

# Comparison of the efficacy and safety of Rumalaya gel with Diclofenac sodium gel in the management of various soft tissue injuries and inflammatory musculoskeletal disorders

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## ABSTRACT

Topical analgesic preparations are preferred for their clinical efficacy, short- & long-term safety, convenience, compliance, and affordability. This comparative clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel with Diclofenac sodium gel, in certain soft tissue injuries and inflammatory musculoskeletal disorders.

This study was an open, prospective, comparative, controlled, phase III clinical trial, and was approved by the "Institutional Ethics Committee". A total of 320 ambulatory patients suffering from certain acute and chronic soft tissue injuries and inflammatory disorders were included in the study. All the patients were advised to apply a small quantity of Rumalaya gel or Diclofenac sodium gel, to the affected area, with gentle massage, twice daily, for a period of 2 weeks, along with hot water fomentation. All the patients were followed twice weekly, for 2 weeks, and a thorough evaluation was carried out at the end

## ABBREVIATIONS

NSAID	:	Nonsteroidal anti-inflammatory drug
GAG	:	Glycosaminoglycan

of 2 weeks. The predefined primary efficacy endpoints were reduction in the pain intensity (at the involved and the adjacent area), swelling, tenderness and early restoration of local/joint movements. The predefined secondary safety endpoints were assessed by the incidence of adverse events 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 scores of pain intensity at the involved area, pain intensity at the adjacent area, swelling and tenderness at the involved area and overall functional improvement in

the local/joint mobility, in both the groups. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent.

These excellent beneficial actions of Rumalaya gel are due to its analgesic, anti-inflammatory, antioxidant, glycosaminoglycan building activities, and the cartilage healing property. Thus, it can be concluded that Rumalaya gel is as effective and safe as Diclofenac sodium gel and is without any adverse effects and has excellent tolerability in the treatment of soft tissue injuries and inflammatory musculoskeletal disorders.

## INTRODUCTION

Numerous clinical trials have confirmed the clinical benefits of topical analgesic preparations in the management of certain acute, and chronic inflammatory musculoskeletal conditions. These topical analgesic preparations are preferred for their clinical efficacy, short- and long-term safety, convenience, compliance, and affordability. The various postulated mechanisms involve local neuronal blockade, neurotransmitter depletion, "gate control", placebo effect, etc. for their clinical effectiveness, involving various receptors (vanilloid receptor subtype I), non-selective cation channels and thermal sensors. Topical applications containing counterirritants cause a reversible 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, topical analgesic preparations offer excellent safety, as their adverse events (e.g. burning, stinging, erythema, etc.) are mainly limited to the site of application only!

Rumalaya gel is a polyherbal formulation recommended for the management of pain and

inflammation associated with certain acute and chronic inflammatory musculoskeletal disorders. Each gram of Rumalaya gel contains the extracts of *Mentha arvensis*, *Gaultheria fragrantissima*, *Pinus roxburghii*, *Cinnamomum zeylanicum*, *Cedrus deodara*, *Vitex negundo*, *Boswellia serrata* and *Zingiber officinalis*. This comparative clinical trial was conducted to evaluate the comparative efficacy and safety of Rumalaya gel with Diclofenac sodium gel (a frequently used topical NSAID preparation), in certain soft tissue injuries and inflammatory musculoskeletal disorders.

## AIM OF THE STUDY

The present clinical trial was conducted to evaluate the comparative clinical efficacy and safety (short- and long-term) of Rumalaya gel with Diclofenac sodium gel (1.00% w/w) in certain acute and chronic soft tissue injuries and inflammatory musculoskeletal disorders such as ankle/knee sprain, hamstring/back muscle strain, frozen shoulder, trapezitis, tennis elbow, DeQuervain's tenosynovitis, and tendonitis/bursitis.

