Evaluation of the efficacy and safety of Rumalaya gel in the management of acute and chronic inflammatory musculoskeletal disorders: An open, prospective, noncomparative, phase III clinical trial

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Medicine Update 2005; 12(10), 39-45

ABSTRACT

Recently, some clinical studies have proved the benefits of topical analgesics in the management of certain acute and chronic painful inflammatory musculoskeletal conditions**.** Topical applications of counterirritants cause a reversible, transient and mild dermal inflammation, and thereby relieve the pain beneath the site of application. Rumalaya gel is a polyherbal formulation, and this clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the symptomatic management of chronic inflammatory musculoskeletal disorders.

This study was an open, prospective, non-comparative, phase III clinical trial and was conducted as per the ethical guidelines of Declaration of Helsinki. A total of 40 patients, suffering from acute and chronic inflammatory musculoskeletal disorders, were included in the study. All the patients were advised to apply a small quantity of Rumalaya gel topically to the affected region, with gentle massage, twice daily for a period of 3 months. All the patients were assessed for the muscular pain, joint swelling, joint tenderness, early morning joint stiffness and joint pain. Response to the treatment was evaluated on a predefined symptom score scale. All the patients were assessed for local adverse reactions like irritation, burning/stinging sensation and erythema. All the patients were followed at monthly intervals, and the symptom score evaluation was done during each monthly follow-up visit. The predefined primary efficacy endpoint was a decrease in the mean symptom score. The predefined secondary safety endpoints were short- and long-term safety, and patient compliance to therapy. All the adverse events, either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Statistical analysis was done according to intent-to-treat principles.

This study observed a highly significant reduction in the mean score for muscular pain, joint swelling, joint tenderness, early morning joint stiffness and joint pain from 1st month onwards, and the similar trend continued till the end of the study. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent.

These excellent beneficial actions of Rumalaya gel might be due to the synergistic actions of its ingredients, which are well documented.

Rumalaya gel has analgesic, anti-inflammatory, antioxidant, counterirritant, glycosaminoglycan building, and cartilage healing properties. Rumalaya gel induces of vasodilation cutaneous vasculature, which produces increased blood circulation and a feeling of warmth. Consequently,

cutaneous receptors are stimulated for thermal sensations, which serve to distract deep-seated pain sensations, from the distant areas from the skin's surface. Further, Rumalaya gel therefore, it may be concluded that, Rumalaya gel is effective and safe in the symptomatic management of chronic inflammatory musculoskeletal disorders.

INTRODUCTION

Despite the associated risk of gastrointestinal,[1] renal,[2] and cardiovascular complications[3] conventionally, systemic NSAIDs are preferred for the management of chronic inflammatory musculoskeletal conditions. Recently, some clinical studies have proved the benefits of topical analgesics in the management of certain acute, and chronic, painful inflammatory musculoskeletal conditions.[4] Topical analgesics, which contain counterirritants, are especially useful in the symptomatic management of arthritis and neuropathies.[5] Topical applications of counterirritants cause a reversible, transient, and mild dermal inflammation, and thereby relieve the pain beneath the site of application. Counterirritants take advantage of the "pain paradox", (i.e. the induced pain reduces existing pain by distracting the nervous system). Furthermore, these agents offer short- and long-term safety, as the adverse events (burning, stinging, erythema), from topical applications are mainly limited to the site of application and the systemic adverse events are rare.[6]

Rumalaya gel is a polyherbal formulation recommended for the management of pain and inflammation associated with the inflammatory musculoskeletal disorders and each gram of Rumalaya gel contains extracts of *Mentha arvensis*, *Gaultheria fragrantissima*, *Pinus roxburghii*, *Cinnamomum zeylanicum*, *Cedrus deodara*, *Vitex negundo*, *Boswellia serrata* and *Zingiber officinalis*. This clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the symptomatic management of chronic inflammatory musculoskeletal disorders.

Study aim

The present clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the management of pain and inflammation associated with OA, RA, frozen shoulder, post-traumatic synovitis, and sprains.

MATERIALS AND METHODS

Study design

This study was an open, prospective, non-comparative, phase III clinical trial and was conducted at Heritage Hospital, Varanasi, India, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case record forms, regulatory clearance documents, product related information and informed consent were submitted to the “Institutional Ethics Committee” and were approved by the same.

Inclusion and exclusion criteria
A total of 40 patients suffering from acute and chronic musculoskeletal inflammatory disorders (8 patients suffering from OA, 10 patients suffering from RA, 12 patients suffering from frozen shoulder, 6 patients suffering from post-traumatic synovitis, and 4 patients suffering from sprains) were included in the study. Patients with clinically active renal, hepatic or peptic ulcer disease, history of alcohol or drug abuse, concomitant skin disease or abrasions at the application site and those patients who were using any other topical product at the application site were excluded from the study. Pregnant and lactating women were also excluded from the study.

