pain (N=12)	9.0 ± 0.0	8.8 ± 0.6	8.0 ± 1.8	7.2 ± 2.2	5.2 ± 3.2 *	3.0 ± 2.6 **	0.4 ± 0.6 **



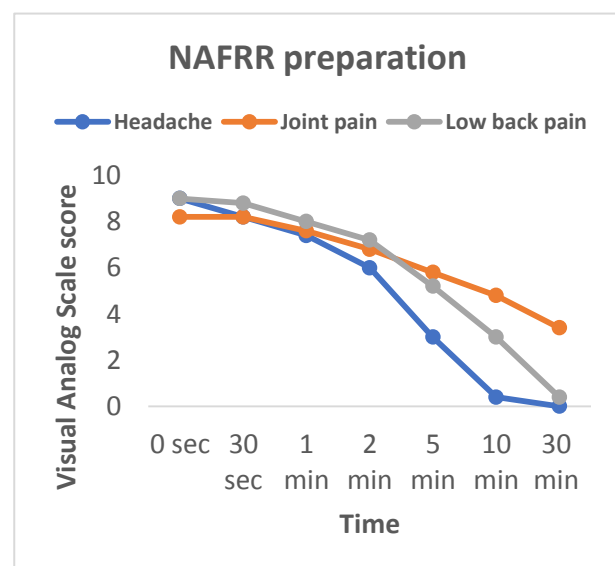
Graph 1: Time course of action of NABEP preparation on headache, joint pain and low back pain



Graph 2: Time course of action of ANMSB preparation on headache, joint pain and low back pain



Graph 3: Time course of action of ASPB preparation on headache, joint pain and low back pain



Graph 4: Time course of action of NAFRR preparation on headache, joint pain and low back pain

Table 6: Other side effects observed during the trial

Condition	Mild skin erythema was Observed (No. of subjects)			
	NAPBEP(T1)	ASPB(T2)	ANMSPB(T3)	NAFRR(T4)
Headache (N=12)	1	0	2	1
Joint Pain (N=12)	0	0	4	1
Low Back Pain (N=12)	1	0	3	1

Table 7: Post study subject feedback on Overall status of improvement

Test group	Condition	Overall status of improvement no. of subjects (%)			
		Good	Minimal	No change	Worse
NAPBEP(T1) (n=36)	Headache	11(92%)	1 (8%)	0 (0 %)	0 (0 %)
	Joint pain	7 (58%)	5 (42%)	0 (0 %)	0 (0 %)
	Low back pain	5 (42%)	7 (58%)	0 (0 %)	0 (0 %)
ASPB(T2) (n=36)	Headache	10 (83%)	2 (17%)	0 (0 %)	0 (0 %)
	Joint pain	6 (50%)	4 (33%)	2 (17%)	0 (0 %)
	Low back pain	5 (42%)	7 (58%)	0 (0 %)	0 (0 %)
ANMSPB(T3) (n=36)	Headache	10 (83%)	2 (17%)	0 (0 %)	0 (0 %)
	Joint pain	9 (75%)	3 (25%)	0 (0 %)	0 (0 %)
	Low back pain	8 (67%)	3 (25%)	1 (8%)	0 (0 %)
NAFRR(T4) (n=36)	Headache	11(92%)	0 (0 %)	1 (8%)	0 (0 %)
	Joint pain	7 (58%)	4 (33%)	1 (8%)	0 (0 %)
	Low back pain	8 (67%)	3 (25%)	1 (8%)	0 (0 %)

Discussion

Body pain disorders like knee pain, low back pain and primary headache disorders impose burdens that include substantial personal suffering, impaired quality of life, and financial cost and employment. Treatment goals for such pain disorders focus on effective pain relief, improved quality of life and enhanced functional ability. Medications, including Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, are commonly prescribed and these drugs are known to cause serious adverse effects. The number of prescriptions for NSAID's, opioids and other controlled substances has increased dramatically in recent years. In parallel the rates of misuse, overuse, diversion, abuse, addiction, and death has also escalated.

Efforts are being made to find out a better alternative for the management of acute and chronic pain disorders. One component of these efforts was focused on topical agents, which has the potential to provide analgesic effects without the risk of abuse, misuse, and addiction or systemic adverse events (AEs) associated with oral analgesics.