## MATERIALS AND METHODS

### Study design

This study was an open, prospective, comparative, controlled, phase III clinical trial, and was conducted at the Department of Orthopedics, Medical College and S.S.G. Hospital, Vadodara, India, as per the ethical guidelines of the Declaration of Helsinki, from March 2004 to December 2004. 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 criteria

A total of 320 ambulatory patients suffering from certain acute and chronic soft tissue injuries and

inflammatory disorders (ankle/knee sprain, hamstring/back muscle strain, frozen shoulder, trapezitis, tennis elbow, DeQuervain's tenosynovitis, and tendonitis/bursitis) were included in the study.

### Exclusion criteria

Patients with renal, hepatic or cardiac failure, patients on long-term corticosteroid therapy, patients with uncontrolled diabetes, patients with history of drug abuse, patients with concomitant skin disease or abrasions at the application site, patients suffering from type III sprain or severe muscle strain or who had evidence of fracture, and those patients who were using any other topical therapy at the application site were excluded from the study. Also, pregnant and lactating women, patients suffering from autoimmune disorders, and genetic disorders of spasticity were excluded from the study.

### Study procedure

All the patients underwent a thorough physical examination, and the diagnosis was confirmed at the time of enrolment in the study. All the patients in the 'sprain group' underwent radiological examination to rule out type III sprain or fracture. In all the patients, routine biochemical blood investigations were done. All the patients were advised to apply a small quantity of Rumalaya gel or Diclofenac sodium gel to the affected area, with gentle massage, twice daily, for a period of 2 weeks, along with hot water fomentation. All the patients were co-prescribed a standard NSAID orally, for 2 weeks and physiotherapy was an essential part of the treatment. All the patients were assessed for the following parameters: (1) pain intensity at the involved area, (2) pain intensity at the adjacent area, (3) swelling at the involved area, (4) tenderness at the involved area and (5) overall improvement of the local/joint mobility. The response to

the treatment was evaluated on a predefined symptom score scale, from 0 to 3 (3=maximum and 0=nil), for above-mentioned 5 parameters, and the final score was calculated by averaging the scores for these parameters.

### Follow-up and assessment

All the patients were followed twice weekly, for 2 weeks, and a thorough evaluation (subjective and objective) was carried out at the end of 2 weeks.

### Primary and secondary endpoints

The predefined primary efficacy

**Table 1: Distribution of patients**

Indications	No. of patients	
	Rumalaya gel	Diclofenac sodium gel
Ankle/knee sprain	25	25
Hamstring/back muscle strain	25	25
Frozen shoulder	25	25
Trapezeitis	25	25
Tennis elbow	25	25
DeQuervain's tenosynovitis	25	25
Tendoachilles tendonitis/bursitis	10	10
Total	160	160

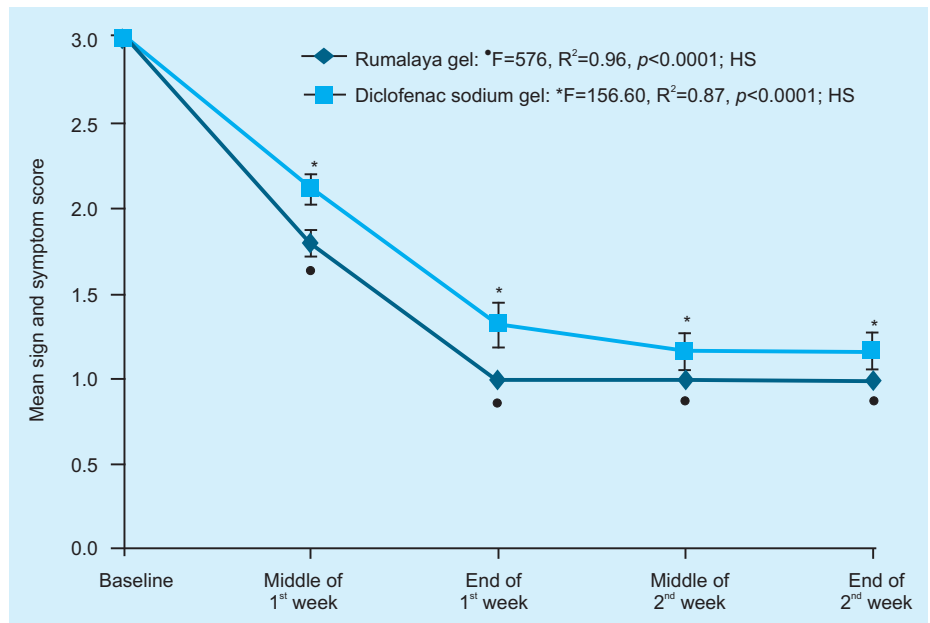
**Table 2: The mean sign and symptom scores in patients with Sprain (ankle/knee) and Hamstring/back muscle strain in both the groups**

