Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Orthopedics

Fast Relief of Acute Musculoskeletal Pain in Different Body Parts Following Exercise - A Randomized Double-Blind Placebo-Controlled Human Study with *Curcuma longa* and *Boswellia serrata* Extracts

Meghana Murthy[1], Girish H. Rudrappa[2*], Sanjeev Kumar Kare[3], Santosh Saklecha[4], Indraneel Basu[5], Ajay Gupta[6]

[1]Vagus Super Speciality Hospital, 4th Main Road, Malleswaram, Bangalore, Karnataka, India - 560003
[2]Department of Orthopedics, Sapthagiri Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India – 560090
[3]Government Medical College and General Hospital, Srikakulam, Andhra Pradesh, India - 532001
[4]Santosh Hospital, Promenade Road, Behind Coles Park, Bangalore, Karnataka, India - 560005
[5]Sudbhawana Hospital, Varanasi, Uttar Pradesh, India - 221005
[6]Nirmal Hospital, Jhansi, Uttar Pradesh, India -284128

DOI: 10.36347/sjams.2022.v10i03.008 | **Received:** 07.02.2022 | **Accepted:** 12.03.2022 | **Published:** 20.03.2022

***Corresponding author:** Dr. Girish H. Rudrappa
Department of Orthopedics, Sapthagiri Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India – 560090

Abstract **Original Research Article**

Acute pain in different parts of the body viz., head and neck, trunk, upper and lower limbs tend to be perceived differently. A randomized double-blinded placebo-controlled study was conducted on 232 healthy participants with acute musculoskeletal pain. The participants were randomized in a 1:1 ratio to receive a single dose of 1000 mg of *Curcuma longa* and *Boswellia serrata* extract formulation (CBF, Rhuleave-K) or placebo. The participants were categorized according to the location of the pain- head and neck, upper limb, lower limb, trunk, and general body following exercise. Pain intensity was analyzed using a numerical rating scale (NRS) at intervals of 30 minutes up to 6 hours. NRS was taken at rest, on movement and applying pressure on the affected part. The perceptible pain relief (PPR) and meaningful pain relief (PPR) was assessed using the double stopwatch method. In the CBF group, the pain intensity in the head and neck region had a 100% reduction at rest, on movement and pressure ($p=0.02$) and in generalized body pain, 100% at rest and movement and 97% reduction on applying pressure ($p=0.06$). Pain in the upper limb, trunk, and lower limb respectively showed a significant reduction of 99%, 97%, and 97% ($p<0.001$) in the CBF group at rest, on movement and pressure whereas the placebo group showed negligent change. The PPR and MPR obtained at head and neck (40, 160 min), upper limb (52, 167 min), trunk (75, 216 min), lower limb (74, 175 min), and generalized body pain (75, 240 min) in CBF group were significantly faster than the placebo group ($p<0.001$). CBF can be recommended as a fast-acting alternative to current therapies for acute musculoskeletal pain affecting head and neck, upper and lower limbs, trunk, and general body pain.

Keywords: acute pain, musculoskeletal, turmeric, boswellia, exercise, anti-inflammatory, NSAID.

Copyright © 2022 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Musculoskeletal pain is common to most people and affects between 13.5% and 47% of the general population (Cimmino *et al.*, 2011), and is the leading cause of disability worldwide. The leading cause, low back pain contributed 10.7% of total years lived with disability (YLDs). Musculoskeletal disorders caused 21·3% of all YLDs. The main contributors were low back pain (83·1 million YLDs), neck pain (33·6 million YLDs), osteoarthritis (17·1 million YLDs), and the other musculoskeletal category (28·2 million YLDs) *(Vos et al.*, 2012). Between 70% and 80% of the world's population experiences low back pain sometime during their lives. The incidence of low back pain in Western industrialized society has been reported to range from a high of 20% of adults in any given 2-week period to a "low" of 10% in 2 years (Frymoyer *et al.*, 1980; Newell & Turner, 1985). Spinal back pain is a very common clinical problem that affects most of a physician's population, whether it consists of heavy laborers or sedentary office workers (Dillane *et al.*, 1966; Troup *et al.*, 1981; White, 1969). Back pain is second only to the common cold as the most common reason for visiting a physician (Cypress, 1983). Neck pain is a far less frequent cause of work absenteeism than is low back pain, but in certain occupations, it results in a substantial amount of lost productivity. The

1-year prevalence of neck pain is approximately 20% in most industrialized countries. Scandinavian studies have reported a 1-year prevalence rate of 16% in men and 18% to 20% in women (Takala *et al*., 1982; Westerling & Jonsson, 1980). In a study of 2684 male employees, Andersson reported cervical problems occurred one-half to one-quarter as often as lumbar spine abnormalities (Anderson, 1971). The majority of cases of the elbow, lower arm, wrist, and hand pain are caused by repetitive use injuries, whether from hobbies or work-related or sports-related activities. Unless wrist, hand, or finger pain has been caused by a traumatic injury, the symptoms are more likely the result of a repetitive strain injury —a general term used to describe pain brought on by repetitive overuse movements, whether work, hobby, or sports-related.

Management of pain continues to be one of the most commonly encountered clinical situations for practitioners. Pain medicine has evolved over recent years into a large specialty area, being recognized as its discipline. At present, paracetamol (acetaminophen) (Yaligod *et al*., 2014) and non-steroidal anti-inflammatory drugs are frequently recommended as first-line analgesic treatments for osteoarthritis and other musculoskeletal pain states (UK, 2014). While acetaminophen is one of the oldest and most used analgesics, the debate on its mechanism of action, concerns about hepatotoxicity with overdose, and other adverse effects continue (Blieden et al., 2014). Opioid analgesics are used line of treatment for moderate to severe pain leading to its overuse and predisposition to dependence even from short-term use (Butler *et al*., 2016). A survey of analgesic treatment recipients reported that in 50,869 patients analyzed with moderate to severe pain, 44% had inadequate analgesia (Milgrom *et al*., 1993; Wiesel *et al*., 1980). Of the 39,6 75 patients treated with an opioid, 28% (10,925 patients) had at least one gastrointestinal side effect requiring dose reduction or stoppage of opioids (Moskovitz *et al*., 2011). Substantial numbers of people with musculoskeletal pain use other potential sources of pain relief including complementary and alternate medicine and traditional remedies (Nahin et al., 2015; Shumer et al., 2014).

In the survey done on adults and the use of alternative therapies, it was reported that 12.1% had used herbal medicine in the previous 12 months (Eisenberg *et al*., 1998). Several herbal preparations are used to treat musculoskeletal symptoms. Some of these herbal and nutritional therapies include S-adenosylmethionine, methylsulfonylmethane, glucosamine, ginger, devil's claw, and willow bark, among others (Ernst, 2000). Few of these therapies have been subjected to clinical trials to determine their efficacy or toxicities. Herbs contain complex mixtures of constituents that may require specific ratios of ingredients to be effective. Rhizomes of *Curcuma longa* and gum-resin of *Boswellia serrata* are responsible for a wide range of biological activities and have been used in ancient traditional medicines against arthritic pain and other inflammatory and chronic degenerative diseases (Nelson *et al*., 2017; Singh & Atal, 1986). In an open-label study done on 88 subjects, Rudrappa *et al*., 2020 reported that high dissolution oil formulation containing turmeric and boswellia reduced the discomfort caused in the musculoskeletal joint during exercise significantly better than acetaminophen (Rudrappa *et al*., 2020).

The present study intended to evaluate the effect of a *Curcuma longa* and *Boswellia serrata* (CBF) formulation in healthy adults presenting with acute musculoskeletal pain of head and neck, upper and lower limbs, trunk, and general body. Moreover, the intensity of pain on each part was studied at rest, on the movement of the affected part, and on the application of pressure.

METHODS

This randomized, placebo-controlled, multicentre study was conducted in India at 6 geographically different sites. The study protocol was evaluated and approved by the respective institutional ethics committees of the study centers. The study was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines and was registered in the clinical trial registry of India (CTRI/2020/06/025601). The study employed a parallel interventional model with an allocation (CBF: placebo) ratio of 1:1 per site and a male to female ratio of 1:1 for the whole study. The study enrolled a total of 232 subjects from August to October 2020.

The study population came from the participants visiting the outpatient department of hospitals of the respective sites. The participants were provided with the information sheet and explained in detail all the aspects of the study by the principal/co-investigator. Those participants who gave voluntary informed consent were taken for screening. The study included 232 healthy participants of both genders aged 18-65 with acute exercise-induced musculoskeletal pain presenting at the site within 24 hours of occurrence. The subjects were asked the time of occurrence of pain, location of pain, and specific history of previous occurrences of similar pain. The intensity of pain was measured using a numerical rating scale (NRS) and subjects greater than or equal to 5 are considered eligible for enrollment. The participants having a history of osteoarthritis or rheumatoid arthritis, Grade 2 & 3 sprain or strain, acute muscle spasms requiring parenteral therapy or surgery; hospital admission for management of painful acute soft tissue injury of the upper or lower extremity, including acute injuries of ligaments, tendons, or were excluded.