Study procedure
All the patients were advised to apply a small quantity of Rumalaya gel topically to the affected region, with gentle massage, twice daily for a period of 3 months. All the patients were assessed for muscular pain, joint swelling, joint tenderness, early morning joint stiffness, and joint pain. Response to the treatment was evaluated on a predefined symptom score scale, from 0 to 3 (3=maximum pain and 0=no pain). All the patients were assessed for local adverse reactions like irritation, burning/stinging sensation and erythema.

Follow-up and assessment
All the patients were followed at monthly intervals, and the symptom score evaluation was done during each monthly follow-up visit.

Primary and secondary endpoints
The predefined primary efficacy endpoints were decrease in the mean symptom score for muscular pain, joint swelling, joint tenderness, early morning joint stiffness, and joint pain. The predefined secondary safety endpoints were short- and long-term safety, as assessed by the incidence of adverse events and patient compliance to therapy.

Adverse events
All the adverse events either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as *"Unrelated", "Possible",* and "*Probable*". Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment.

Statistical analysis
Statistical analysis was done according to intent-to-treat principles. Statistical analysis was done using *"Repeated Measure One-Way ANOVA",* followed by *"Post Test For Linear Trend"*. The minimum level of significance was fixed at 99% confidence limit and a 2-sided '*p*' value of <0.001 was considered highly significant.

RESULTS
There were a total of 40 patients included in the study, and 6 patients were lost to follow up. The mean age of included patients was 44.26 years (SD=14.31, SEM=2.569, lower 99% confidence interval of mean=37.19, and upper 99% confidence interval of mean=51.32).

There was a statistically significant reduction in the mean score for muscular pain (F=19.49, R^2=0.3714, p<0.0001; HS) (Table 1 and Figure 1), joint swelling (F=22.53, R^2=0.4057, p<0.0001; HS) (Table 2 and Figure 2), joint tenderness (F=178.5, R^2=0.844, p<0.0001; HS) (Table 3 and Figure 3), early morning joint stiffness (F=70.41, R^2=0.6809, p<0.0001; HS) (Table 4 and Figure 4), and joint pain (F=197.1, R^2=0.8566, p<0.0001; HS) (Table 5 and Figure 5) from 1st month onwards, and the similar trend continued till the end of the study.

Table 1: Effect of Rumalaya gel on muscular pain

Parameter	Baseline	1st month	2nd month	3rd month
Mean	0.9412	0.4706	0.2353	0.1471
Std. Deviation	1.0430	0.7481	0.4306	0.4357
Std. Error	0.1788	0.1283	0.0738	0.0747
Lower 99% CI	0.4524	0.1199	0.0335	-0.0572
Upper 99% CI	1.4300	0.8213	0.4371	0.3513
Repeated Measures ANOVA Test summary	F=19.49, R^2=0.3714, p<0.0001; HS			
Post test for linear trend summary	Slope=-0.1309, R^2=0.1463, p<0.0001; HS			

There were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions (either reported by the patients, or observed by the investigators), and the overall compliance to the treatment was excellent.

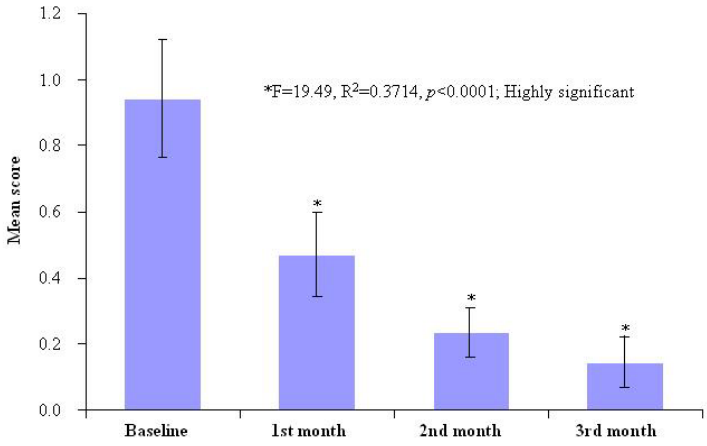


Figure 1: Effect of Rumalaya gel on muscular pain

DISCUSSION

The hypothesized mechanism of action of counterirritants and rubefacients include stimulation of the nociceptors, the "gate theory"[7,8] and the release of endogenous opioids.[9] Counterirritants inflame and irritate the skin, increase cutaneous blood flow, stimulate thermoreceptors and stimulate/depress pain receptors. By activating the nociceptors with a peripheral noxious stimulus, counterirritants inhibit the response of central neurons that transmit pain or nociceptor desensitization.[10] Some researchers suggest that a placebo effect is the most likely source of the analgesic effects acting through the power of autosuggestion. The power of autosuggestion psychologically stimulates the nervous system; alternatively the topical or subcutaneously applied analgesics could be depleting the nerve terminals of substance P, which is a nociceptive neurotransmittor.[11]