Parameters	Sprain (ankle/knee)		Hamstring/back muscle strain	
	Rumalaya Gel	Diclofenac sodium gel	Rumalaya Gel	Diclofenac sodium gel
Baseline	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
Middle 1st week	1.80 ± 0.08	2.12 ± 0.09	1.48 ± 0.10	1.72 ± 0.12
End of 1st week	1.00 ± 0.00	1.32 ± 0.13	1.16 ± 0.07	1.36 ± 0.13
Middle 2nd week	1.00 ± 0.00	1.16 ± 0.11	1.00 ± 0.00	1.16 ± 0.11
End of 2nd week	1.00 ± 0.00	1.16 ± 0.11	0.96 ± 0.04	1.12 ± 0.12
Repeated measures ANOVA test	F=576.00, R <sup>2</sup> =0.96, p<0.0001; HS	F=156.60, R <sup>2</sup> =0.87, p<0.0001; HS	F=224.70, R <sup>2</sup> =0.90, p<0.0001; HS	F=117.10, R <sup>2</sup> =0.83, p<0.0001; HS
Post test for Linear Trend	Slope= -0.48, R <sup>2</sup> =0.71, p<0.0001; HS	Slope= -0.46, R <sup>2</sup> =0.58, p<0.0001; HS	Slope= -0.46, R <sup>2</sup> =0.62, p<0.0001; HS	Slope= -0.43, R <sup>2</sup> =0.49, p<0.0001; HS

endpoints were reduction in the pain intensity (at the involved and the adjacent area), swelling, tenderness and early restoration of local/joint movements. The predefined secondary safety endpoints were assessed by the incidence of adverse events and patient compliance to therapy.

### Adverse events

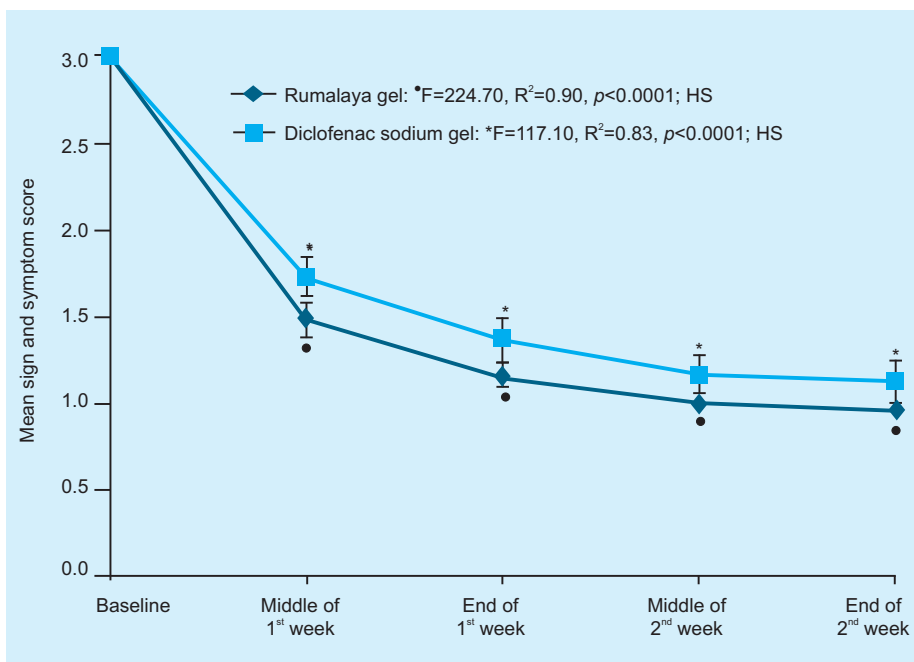
All the adverse events, either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "Unrelated", "Possible", and "Probable". Patients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