The test product was a formulation of *Curcuma longa* and *Boswellia serrata* in black sesame seed oil made using speed technology. The dosage was 500mg x 2 size '0' vegetarian reddish-brown colored soft gel (Rhuleave-K, Arjuna Natural Pvt. Ltd, Kerala, India) as a single dose. The test product is standardized to contain 26.6% curcuminoids and 1% acetyl keto-boswellic acid. The matching placebo dosage was 500 mg x 2 size '0' vegetarian reddish-brown colored soft gel as a single dose.

An independent statistician not involved with the study site prepared master randomization lists for each site. The random sequence was generated with the software WinPepi version 11.65 (2016) using balanced stratified randomization. The allocation was concealed using opaque bottles and alphanumeric codes. The interventional products and the allocation-concealed random lists were under the restricted access of the pharmacist to prevent selection bias. The pharmacist dispensed the interventional products serially and kept the investigational product (IP) dispensing and accountability logs. This study was a double-blinded placebo-controlled study. The investigators and the participants were blinded using a placebo with similar size, color, packaging, and labeling. The IPs were identified only by their allocation codes. Opaque and sealed envelopes with package inserts of the identity of each IP were kept under the custody of the pharmacist for unblinding purposes. In case of emergency or a need to know the identity of the blinded IP, the investigator would request the pharmacist to provide the envelope of the required IP and promptly inform the sponsor of the need to do so.

The study focused on analyzing the data segregated based on the location of musculoskeletal pain reported by the subjects upon entry into the study. The location of pain was segregated into 5 categories.

- Head and neck: Neck
- Trunk: Back, Pelvic
- Upper limb: Shoulder, Hand, Arm, Forearm, Clavicle, Wrist, Elbow
- Lower limb: Hip and Thigh Muscles, Leg, Foot Muscles, Knees, Ankle
- General musculoskeletal pain

The primary objective of the study was to determine the efficacy of the test product by measuring the pain intensity. The pain intensity was measured by a numerical pain rating scale (NRS) (Johnson, 2016). The NRS is an 11-point scale in which 0 represents 'no pain' and 10 represents the worst pain possible. The rating score of 1-4 is considered as mild, 5-6 is moderate and 7-10 is severe pain (Fishman, 2012). The participants were asked to rate their pain intensity as a number from 0 to 10. The NRS was taken post-dose every 30 minutes up to 6 hours. when the subject was seated at rest, on the movement of the affected part, and on applying pressure to the affected part. Those participants who had a 5 or above score during the screening were enrolled in the study. The total duration of the study was 6 hours. The sum of pain intensity difference was calculated for 6 hours (SPID6) from baseline. The onset of analgesia was measured in hours and minutes and the seconds were rounded to the nearest minute.

The onset of analgesia was measured using the two stop-watch method. Two stop-watches are started immediately after the subject consumes the test products. When the subject perceives pain relief, one of the stopwatches was stopped and the time was recorded as a time to perceptible pain relief (PPR). The second stopwatch was stopped when the subject reports complete pain relief and was recorded as meaningful pain relief (MPR). Median Survival Time and Restricted Mean Survival Time (RMST) analysis of onset to analgesia were done. The restricted mean survival time (symptom resolution time) is a measure of treatment effect wherein the average time of a subject who continues in pain from time 0 to cessation of pain at time t is taken. The RMST difference measures the effect of treatment on the restricted symptom resolution time at t. The RMST value can also be an absolute measure of symptom resolution time, this dual mode of presentation as both an absolute and a relative measure is an added advantage of this measure (Royston & Parmar, 2013).

RESULTS

In the study, 235 participants were screened, and 232 participants were enrolled. The study flow diagram is presented in Figure 1. The demographics of subjects categorized into 5 groups are given in Table 1. The most common location of musculoskeletal pain was trunk and lower limb followed by upper limb. The location-wise distribution of pain was statistically not different in both *Curcuma longa* and *Boswellia serrata* formulation (CBF) and placebo groups (chi-square =1.49, p=0.8277) (Table 2). There was no significant difference in the distribution of pain gender-wise and location-wise in both groups (Table 3).

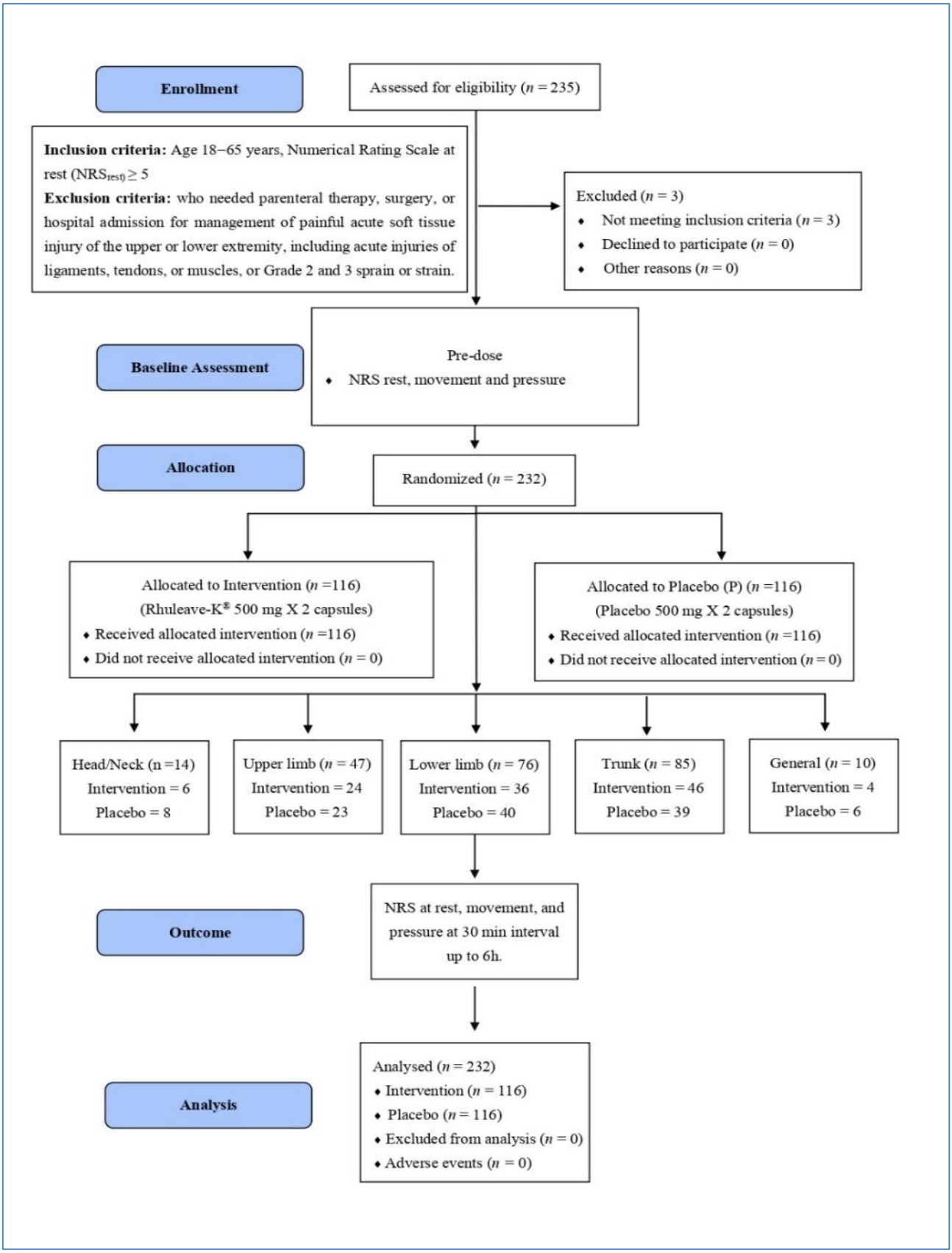


Fig-1: Participants flow diagram

Table-1: Demographics of Participants with Acute Musculoskeletal Pain

Location of pain	CBF				Placebo			
	N	Mean Age in years	Mean height in cm	Mean Weight in Kg	N	Mean Age in years	Mean height in cm	Mean Weight in Kg
Head and neck	6	27.83	164.00	61.67	8	37.50	162.17	64.17
Upper limb	24	33.83	164.46	64.46	23	32.00	165.00	65.30
Trunk	46	40.89	168.46	72.65	39	38.21	168.36	72.69
Lower limb	36	35.89	166.44	70.86	40	40.55	165.80	69.63
General	4	40.25	170.75	72.00	6	37.50	162.17	64.17