This study observed a highly significant reduction in the mean score for muscular pain, joint swelling, joint tenderness, early morning joint stiffness, and joint pain from 1st month onwards, and the similar trend continued till the end of the study. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent.

Table 2: Effect of Rumalaya gel on joint swelling

Parameter	Baseline	1st month	2nd month	3rd month
Mean	1.1470	0.7647	0.4412	0.0294
Std. Deviation	1.3290	0.9231	0.6126	0.1715
Std. Error	0.2279	0.1583	0.1051	0.0294
Lower 99% CI	0.5242	0.3320	0.1540	-0.0510
Upper 99% CI	1.7700	1.1970	0.7283	0.1098
Repeated Measures ANOVA Test summary	F==22.53, R^2=0.4057, p<0.0001; HS F=178.5, R^2=0.844, p<0.0001; HS			
Post test for linear trend summary	Slope=-0.1838, R^2=0.1872, p<0.0001; HS Slope=-0.2838, R^2=0.5593, p<0.0001; HS			

Table 3: Effect of Rumalaya gel on joint tenderness 3rd

Parameter	Baseline	1st month	2nd month	3rd month
Mean	2.5290	1.6470	1.0880	0.8235
Std. Deviation	0.6622	0.5971	0.4518	0.4586
Std. Error	0.1136	0.1024	0.0775	0.0787
Lower 99% CI	2.2190	1.3670	0.8765	0.6085
Upper 99% CI	2.8400	1.9270	1.3000	1.0390
Repeated Measures ANOVA Test summary	F=178.5, R^2=0.844, p<0.0001; HS			
Post test for linear trend summary	Slope=-0.2838, R^2=0.5593, p<0.0001; HS			

These excellent beneficial actions of Rumalaya gel might be due to the synergistic actions of its ingredients, which are well documented.

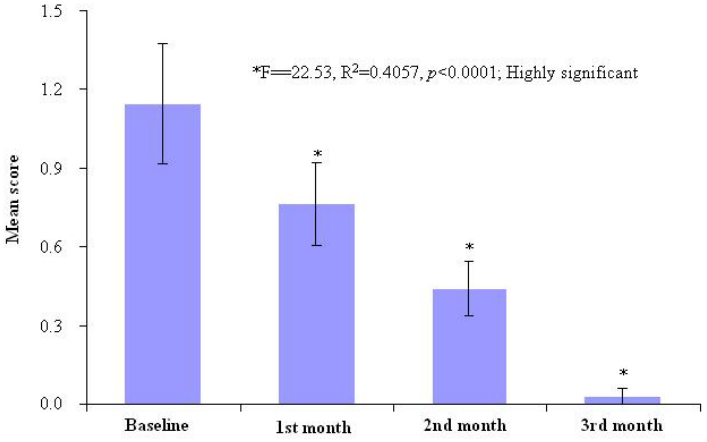


Figure 2: Effect of Rumalaya gel on joint swelling

The active constituents of *Mentha arvensis* are menthol, monooterpene and sesquiterpene hydrocarbons, which include alcohols, aldehydes, esters, ethers, ketones, phenols and oxides.[12] The principle constituent of *Gaultheria fragrantissima* is methyl salicylate. The active constituents of the *Pinus roxburghii* (turpentine) are hydrocarbons (d- and l-pinene), resin acids, camphene, fenchene, dipentene and polymeric terpenes.[12] *Cinnamomum zeylanicum* contains water extractable L-arabino-D-xylan, D-glucan, diterpenes, cinnzeylanin, cinnzeylanol and tannin (cinnamm and tannin B1). The active ingredients of *Cedrus deodara* are matairesinol, nortrachelogenin, and a dibenzylbutyrolactollignan (4,4', 9-trihydroxy-3, 3'-dimethoxy-9, 9'-epoxylignan).[13] The principal constituents of *Vitex negundo* are casticin, isoorientin, chrysophenol D, luteolin, p–hydroxybenzoic acid, D-fructose, lignans (negundins A and B), diasyringaresinol, lyoniresinol, vitrofolal E, vitrofolal[14] and a flavone (vitexicarpin).[15] The principle constituents *Boswellia serrata* are acetyl 11-keto-beta boswellic acid, 11-keto beta-boswellic acid, acetyl beta-boswellic acid and beta-boswellic acid.[16] The principal constituents of *Zingiber officinalis* are Zingiberene (a and b), and zingiberol.[17]