**Figure 1: The Mean sign and symptom scores in patients with Sprain (ankle/knee) in both the groups**

**Table 3: The mean sign and symptom scores in patients with Frozen Shoulder, Trapezitis and Tennis Elbow in both the groups**

Parameters	Frozen shoulder		Trapezitis		Tennis elbow	
	Rumalaya gel	Diclofenac sodium gel	Rumalaya gel	Diclofenac sodium gel	Rumalaya gel	Diclofenac sodium gel
Baseline	1.52± 0.17	2.32± 0.10	2.96± 0.04	3.00± 0.00	3.00± 0.00	3.00± 0.00
Middle 1st week	1.14 ± 0.18	2.04± 0.04	2.04± 0.04	2.20± 0.08	2.16± 0.07	2.00± 0.00
End of 1st week	0.96 ± 0.20	1.72± 0.16	1.92± 0.08	2.00± 0.10	2.00± 0.10	2.00± 0.00
Middle 2nd week	0.12± 0.09	0.44± 0.18	1.04± 0.20	1.28± 0.22	1.76± 0.17	2.00± 0.00
End of 2nd week	0.04± 0.04	0.28± 0.16	0.32± 0.15	0.72± 0.22	1.20± 0.22	1.36± 0.19
Repeated measures ANOVA test	F=34.56, R <sup>2</sup> =0.59, p<0.0001; HS	F=73.88, R <sup>2</sup> =0.76, p<0.0001; HS	F=80.69, R <sup>2</sup> =0.78, p<0.0001; HS	F=50.47, R <sup>2</sup> =0.68, p<0.0001; HS	F=82.59, R <sup>2</sup> =0.58, p<0.0001; HS	F=47.69, R <sup>2</sup> =0.67, p<0.0001; HS
Post test for Linear Trend	Slope= -0.43, R <sup>2</sup> =0.39, p<0.0001, HS	Slope= -0.57, R <sup>2</sup> =0.56, p<0.0001; HS	Slope= -0.63, R <sup>2</sup> =0.67, p<0.0001; HS	Slope= -0.55, R <sup>2</sup> =0.52, p<0.0001; HS	Slope= -0.59, R <sup>2</sup> =0.61, p<0.0001; HS	Slope= -0.38, R <sup>2</sup> =0.48, p<0.0001; HS



**Figure 2: The mean sign and symptom scores in patients with Hamstring/back muscle strain in both the groups**

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

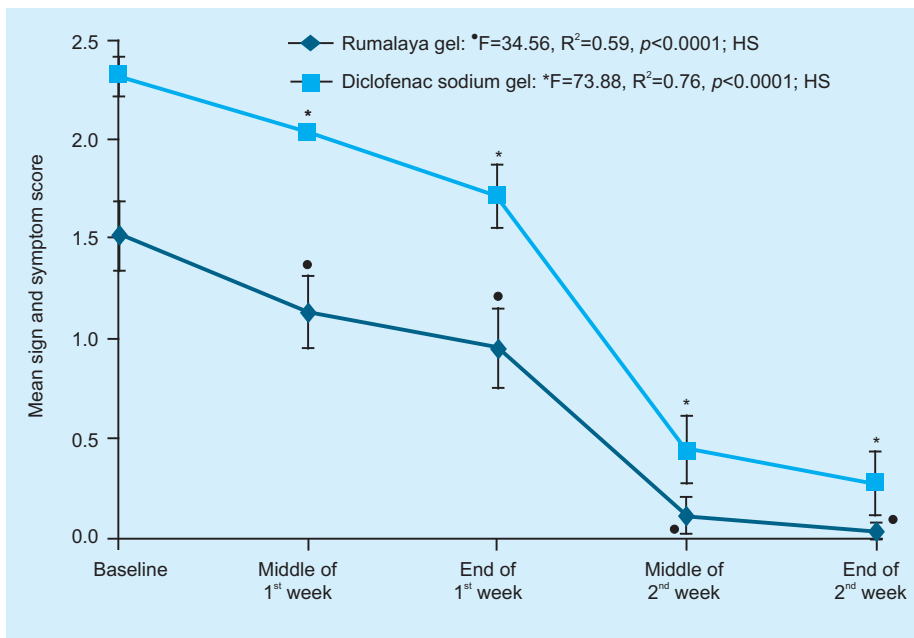
A total of 320 patients were enrolled in the study (160 patients each in the Rumalaya gel and Diclofenac sodium gel groups), and there were 25 patients of ankle/knee sprain, 25