Table-2: Categorization of subjects based the on distribution of pain

Location of pain	CBF	Placebo	Total
	N =116	N = 116	N=232
	n (%)	n (%)	n (%)
Head and neck	6 (5.2)	8 (6.9)	14 (6)
Upper limb	24 (20.7)	23 (19.8)	47 (20.3)
Trunk	46 (39.7)	39 (33.6)	85 (36.6)
Lower limb	36 (31)	40 (34.5)	76 (32.8)
General	4 (3.4)	6 (5.2)	10 (4.3)
Chi-Square	1.493988		
DF	4		
P	0.827706		
Effect size(W)	0.080247		

Table-3: Gender wise categorization of subjects based on the distribution of pain

Location of pain	CBF (N=116)			Placebo (N=116)			Combined Total (N=232)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
	n	n	n	n	n	n	n	n	n
Head and neck	4	2	6	6	2	8	10	4	14
Upper limb	14	10	24	11	12	23	25	22	47
Trunk	19	27	46	19	20	39)	38	47	85
Lower limb	18	18	36	19	21	40	37	39	76
General	3	1	4	3	3	6	6	4	10
Chi-Square	3.724638			2.169119			4.168491		
DF	p-value			4			4		
p value	0.444553			0.704687			0.383683		
Effect size(W)	0.17919			0.136745			0.134043		

The pain intensity decreased in the head and neck, lower limb, trunk, upper limb, and general pain category were highly significant ($p<0.05$) in the treatment group in the three modalities of rest, movement and pressure. In the generalized musculoskeletal pain (n=4) there was a near significant decrease ($p=0.065$) in all the three modalities of NRS measurement (Table 4).

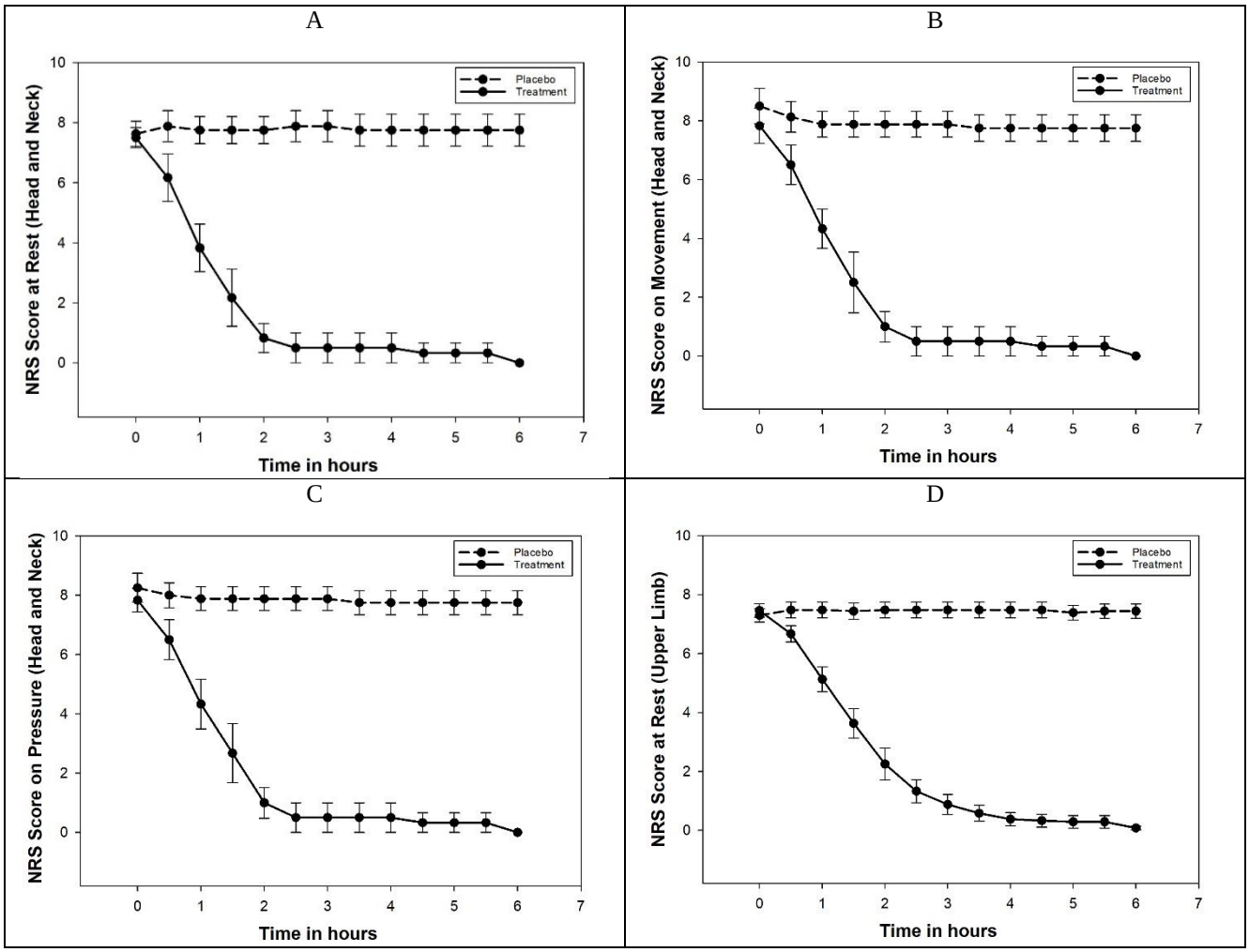
Table-4: Analysis of Pain Intensity Score using Numerical Rating Scale in CBF Group

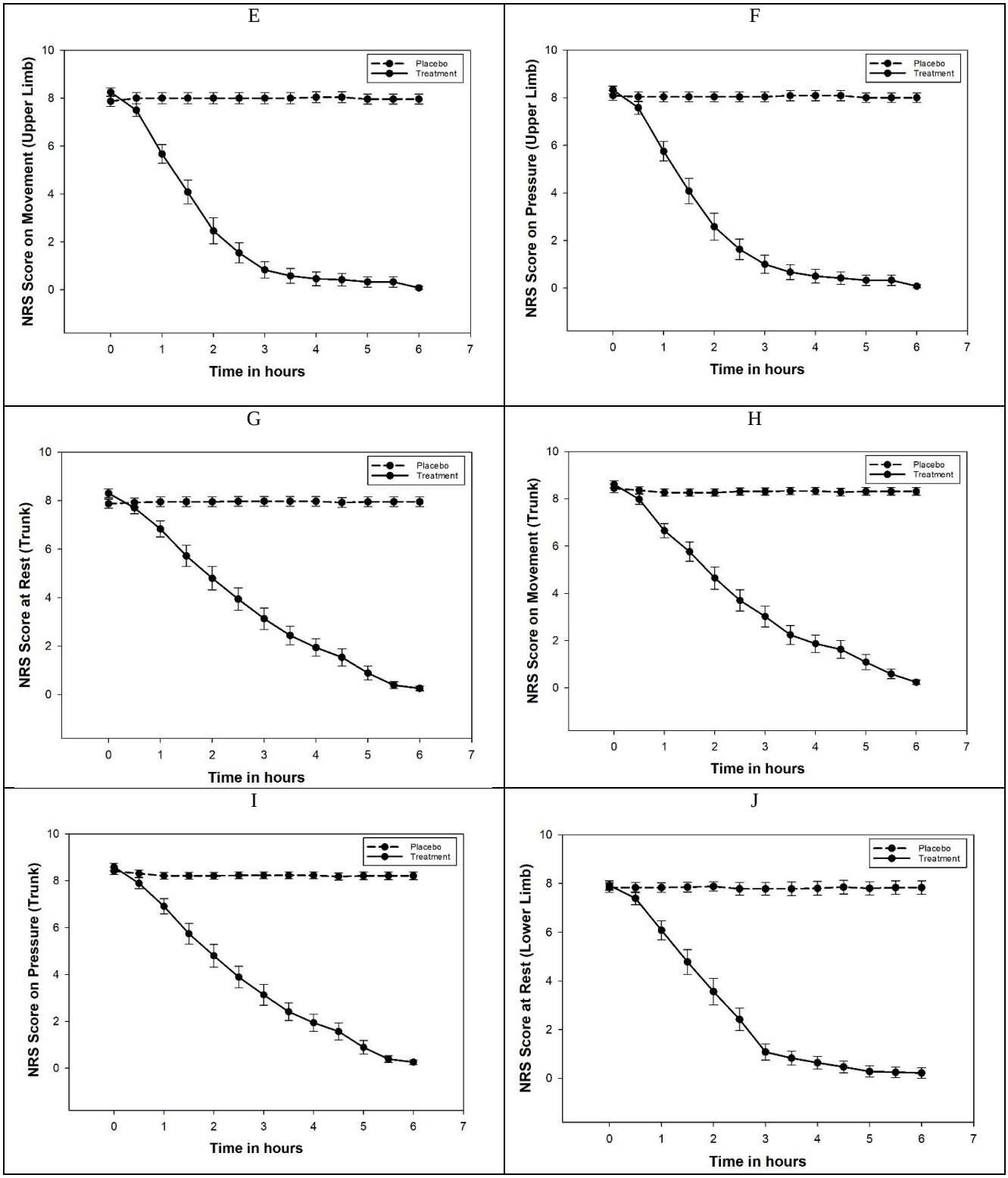
Location of pain and domain	Number	Base	End	Mean difference	p	▼~▲	% Change
		Mean ± SEM	Mean ± SEM	Mean diff ± SE			
Head and neck							
Pain at rest	6	7.50 ± 0.34	0.00	7.50 ± 0.34	0.0235	▼***	▼100.00
Pain during movement	6	7.83 ± 0.60	0.00	7.83 ± 0.60	0.0273	▼***	▼100.00
Pain on pressure	6	7.83 ± 0.40	0.00	7.83 ± 0.40	0.0256	▼***	▼100.00
Upper limb							
Pain at rest	24	7.46 ± 0.23	0.08 ± 0.06	7.38 ± 0.22	<0.001	▼***	▼98.88
Pain during movement	24	8.25 ± 0.18	0.08 ± 0.06	8.17 ± 0.19	<0.001	▼***	▼98.99
Pain on pressure	24	8.33 ± 0.16	0.08 ± 0.06	8.25 ± 0.16	<0.001	▼***	▼99.00
Trunk							
Pain at rest	46	8.30 ± 0.18	0.26 ± 0.10	8.04 ± 0.19	<0.001	▼***	▼96.86