Rumalaya gel has analgesic, anti-inflammatory, antioxidant, counterirritant, glycosaminoglycan building and cartilage healing properties. Rumalaya gel induces vasodilation of cutaneous vasculature, which produces increased blood circulation and a feeling of warmth. Consequently,

cutaneous receptors are stimulated for thermal sensations, which serve to distract deep-seated pain sensations, from the distant areas from the skin's surface.

Mentha arvensis, Gaultheria fragrantissima,[18] *Cedrus deodara,*[19] *Vitex negundo,*[20] and *Boswellia serrata*[10] have potent analgesic activity. Rumalaya gel depresses cutaneous sensory pain receptors and acts directly to diminish or obliterate pain.

Mentha arvensis, Gaultheria fragrantissima,[21] *Pinus roxburghii,*[22] *Cedarus deodara*, *Vitex negundo*, *Boswellia serrata,*[23] and *Zingiber officinalis* have potent anti-inflammatory activities. Rumalaya gel penetrates superficial inflamed tissues, and increases blood flow to the affected area, and inhibits release of proinflammatory chemomediators. Rumalaya gel reduces swelling associated with inflammatory conditions, shortens recovery time and increases mobility of joints.

Mentha arvensis,[24] *Gaultheria frangantissima,*[25] *Pinus roxburghii,*[26] *Cinnamomum zeylanicum,*[27] *Vitex negundo,*[28] and *Zingiber officinalis*[29] are potent antioxidants and the antioxidant activity of above ingredients adds synergism to the anti-inflammatory property.

Glycosaminoglycans (GAGs) are amorphous gels, which attach specifically to linking proteins in the extracellular matrix. Glycosaminoglycans provide the structural support to the body. Boswellic acids from *Boswellia serrata* prevent the catabolism of GAGs.[30]

Cinnamon zeylanicum increases the hydroxyproline content in tissues, which is reduced in degenerative diseases like OA,[31] and thus

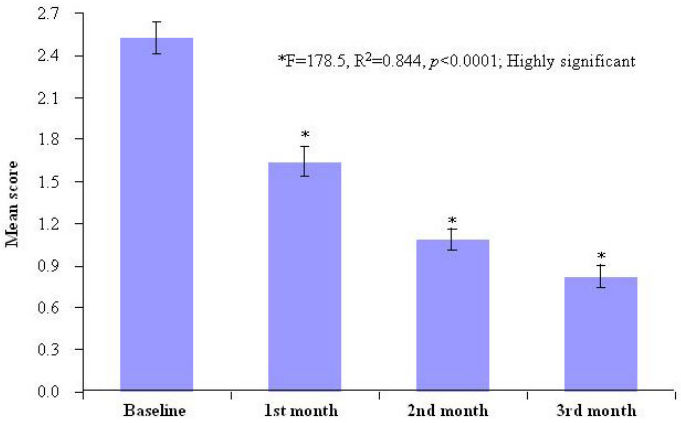


Figure 3: Effect of Rumalaya gel on joint tenderness

Table 4: Effect of Rumalaya gel on early morning joint stiffness

Parameter	Baseline	1st month	2nd month	3rd month
Mean	2.0000	1.2350	0.7059	0.1471
Std. Deviation	1.2310	0.9553	0.6291	0.3595
Std. Error	0.2111	0.1638	0.1079	0.0617
Lower 99% CI	1.4230	0.7875	0.4110	-0.0215
Upper 99% CI	2.5770	1.6830	1.0010	0.3156
Repeated Measures ANOVA Test summary	F=70.41, R^2=0.6809, p<0.0001; HS			
Post test for linear trend summary	Slope=-0.3044, R^2=0.3915, p<0.0001; HS			

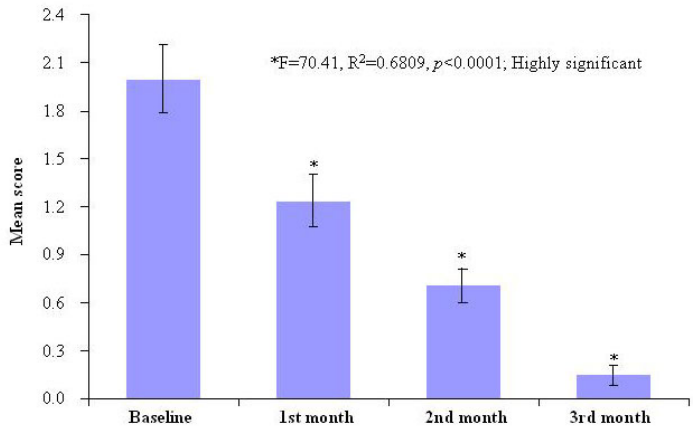


Figure 4: Effect of Rumalaya gel on early morning joint stiffness

Rumalaya gel promotes damaged cartilage repair and healing.