patients of hamstring/back muscle strain, 25 patients of frozen shoulder, 25 patients of trapezitis, 25 patients of tennis elbow, 25 patients of DeQuervain's tenosynovitis and 10 patients of tendoachilles tendonitis/bursitis in each group. In total, 7 patients were lost to follow-up (4 patients in Rumalaya gel group and 3 patients from Diclofenac sodium gel). The age and sex profile of all included patients indicated a male preponderance in the study population. The patient distribution in the Rumalaya gel and Diclofenac sodium gel is provided in Table 1.

There was a highly significant reduction in the mean scores of pain intensity at the involved area, pain intensity at the adjacent area, swelling and tenderness at the involved area and overall functional improvement in the local/joint mobility in the patients suffering from ankle/knee sprain (Table 2 and Figure 1), hamstring/back muscle strain (Table 2 and Figure 2), frozen shoulder (Table 3 and Figure 3), trapezitis (Table 3 and Figure 4), tennis elbow (Table 3 and Figure 5), DeQuervain's tenosynovitis (Table 4 and Figure 6), tendonitis/bursitis (Table 4 and Figure 7), in both the groups. At the end of 2 weeks of

**Table 4: The mean sign and symptom scores in patients with DeQuervain's tenosynovitis and Tendoachilles tendonitis/bursitis in both the groups**

Parameters	DeQuervain's tenosynovitis		Tendoachilles tendonitis/bursitis	
	Rumalaya gel	Diclofenac sodium gel	Rumalaya gel	Diclofenac sodium gel
Baseline	2.76 ± 0.09	2.92 ± 0.06	2.36 ± 0.28	2.00 ± 0.23
Middle 1st week	2.28 ± 0.10	2.12 ± 0.07	1.81 ± 0.30	2.09 ± 0.25
End of 1st week	1.76 ± 0.09	1.80 ± 0.08	1.64 ± 0.20	1.27 ± 0.27
Middle 2nd week	1.28 ± 0.15	1.68 ± 0.10	0.55 ± 0.16	0.36 ± 0.20
End of 2nd week	1.16 ± 0.19	1.32 ± 0.18	0.18 ± 0.12	0.45 ± 0.16
Repeated measures ANOVA test	F=27.57, R <sup>2</sup> =0.53, p<0.0001; HS	F=32.83, R <sup>2</sup> =0.58, p<0.0001; HS	F=15.18, R <sup>2</sup> =0.60, p<0.0001; HS	F=11.90, R <sup>2</sup> =0.54, p<0.0001; HS
Post test for Linear Trend	Slope= -0.42, R <sup>2</sup> =0.47, p<0.0001; HS	Slope= -0.36, R <sup>2</sup> =0.47, p<0.0001; HS	Slope= -0.56, R <sup>2</sup> =0.55, p<0.0001; HS	Slope= -0.48, R <sup>2</sup> =0.44, p<0.0001; HS



**Figure 3: The mean sign and symptom scores in patients with Frozen shoulder in both the groups**

therapy, there was complete improvement in all the subjective and objective parameters.

There were no clinically significant changes in any of the haematological 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.

These excellent beneficial actions of Rumalaya gel are due to its

analgesic, anti-inflammatory, antioxidant, GAG building activities, and the cartilage healing property.