Therefore, the ideal method for relieving pain is a simple method of external application of liniment. There is no time limitation regarding the duration of treatment by external applications. This can be used for prolonged period.

Amrutanjan Pain Balm is one such better alternative for the management of acute and chronic pain disorders. It is still one of the most trusted brand in India since 1893. Amrutanjan Pain Balm has ten active ingredients which provide relief from headaches and cold related body pains. It has a soothing aroma which acts as a relaxant for the day to day stress. Previous studies have also shown that herbal ointments are effective in relieving the pain and stiffness of osteoarthritis without adverse effects.

Four different preparations are available namely; New Amrutanjan Pain Balm Extra Power (NAPBEP), Amrutanjan Strong Pain Balm (ASPB), Amrutanjan New Maha Strong Pain Balm (ANMSPB) and New Amrutanjan Headache Faster Relaxation Roll-on (NAFRR). The present study has shown that all the four different preparations are effective in treating headache, joint pain and low back pain, which was evident from the

significant improvement in the visual analog scale values. Though the onset and duration of action seems to be different for each preparation, it has shown to be of a better alternative for systemic analgesics. Also, there were no documented adverse events during the study period. All the subjects gave a good positive response towards the use of topical Amrutanjan pain balms in various types of headache, joint pain and low back pain disorders.

Cinnamomum camphora which is one of the major components of Amrutanjan preparations has long been prescribed in traditional medicine for the treatment of inflammation-related diseases such as rheumatism, sprains, bronchitis and muscle pains. Its anti-inflammatory effect was proven to be due to modulation of cytokine, NO and PGE [2] production and oxidative stress [10]. Another major component present is Amrutanjan preparation is *Gaultheria fragrantissima*. Phytochemical investigations have revealed the presence of methyl salicylate derivatives, C₆-C₃ constituents, organic acids, terpenoids, steroids, and other compounds. Methyl salicylate glycoside content is 98% and is considered as a characteristic ingredient with anti-rheumatic and analgesic effects which helps in pain reduction [11]. *Mentha arvensis* is another major component of Amrutanjan preparations which yields menthol. Menthol exerts antioxidant, anti-inflammatory, local anesthetic and anodyne action which helps in relieving body pain and headache [12]. A study evaluated the efficacy and safety of herbal liniment in orthopaedic disorders revealed the presence of *Cinnamomum camphora*, *Gaultheria fragrantissima* and *Mentha arvensis*. It showed that the main clinical benefits of the herbal liniment were relief from pain, and reduction in swelling and muscle spasms [13]. In this study, it was observed that at the end of the study there was much relief of pain from headache, knee pain and low back pain. *Mentha arvensis* and *Cinnamomum camphora* are also used as rubefacients for external application. They produce redness of the skin by causing dilation of the capillaries and increasing blood circulation, thus distracting from the deep-seated pain and providing relief in various conditions such as lumbago, arthritis, and headache [14]. Similarly other ingredients namely *Carum copticum*, *Eugenia caryophyllus*, *Turpentine ka tel*, *Cymbopogon citratus*, *Dalchini ka tel*, *Mentha piperita*, and *Nilgiri ka tel* have counter irritant,

analgesic and rubefacient properties which had led to the reduction in pain in patients with pain disorders in this study [15].

These findings suggest the synergistic action of the ingredients of Amrutanjan preparations.

Conclusions

All the four types of topical Amrutanjan pain products were found to be effective and safe for the treatment of primary headache and body pain disorders. All four formulations has shown a very quick onset of action and prolonged duration of action. The traditional herbal composition of Amrutanjan gives a better pain relief, simple dose determination, provide direct access to the target site and are easy for patients to apply. It also lowers the risk of systemic adverse events, drug–drug interactions and thus provides a good patient compliance.

Data Availability

All data used by our work as well as spreadsheets, images and others that support the results conclusions of this study are readily available through the corresponding author.

Conflicts of Interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

Funding Statement

The financial support to conduct this study was given by Amrutanjan Healthcare Limited, Chennai

Authors' contributions

RK, SB and RJ worked on the concept and study design. AK helped in writing of the protocol and manuscript. RK, MG and AB helped in conduct of the study at their respective centres. They were involved in data collection and analysis. All authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank Mr. Sambhu Sivalenka, Chairman and Managing Director, Amrutanjan Health Care Ltd and Ki3 Clinical Research Organization, Chennai for their encouragement and support in conducting this study.

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