Pain during movement	46	8.61 ± 0.15	0.24 ± 0.09	8.37 ± 0.17	<0.001	▼***	▼97.22
Pain on pressure	46	8.59 ± 0.16	0.26 ± 0.10	8.33 ± 0.19	<0.001	▼***	▼96.96
Lower limb							
Pain at rest	36	7.92 ± 0.19	0.22 ± 0.22	7.69 ± 0.27	<0.001	▼***	▼97.19
Pain during movement	36	8.31 ± 0.17	0.28 ± 0.23	8.03 ± 0.26	<0.001	▼***	▼96.66
Pain on pressure	36	8.39 ± 0.19	0.22 ± 0.22	8.17 ± 0.25	<0.001	▼***	▼97.35
General							
Pain at rest	4	8.25 ± 0.75	0.00	8.25 ± 0.75	0.0656	▼**	▼100.00
Pain during movement	4	9.00 ± 0.41	0.00	9.00 ± 0.41	0.0656	▼**	▼100.00
Pain on pressure	4	8.75 ± 0.25	0.25 ± 0.25	8.50 ± 0.29	0.0633	▼**	▼97.14

*** means p <0.05
** Near significant(0.05<p<0.09)
▲ increase
▼decrease
~ no difference
n.s: Non-Significant

In the placebo group there was no significant decrease in any of the 5 categories of pain location (Table 5). Figure 2 represents the comparison of the numerical rating score at five major locations of pain in the three modalities of rest, movement, and pressure at every 30 minutes from baseline to 6 hours in CBF and placebo groups.




E
NRS Score on Movement (Upper Limb)
Placebo
Treatment
Time in hours
F
NRS Score on Pressure (Upper Limb)
Placebo
Treatment
Time in hours
G
NRS Score at Rest (Trunk)
Placebo
Treatment
Time in hours
H
NRS Score on Movement (Trunk)
Placebo
Treatment
Time in hours
I
NRS Score on Pressure (Trunk)
Placebo
Treatment
Time in hours
J
NRS Score at Rest (Lower Limb)
Placebo
Treatment
Time in hours

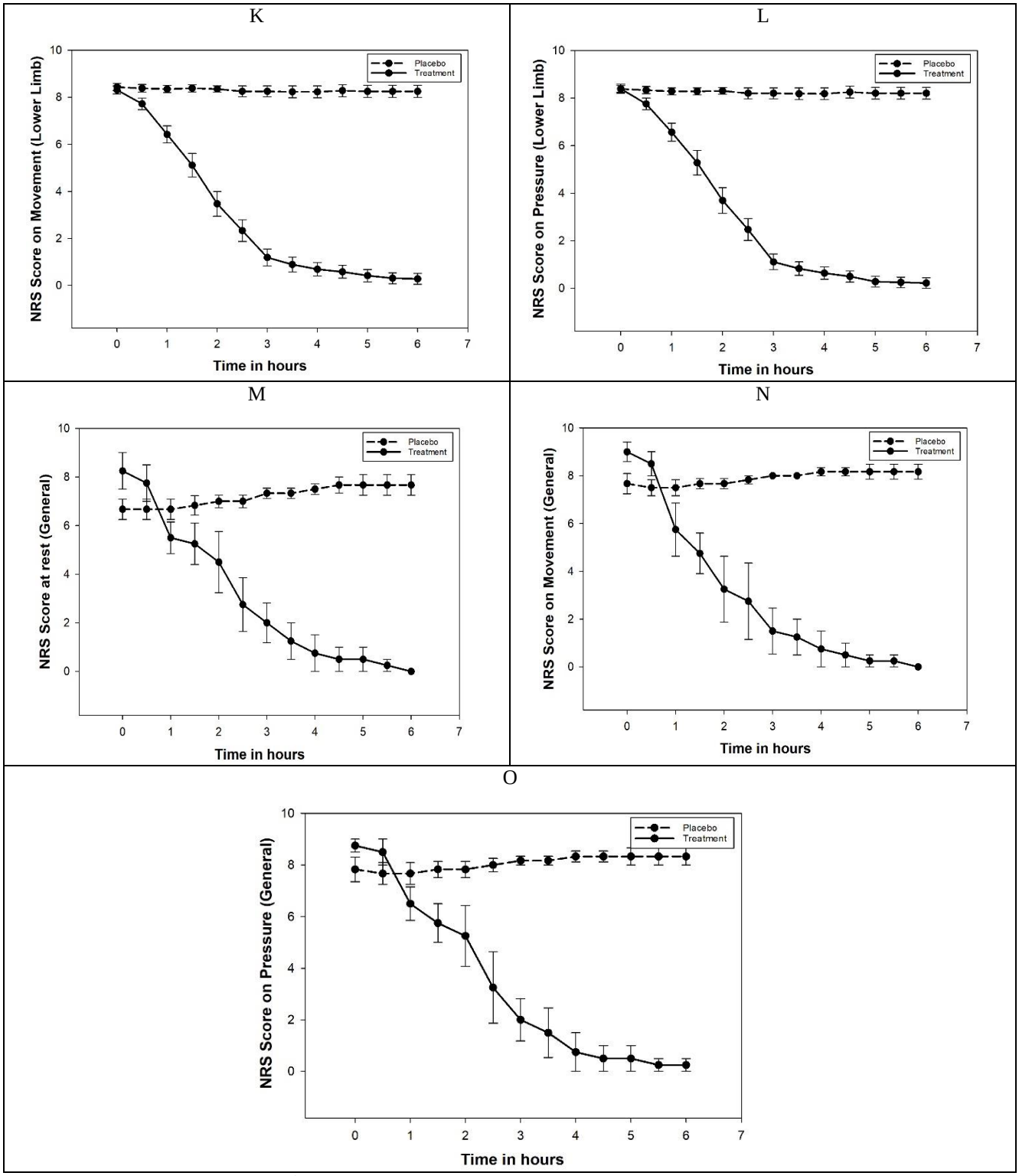


Fig-2: Numerical Rating Scale – Pain for 6 hours (A) Head and Neck – NRS at Rest (B) Head and Neck – NRS on Movement (C) Head and Neck – NRS on Pressure (D) Upper limb - NRS at Rest (E) Upper limb - NRS on Movement (F) Upper limb - NRS on Pressure (G) Trunk - NRS at Rest (H) Trunk - NRS on Movement (I) Trunk - NRS on Pressure (J) Lower limb - NRS at Rest (K) Lower limb - NRS on Movement (L) Lower limb - NRS on Pressure (M) General - NRS at Rest (N) General - NRS on Movement (O) General - NRS on Pressure

Table-5: Analysis of Pain Intensity Score using Numerical Rating Scale in Placebo Group