Thus, it can be concluded that Rumalaya gel is as effective and safe, and without any adverse effects and with excellent tolerability profile as Diclofenac sodium gel in the treatment of soft tissue injuries and inflammatory musculoskeletal disorders.

### DISCUSSION

The International Association for the

Study of Pain (IASP) had defined pain as, "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage". "Acute pain" is a signal of ongoing or impending tissue damage, which provokes the patient to escape from the event or seek relief. "Chronic pain" persists beyond a reasonable time (usually 3-6 months), and can be provoked by a pathologic process, or may recur at intervals (for months or years). Contrary to acute pain, chronic pain never has a protective biological function, but has an adverse effect, which usually imposes severe physical and emotional stress on the individual. Classically, pain is categorized as "nociceptive pain" (acute, subacute and inflammatory), and "pathophysiological pain" (neuropathic, deafferentation and central). Nociceptive pain results from noxious stimuli and inflammation in otherwise intact tissues, and pathophysiological pain (chronic pain), is associated with injury to neural tissues. The 4 processes involved in nociception are "transduction" (when noxious stimuli are transformed into electrical impulses at the sensory endings of the nerve), "transmission" (transfer of the impulse via the sensory nervous system), "modulation" (modification of the nociceptive transmission by a

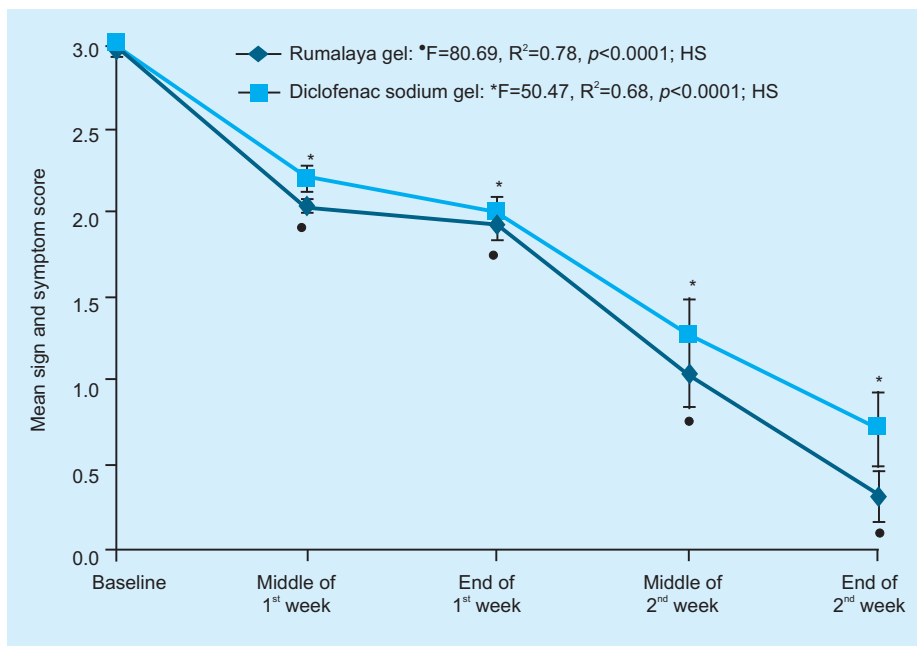


Figure 4: The mean sign and symptom scores in patients with Trapezitis in both the groups