Therefore, it can be summarized that the beneficial effects of Rumalaya gel are due to its analgesic activities (of *Mentha arvensis, Gaultheria fragrantissima*, *Cedarus deodara, Vitex negundo* and *Boswellia serrata*), anti-inflammatory activities (of *Mentha arvensis, Gaultheria fragrantissima*, *Pinus roxburghii*, *Cedrus deodara*, *Vitex negundo*, *Boswellia serrata* and *Zingiber officinalis*), antioxidant activities (of *Mentha arvensis*, *Gaultheria frangantissima*, *Pinus roxburghii*, *Cinnamomum zeylanicum*, *Vitex negundo*, and *Zingiber officinalis*), glycosaminoglycan building activity (of *Boswellia serrata*), and the cartilage healing property (of *Cinnamon zeylanicum*).

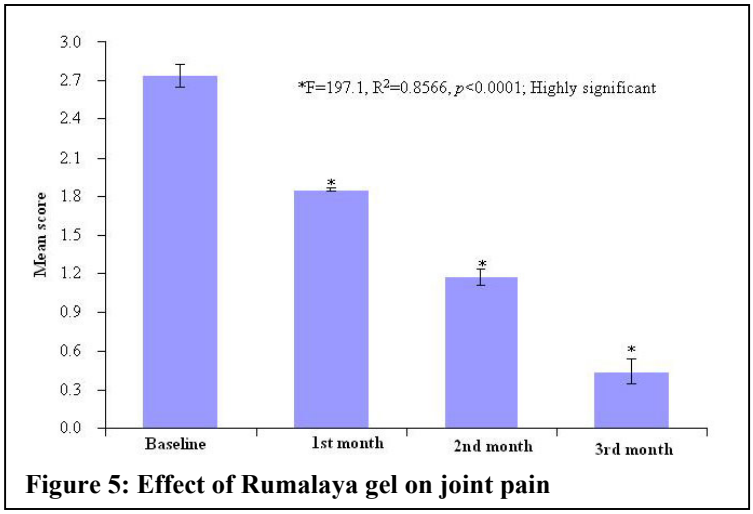
CONCLUSION

Recently, some clinical studies have proved the benefits of topical analgesics in the management of certain acute, and many of the chronic painful inflammatory musculoskeletal conditions**.** Topical applications of counterirritants cause a reversible, transient and mild dermal inflammation, and thereby relieve the pain beneath the site of application. Rumalaya gel is a polyherbal formulation recommended for the management of pain and inflammation associated with the inflammatory musculoskeletal disorders, and this clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel in the symptomatic management of chronic inflammatory musculoskeletal disorders.

This study observed a highly significant reduction in the mean score for muscular pain, joint swelling, joint tenderness, early morning joint stiffness, and joint pain from 1st month onwards, and the similar trend continued till the end of the study. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent.

Table 5: Effect of Rumalaya gel on joint pain

Parameter	Baseline	1st month	2nd month	3rd month
Mean	2.7350	1.8530	1.1760	0.4412
Std. Deviation	0.5110	0.4357	0.3870	0.5609
Std. Error	0.0876	0.0747	0.0664	0.0962
Lower 99% CI	2.4960	1.6490	0.9951	0.1782
Upper 99% CI	2.9750	2.0570	1.3580	0.7041
Repeated Measures ANOVA Test summary	F=197.1, R^2=0.8566, p<0.0001; HS			
Post test for linear trend summary	Slope=-0.3799, R^2=0.761, p<0.0001; HS			



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Rumalaya gel has analgesic, anti-inflammatory, antioxidant, counterirritant, glycosaminoglycan building and cartilage healing properties. Rumalaya gel induces cutaneous vasculature vasodilatation, which produces increased blood circulation and a feeling of warmth. Consequently, cutaneous receptors are stimulated for thermal sensations, which serve to distract deep-seated pain sensations, from the distant areas from the skin's surface. Therefore, it may be concluded that Rumalaya gel is effective and safe in the symptomatic management of chronic inflammatory musculoskeletal disorders.

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