Location of pain and domain	Number	Base	End	Mean Difference	p	▼~▲	% Change
		Mean ± SEM	Mean ± SEM	Mean diff ± SE			
Head and neck							
Pain at rest	8	7.63 ± 0.42	7.75 ± 0.53	-0.13 ± 0.23	0.564	▲$^{n.s}$	▲-1.64
Pain during movement	8	8.50 ± 0.60	7.75 ± 0.45	0.75 ± 0.37	0.047	▼***	▼8.82
Pain on pressure	8	8.25 ± 0.49	7.75 ± 0.41	0.50 ± 0.38	0.158	▼$^{n.s}$	▼6.06
Upper limb							
Pain at rest	23	7.30 ± 0.23	7.43 ± 0.24	-0.13 ± 0.07	0.083	▲**	▲-1.79
Pain during movement	23	7.87 ± 0.21	7.96 ± 0.21	-0.09 ± 0.09	0.317	▲$^{n.s}$	▲-1.10
Pain on pressure	23	8.09 ± 0.21	8.00 ± 0.20	0.09 ± 0.11	0.414	▼$^{n.s}$	▼1.08
Trunk							
Pain at rest	39	7.87 ± 0.19	7.95 ± 0.20	-0.08 ± 0.08	0.115	▲$^{n.s}$	▲-0.98
Pain during movement	39	8.44 ± 0.18	8.31 ± 0.16	0.128 ± 0.12	0.411	▼$^{n.s}$	▼1.52
Pain on pressure	39	8.41 ± 0.15	8.21 ± 0.16	0.205± 0.11	0.066	▼**	▼2.44
Lower limb							
Pain at rest	40	7.83 ± 0.19	7.83 ± 0.27	0.00 ± 0.27	0.268	~	▼0.00
Pain during movement	40	8.43 ± 0.15	8.25 ± 0.26	0.18 ± 0.27	0.883	▼$^{n.s}$	▼2.08
Pain on pressure	40	8.38 ± 0.14	8.20 ± 0.25	0.18 ± 0.24	0.943	▼$^{n.s}$	▼2.09
General							
Pain at rest	6	6.67 ± 0.42	7.67 ± 0.42	-1.00 ± 0.82	0.425	▲$^{n.s}$	▲-15.00
Pain during movement	6	7.67 ± 0.42	8.17 ± 0.31	-0.50 ± 0.72	0.493	▲$^{n.s}$	▲-6.52
Pain on pressure	6	7.83 ± 0.48	8.33 ± 0.33	-0.50 ± 0.72	0.493	▲$^{n.s}$	▲-6.38

*** means p <0.05
▲ increase
▼decrease
~ no difference
n.s: Non-Significant

Improvement of Pain Intensity

Treatment response over 360 minutes was summarised as a sum of pain intensity difference (SPID6) and analysis was carried out. In the study, the treatment response of CBF was significantly better than the placebo (p<0.0001) at rest, on movement, and on pressure. In all the five categories of general musculoskeletal pain, head and neck, lower and upper limbs, and trunk, CBF showed a significant pain intensity decrease compared to placebo (Table 6).

Table-6: Analysis of Sum of Pain Intensity Difference at 6 hours (SPID6) between CBF and Placebo groups

Location of pain and domain	Number (Placebo, CBF)	Placebo Mean ± SEM	CBF Mean ± SEM	Mean diff ± SE	p
Head and neck					
Pain at rest	8, 6	-56.25 ± 61.18	2220.00 ± 80.12	-2276.25 ± 98.87	0.002
Pain during movement	8, 6	240.53 ± 111.98	2305.00 ± 144.08	-2064.48 ± 179.46	0.002
Pain on pressure		154.50 ± 114.86	2298.10 ± 136.33	-2143.60 ± 177.51	0.001
Upper limb					
Pain at rest	23, 24	-56.09 ± 30.89	2030.00 ± 76.67	-2086.09 ± 82.66	< 0.0001
Pain during movement	23, 24	-46.02 ± 23.13	2244.03 ± 81.30	-2290.04 ± 84.53	< 0.0001
Pain on pressure	23, 24	16.02 ± 34.05	2253.00 ± 90.50	-2236.98 ± 96.70	< 0.0001
Trunk					
Pain at rest	39, 46	-29.23 ± 17.58	1802.61 ± 69.51	-1831.84 ± 71.70	< 0.0001
Pain during movement	39, 46	48.38 ± 36.48	1917.70 ± 80.57	-1869.32 ± 88.45	< 0.0001
Pain on pressure	39, 46	68.71 ± 31.61	1897.63 ± 77.05	-1828.92 ± 83.28	< 0.0001
Lower limb					
Pain at rest	40, 36	3.00 ± 67.63	2010.00 ± 68.57	-2007.00 ± 96.51	< 0.0001
Pain during movement	45, 36	50.15 ± 70.49	2109.13 ± 71.12	-2058.99 ± 100.37	< 0.0001
Pain on pressure		51.74 ± 62.23	2133.98 ± 61.10	-2082.25 ± 87.54	< 0.0001
General					
Pain at rest	6, 4	-210.00 ± 149.00	2040.00 ± 288.01	-2250.00 ± 294.16	0.010
Pain during movement	6, 4	-89.70 ± 155.13	2357.55 ± 291.11	-2447.25 ± 300.95	0.010
Pain on pressure	6, 4	-89.80 ± 155.06	2100.45 ± 161.29	-2190.25 ± 232.00	0.010

For all modalities of NRS measurement (Rest, Movement and Pressure) the standardised differences is within the limits showing that the covariate has no selection bias (Table 7). The distribution of logit propensity score approximates to normal and logit of propensity score to match samples was used (Rosenbaum & Rubin, 1985). All observed confounding variables have means with relatively small standardized differences between the treatment and control groups which is within the limits recommended by Rubin (2001) and Stuart (2010) (Figure3).

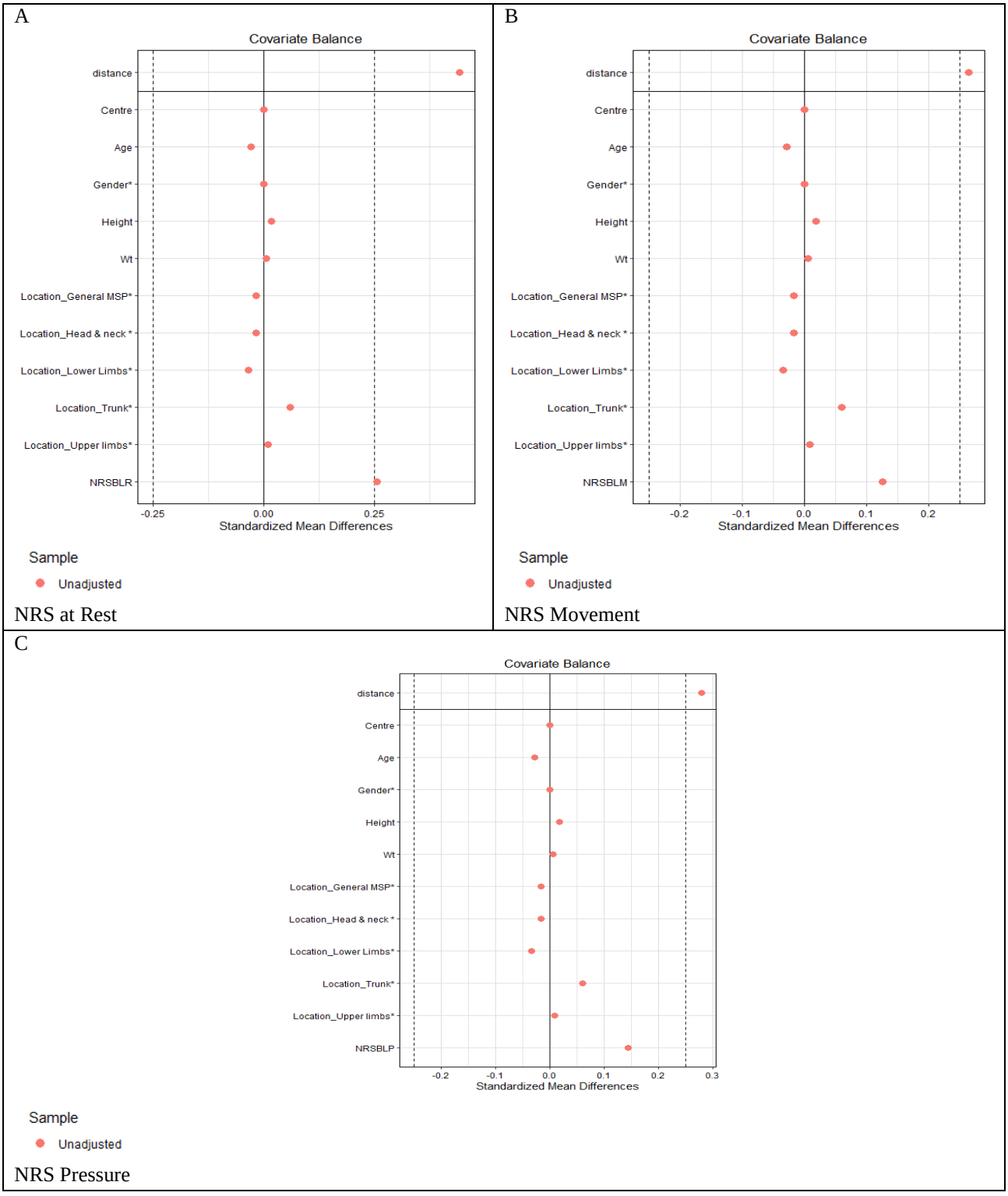


Fig-3: Covariate Balance (A) NRS at Rest (B) NRS on Movement (C) NRS on pressure

Table-7: Covariate Balance

Matched Data			Means		Std Mean Difference	Var. Ratio
			CBF	Placebo		
NRS at Rest	Distance		0.525	0.475	0.4422	1.1474
	Centre		3.5172	3.5172	0	1
	Age		37.181	37.5517	-0.0289	0.9041
	Gender		0.5	0.5	0	*
	Height		166.8534	166.6897	0.0175	1.161
	Weight		69.8103	69.75	0.0052	0.9923
	Location of pain	General	0.0345	0.0517	-0.0945	*
		Head and neck	0.0517	0.069	-0.0778	*
		Lower limb	0.3103	0.3448	-0.0745	*
		Trunk	0.3966	0.3362	0.1234	*
		Upper limb	0.2069	0.1983	0.0213	*
		NRS Baseline	7.9655	7.6638	0.2559	0.9875
NRS at Movement	Distance		0.5079	0.4921	0.2636	0.8309
	Centre		3.5172	3.5172	0	1
	Age		37.181	37.5517	-0.0289	0.9041
	Gender		0.5	0.5	0	*
	Height		166.8534	166.6897	0.0175	1.161
	Weight		69.8103	69.75	0.0052	0.9923
	Location of pain	General	0.0345	0.0517	-0.0945	*
		Head and neck	0.0517	0.069	-0.0778	*
		Lower limb	0.3103	0.3448	-0.0745	*
		Trunk	0.3966	0.3362	0.1234	*
		Upper limb	0.2069	0.1983	0.0213	*
		NRS Baseline	8.4138	8.2845	0.1255	0.8748
NRS at Pressure		Distance	0.5087	0.4913	0.2784	0.8205
		Centre	3.5172	3.5172	0	1
		Age	37.181	37.5517	-0.0289	0.9041
		Gender	0.5	0.5	0	*
		Height	166.8534	166.6897	0.0175	1.161
		Weight	69.8103	69.75	0.0052	0.9923
	Location of pain	General	0.0345	0.0517	-0.0945	*
		Head and neck	0.0517	0.069	-0.0778	*
		Lower limb	0.3103	0.3448	-0.0745	*
		Trunk	0.3966	0.3362	0.1234	*
		Upper limb	0.2069	0.1983	0.0213	*
		NRS Baseline	8.4397	8.2931	0.1431	1.0958

In the general pain category, CBF had a perceptible pain relief as early as 75 minutes and a complete pain relief by 240 minutes. Subjects in the head and neck category had the fastest PPR at 40 minutes and an MPR of 160 min. Lower limb category was close by 74.2 min in PPR and 175.8 min in MPR. The upper limb and trunk category has a close PPR at 52.3 and 75.6 and the MPR was 167.9 and 216.1 min respectively (Figure 4). Table 8 represents the median survival time, restricted mean survival time of onset to analgesia.

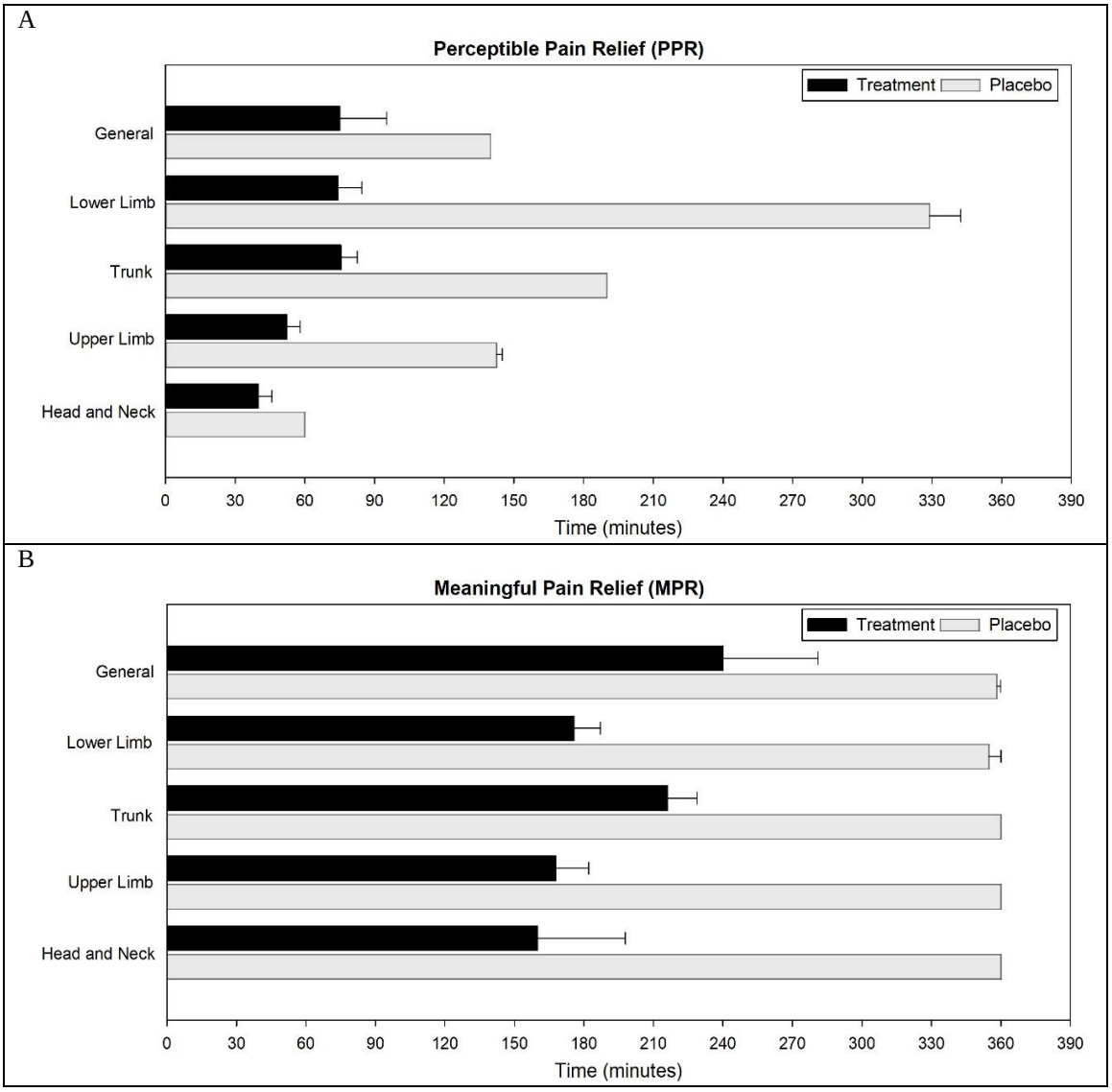


Fig-4: Comparison of Mean Time to achieve (A) perceptible pain relief (PPR) and (B) meaningful pain relief (MPR) in treatment (CBF) and placebo groups

Table-8: Median Survival Time, Restricted Mean Survival Time analysis of onset to analgesia using the double-stopwatch method.

Location of pain	Parameter	Perceptible Pain Relief		Meaningful Pain Relief	
		Treatment	Placebo	Treatment	Placebo
Head and neck	Symptom resolved (n of N)	6 of 6	2 of 8	6 of 6	0 of 8
	Median Survival Time	30	NE	120	NE
	Restricted Mean Survival Time (RMST ± SE)	40 ± 5.77	60	160 ± 37.86	360
	RMST Difference ± SE (P-T) (p-value)	20 ± 5.77 (p = 0.0005)		200 ± 37.86 (p < 0.0001)	
	RMST Ratio (P/T) ± SE	1.5 ± 0.14 (p = 0.005)		2.25 ± 0.24 (p = 0.001)	
Upper limb	Symptom resolved (n of N)	24 of 24	2 of 23	23 of 24	0 of 23
	Median Survival Time	30	NE	150	NE
	Restricted Mean Survival Time (RMST ± SE)	52.3 ± 5.75	142.6 ± 2.34	167.9 ± 14.18	360
	RMST Difference ± SE (P-T) (p-value)	90.30 ± 6.21 (p<0.0001)		192.1 ± 14.18 (p<0.0001)	
	RMST Ratio (P/T) ± SE	2.73 ± 0.11 (p<0.0001)		2.14 ± 0.08 (p<0.0001)	
Trunk	Symptom resolved (n of N)	46 of 46	1 of 39	43 of 46	0 of 39
	Median Survival Time	60	NE	200	NE
	Restricted Mean Survival Time (RMST ±	75.6 ± 6.89	190	216.1 ±	360

	SE)			12.78	
	RMST Difference ± SE (P-T) (p-value)	114.4 ± 6.89 (p<0.0001)		143.9 ± 12.78 (p<0.0001)	
	RMST Ratio (P/T) ± SE	2.51 ± 0.09 (p<0.0001)		1.67 ± 0.06 (p<0.0001)	
Lower limb	Symptom resolved (n of N)	35 of 36	6 of 40	35 of 36	1 of 40
	Median Survival Time	60	NE	150	NE
	Restricted Mean Survival Time (RMST ± SE)	74.2 ± 10.32	328.9 ± 13.45	175.8 ± 11.39	354.8 ± 5.18
	RMST Difference ± SE (P-T) (p-value)	254.7 ± 16.96 (p<0.0001)		178.9 ± 12.51 (p<0.0001)	
	RMST Ratio (P/T) ± SE	4.43 ± 0.145 (p<0.0001)		2.02 ± 0.07 (p<0.0001)	
General	Symptom resolved (n of N)	4 of 4	1 of 6	4 of 4	1 of 6
	Median Survival Time	60	NE	180	NE
	Restricted Mean Survival Time (RMST ± SE)	75 ± 20.16	140	240 ± 41.08	358.3 ± 1.52
	RMST Difference ± SE (P-T) (p-value)	65 ± 20.16 (p = 0.001)		118.3 ± 41.11 (p = 0.004)	
	RMST Ratio (P/T) ± SE	1.87 ± 0.27 (p = 0.020)		1.49 ± 0.17 (p = 0.019)	
n= no. of participants whose symptoms got resolved N= Total no. of participants in the group					

DISCUSSION

The graduated approach for the management of pain depends upon the severity of pain *(Airaksinen et al.*, 2006). The World Health Organization recommends three steps corresponding to pain levels on a numerical rating scale (NRS). The pain was categorized on a scale of 0 to 10 where in the scores from 0 to 3 would be mild, 4 to 6 moderate and 7 to 10 severe pain. The graduated approach considers simple analgesics and NSAIDs on the first level and opioids on the highest level (Gould III, 2006). This study excluded subjects that had a pain intensity of less than 5 on the NRS scale. In this study participants enrolled reported a pain score of 7-9 on the baseline NRS scale. These participants, who reported a complete pain relief at the end of the study according to WHO were eligible for a higher level of analgesic like morphine.

This study had a male-to-female ratio of 1:1 which avoids a bias based on gender. The study staff made sure that no leading questions were asked to elicit a response, ruling out response bias. A systematic literature review on studies comparing NRS, VRS, and VAS found that NRS had better compliance than VAS and VRS in 15 of 19 studies. NRS had better responsiveness, ease of use, and applicability than VAS/VRS (Hjermstad *et al.*, 2011).

In the study, CBF showed fast pain recovery compared to placebo. The pain relief started as early as 40 minutes and complete pain relief was achieved as early as 160 min. CBF which is a formulation made of turmeric and boswellia acts through multiple pain pathways that are synergistically active to control pain. The roots of turmeric contain active constituents called curcuminoids. The exact mechanism for reducing pain by curcumin is unknown, however, it is thought that curcumin can inhibit transient receptor potential vanilloid (TRPV1)-mediated pain. A pain-relieving activity was reported for AKBA which is the active component of Boswellia serrata which produced a dose-dependent and significant analgesic effect in several different experimental models of nociception and potentiated the analgesic effect of selective cyclooxygenase inhibitors such as nimesulide [35] (Bishnoi *et al.*, 2006).

There was no significant difference between the number of subjects in the placebo and CBF group with respect to the location of pain viz: head and neck, upper and lower limbs, trunk, and general musculoskeletal pain. Most of the subjects (37%) reported exercise-induced acute pain in the trunk region. The trunk contains the chest, pelvis, abdomen, and back. While mild to moderate exercising can be beneficial to these parts, overexertion leads to muscle fatigue, overstretching of muscles, and cause inflammation. Besides lifting items incorrectly, sitting with poor posture, standing in awkward postures, sudden body movements like twisting, bending, pushing, and pulling are all common reasons for musculoskeletal pain in these regions. Overexertion pain feels sharp or achy and is more of a tingling, burning, pinching, or throbbing sensation. The leukotrienes that mediate inflammation are generated from 5-lipoxygenase (5-LO). One study reports that exercise-induced stress increases transcription of genes encoding 5-LO and 5-LO-activating protein (FLAP), thereby increasing production of LTB_4 and LTC_4 in plasma after the exercise (Hilberg *et al.*, 2005). Acetyl-11-keto-β-boswellic acid (AKBA), one of the most effective of the four boswellic acids in Boswellia serrata, inhibits 5-LO.

In our study at the baseline, subjects rated pain when they are comfortably seated as lower compared to when they were asked to move the affected part. A higher pain response was also elicited when pressure was applied to the affected part than pain reported at rest. When acute pain is experienced, our body's natural response is to tense up and limit movement. At the end of the study, the CBF group showed more range of

movement but the placebo group had little to no change in the movement of the affected part.

In this study, 21% subjects reported upper limb pain and 33% reported lower limb pain. The muscle has nociceptors that transduce pain signals to the brain. These nociceptors get sensitized by endogenous mediators such as bradykinin (BK) and PGE2. This is one of the reasons why people with muscle lesions suffer from tenderness to pressure or pain on movement or exercise of the muscle. Prostaglandins are synthesized from arachidonic acid by the action of cyclooxygenase and BK is synthesized from plasma proteins by the enzyme kallikrein. This is why many types of muscle pain respond well to the administration of non-steroidal anti-inflammatory drugs (NSAID) (Mense, 2008).

One of the problems with relying on NSAIDs for continued use is that they are known to disrupt glycosaminoglycan synthesis and accelerate articular damage. Boswellic acids have been shown to significantly reduce glycosaminoglycan degradation (Brandt & Palmoski, 1984; Dekel *et al*., 1980). Another study examining the effect of boswellia and ketoprofen on glycosaminoglycan metabolism showed boswellic acids reduced glycosaminoglycan degradation while ketoprofen caused a reduction in total tissue glycosaminoglycan content (Reddy *et al*., 1989).

Curcumin is thought to act as an anti-inflammatory agent through inhibition of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). The improvement of the range of movement of the upper and lower extremities in the CBF group could be explained based on this mechanism when compared to a placebo that had little to no change in the pain on movement and pressure.

In all the five locations of pain and three modalities of rest, movement and pressure, head and neck, upper and lower limbs, and trunk, CBF showed a significant pain intensity decrease compared to placebo. CBF is safe and effective for acute pain irrespective of the location of the pain.

This study has significant generalizability as the variance of treated and untreated groups matches the propensity scores (Figure 3). Propensity scores reduce selection bias by matching groups based on covariates. The treated-to-control variance ratios between the two groups are between 0.8 and 1.2 for all variables in the matched observations and for all modalities of NRS measurement (rest, movement, pressure) which is within the recommended range of 0.5 to 2 (Rubin, 2001; Stuart, 2010). Propensity score matching (PSM) tries to reduce the confounding variable bias that occurs in the estimate of treatment effect obtained from common comparison of groups that received treatment and those that did not (Rosenbaum & Rubin, 1983).

CONCLUSION

In conclusion, CBF was effective in reducing the pain at locations of head and neck, upper limb, lower limb, trunk, and general body. In the five major locations of pain, the CBF group had above 96% reduction in pain intensity in all the modalities of rest, movement, and pressure whereas the placebo group showed negligent change. The study findings suggest that the efficacy of CBF may be actively considered as a fast relief for acute pain irrespective of the location of the pain. Importantly, CBF could potentially be a safe alternative to analgesics commonly recommended for acute pain such as NSAIDs.

ACKNOWLEDGMENTS

The authors acknowledge Arjuna Natural Pvt Ltd., Kerala, India for providing the test product (Rhuleave-K) and placebo capsules.

REFERENCE

- Airaksinen, O., Brox, J. I., Cedraschi, C., Hildebrandt, J., Klaber-Moffett, J., Kovacs, F., Mannion, A. F., Reis, S., Staal, J. B., Ursin, H., & Zanoli, G. (2006). Chapter 4 European guidelines for the management of chronic nonspecific low back pain. *European Spine Journal*, *15*(S2), s192–s300. https://doi.org/10.1007/s00586-006-1072-1
- Anderson, J. A. (1971). Rheumatism in industry: a review. *British Journal of Industrial Medicine*, *28*(2), 103–121. https://doi.org/10.1136/oem.28.2.103
- Bishnoi, M., Patil, C. S., Kumar, A., & Kulkarni, S. K. (2006). Potentiation of antinociceptive effect of NSAIDs by a specific lipooxygenase inhibitor, acetyl 11-keto-beta boswellic acid. *Indian Journal of Experimental Biology*, *44*(2), 128–132. http://www.ncbi.nlm.nih.gov/pubmed/16480179
- Blieden, M., Paramore, L. C., Shah, D., & Ben-Joseph, R. (2014). A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. *Expert Review of Clinical Pharmacology*, *7*(3), 341–348.
- Brandt, K. D., & Palmoski, M. J. (1984). Effects of Salicylates and Other Nonsteroidal Anti-inflammatory Drugs on Articular Cartilage. *American Journal of Medicine*, *77*(1), 65–69. https://doi.org/10.1016/S0002-9343(84)80021-2
- Butler, M. M., Ancona, R. M., Beauchamp, G. A., Yamin, C. K., Winstanley, E. L., Hart, K. W., Ruffner, A. H., Ryan, S. W., Ryan, R. J., & Lindsell, C. J. (2016). Emergency department prescription opioids as an initial exposure preceding addiction. *Annals of Emergency Medicine*, *68*(2), 202–208.
- Cimmino, M. A., Ferrone, C., & Cutolo, M. (2011).

Epidemiology of chronic musculoskeletal pain. *Best Practice & Research Clinical Rheumatology*, *25*(2), 173–183.

- Cypress, B. K. (1983). Characteristics of physician visits for back symptoms: A national perspective. *American Journal of Public Health*, *73*(4), 389–395. https://doi.org/10.2105/AJPH.73.4.389
- Dekel, S., Falconer, J., & Francis, M. J. 0. (1980). The effect of anti-inflammatory drugs on glycosaminoglycan sulphation in pig cartilage. *Prostaglandines and Medicine*, *4*(3), 133–140. https://doi.org/10.1016/0161-4630(80)90074-9
- Dillane, J. B., Fry, J., & Kalton, G. (1966). Acute Back Syndrome—A Study from General Practice. *British Medical Journal*, *2*(5505), 82–84. https://doi.org/10.1136/bmj.2.5505.82
- Eisenberg, D. M., Davis, R. B., Ettner, S. L., Appel, S., Wilkey, S., Van Rompay, M., & Kessler, R. C. (1998). Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. *Journal of the American Medical Association*, *280*(18), 1569–1575. https://doi.org/10.1001/jama.280.18.1569
- Ernst, E. (2000). Complementary and alternative medicine in rheumatology. *Best Practice and Research: Clinical Rheumatology*, *14*(4), 731–749. https://doi.org/10.1053/berh.2000.0110
- Fishman, S. M. (2012). *Bonica's management of pain*. Lippincott Williams & Wilkins.
- Frymoyer, J. W., Pope, M. H., Costanza, M. C., Rosen, J. C., Goggin, J. E., & Wilder, D. G. (1980). Epidemiologic studies of low-back pain. *Spine*, *5*(5), 419–423.
- Gould III, H. J. (2006). *Understanding pain: What it is, why it happens, and how it's managed*. Demos Medical Publishing.
- Hilberg, T., Deigner, H., Möller, E., Claus, R. A., Ruryk, A., Gläser, D., Landre, J. B. P., Brunkhorst, F. M., Reinhart, K., Gabriel, H. H. W., & Russwurm, S. (2005). Transcription in response to physical stress—clues to the molecular mechanisms of exercise-induced asthma. *The FASEB Journal*, *19*(11), 1492–1494. https://doi.org/10.1096/fj.04-3063fje
- Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., Fainsinger, R., Aass, N., & Kaasa, S. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management*, *41*(6), 1073–1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016
- Johnson, J. R. (2016). *PhUSE 2016 Standard Methods for Analysis and Reporting of VAS or NRS Derived Pain Relief Response Scores*. https://www.lexjansen.com/phuse/2016/sp/SP01.pdf
- Mense, S. (2008). Muscle pain: mechanisms and clinical significance. *Deutsches Ärzteblatt International*, *105*(12), 214.
- Milgrom, C., Finestone, A., Lev, B., Wiener, M., & Floman, Y. (1993). Overexertional lumbar and thoracic back pain among recruits: a prospective study of risk factors and treatment regimens. *Journal of Spinal Disorders*, *6*(3), 187–193.
- Moskovitz, B. L., Benson, C. J., Patel, A. A., Chow, W., Mody, S. H., McCarberg, B. H., & Kim, M. S. (2011). Analgesic treatment for moderate-to-severe acute pain in the United States: patients' perspectives in the Physicians Partnering Against Pain (P3) survey. *Journal of Opioid Management*, *7*(4), 277–286.
- Nahin, R. L., Stussman, B. J., & Herman, P. M. (2015). Out-of-pocket expenditures on complementary health approaches associated with painful health conditions in a nationally representative adult sample. *The Journal of Pain*, *16*(11), 1147–1162.
- Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The Essential Medicinal Chemistry of Curcumin. *Journal of Medicinal Chemistry*, *60*(5), 1620–1637. https://doi.org/10.1021/acs.jmedchem.6b00975
- Newell, R. L. M., & Turner, J. G. (1985). Orthopaedic Disorders in General Practice. In *Orthopaedic Disorders in General Practice*. Butterworth-Heinemann. https://doi.org/10.1016/c2013-0-06233-0
- Reddy, G. K., Chandrakasan, G., & Dhar, S. C. (1989). Studies on the metabolism of glycosaminoglycans under the influence of new herbal anti-inflammatory agents. *Biochemical Pharmacology*, *38*(20), 3527–3534. https://doi.org/10.1016/0006-2952(89)90124-X
- Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, *70*(1), 41–55.
- Rosenbaum, P. R., & Rubin, D. B. (1985). Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *The American Statistician*, *39*(1), 33–38.
- Royston, P., & Parmar, M. K. B. (2013). Restricted mean survival time: An alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Medical Research Methodology*, *13*(1), 1–15. https://doi.org/10.1186/1471-2288-13-152
- Rubin, D. B. (2001). Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Services and Outcomes Research Methodology*, *2*(3), 169–188.
- Rudrappa, G. H., Chakravarthi, P. T., & Benny, I. R. (2020). Efficacy of high-dissolution turmeric-sesame formulation for pain relief in adult subjects with acute musculoskeletal pain compared to acetaminophen: A randomized controlled study.

Medicine, *99*(28), e20373–e20373. https://doi.org/10.1097/MD.0000000000020373

- Shumer, G., Warber, S., Motohara, S., Yajima, A., Plegue, M., Bialko, M., Iida, T., Sano, K., Amenomori, M., & Tsuda, T. (2014). Complementary and alternative medicine use by visitors to rural Japanese family medicine clinics: results from the international complementary and alternative medicine survey. *BMC Complementary and Alternative Medicine*, *14*(1), 1–10.
- Singh, G. B., & Atal, C. K. (1986). Pharmacology of an extract of salai guggal ex-Boswellia serrata, a new non-steroidal anti-inflammatory agent. *Agents and Actions*, *18*(3–4), 407–412. https://doi.org/10.1007/BF01965005
- Stuart, E. A. (2010). Matching methods for causal inference: A review and a look forward. *Statistical Science*, *25*(1), 1–21. https://doi.org/10.1214/09-STS313
- Takala, J., Sievers, K., & Klaukka, T. (1982). Rheumatic symptoms in the middle-aged population in Southwestern Finland. *Scandinavian Journal of Rheumatology*, *11*(Suppl. 47), 15–29.
- Troup, J. D. G., Martin, J. W., & Lloyd, D. C. E. F. (1981). Back pain in industry: A prospective survey. *Spine*, *6*(1), 61–69. https://doi.org/10.1097/00007632-198101000-00014
- UK, N. C. G. C. (2014). *Osteoarthritis: care and management in adults*.
- Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., Almazroa, M. A., Alvarado, M., Anderson, H. R., Anderson, L. M., … Murray, C. J. L. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, *380*(9859), 2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2
- Westerling, D., & Jonsson, B. G. (1980). Pain from the neck-shoulder region and sick leave. *Scandinavian Journal of Social Medicine*, *8*(3), 131–136. https://doi.org/10.1177/140349488000800308
- White, A. W. (1969). Low back pain in men receiving workmen's compensation: a follow-up study. *Canadian Medical Association Journal*, *101*(2), 61–67.
- Wiesel, S. W., Cuckler, J. M., Deluca, F., Jones, F., Zeide, M. S., & Rothman, R. H. (1980). Acute low-back pain. An objective analysis of conservative therapy. *Spine*, *5*(4), 324–330.
- Yaligod, V., Raj, D. G., & Sharma, A. B. (2014). Dual release paracetamol in osteoarthritis of knee: a randomized controlled clinical trial. *Journal of Clinical and Diagnostic Research: JCDR*, *8*(11), LC11.