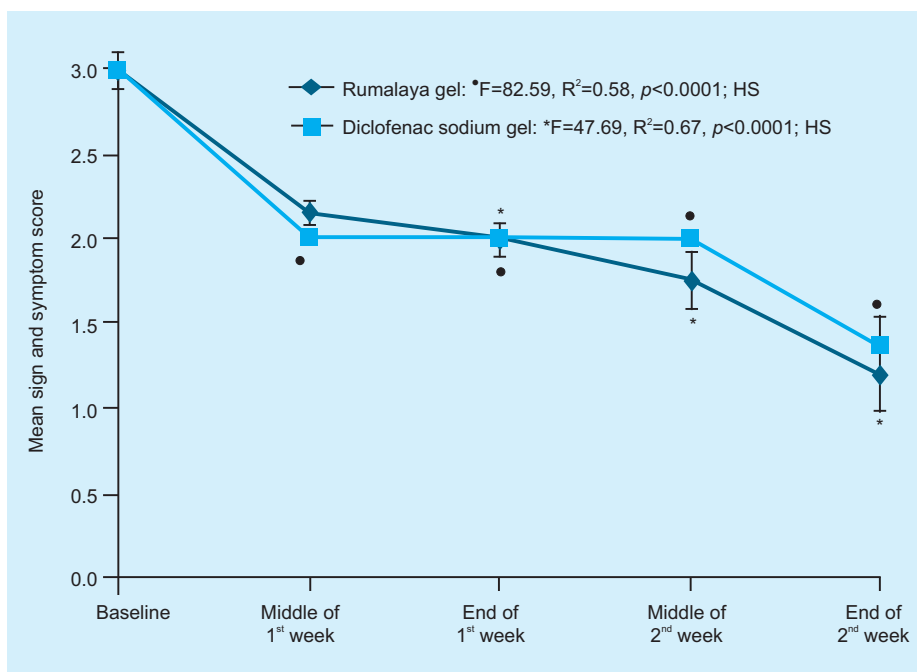


Figure 5: The mean sign and symptom scores in patients with Tennis elbow in both the groups

number of neural inferences), and "perception" (the subjective sensory and emotional experience of pain that occurs at the cortical level).

The hypothesized mechanism of action of counterirritants and rubefaciants include stimulation of the nociceptors, the "gate theory",<sup>1,2</sup>

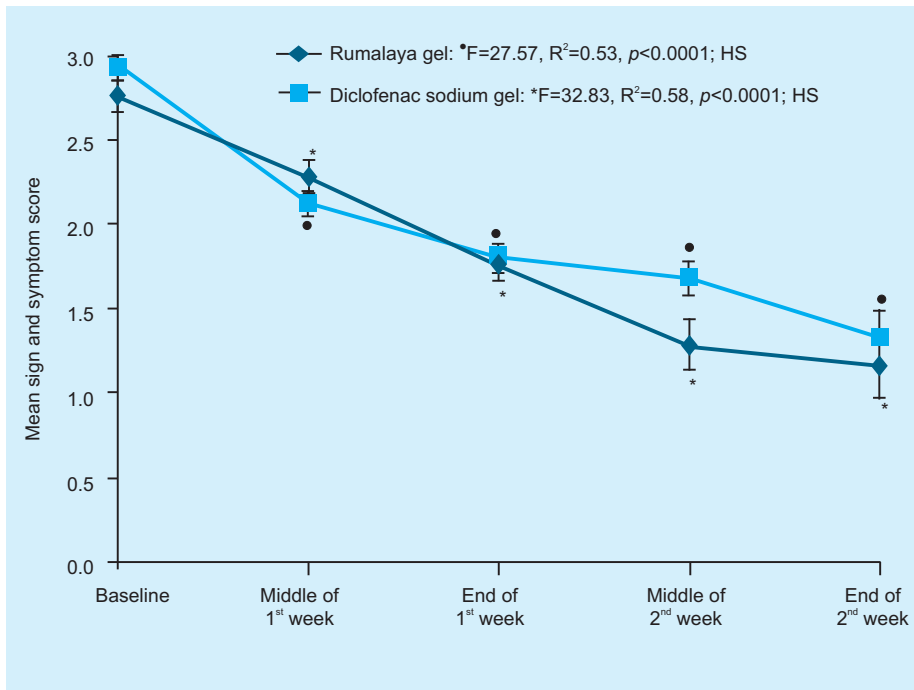
and the release of endogenous opioids.<sup>3</sup> Counterirritants inflame and irritate the skin, increase cutaneous blood flow, stimulate thermoreceptors and stimulate/depress pain receptors. By activating the nociceptors with a peripheral noxious stimulus,

counterirritants inhibit the response of central neurons that transmit pain or nociceptor desensitization.<sup>4</sup> 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 neurotransmitter.<sup>5</sup>

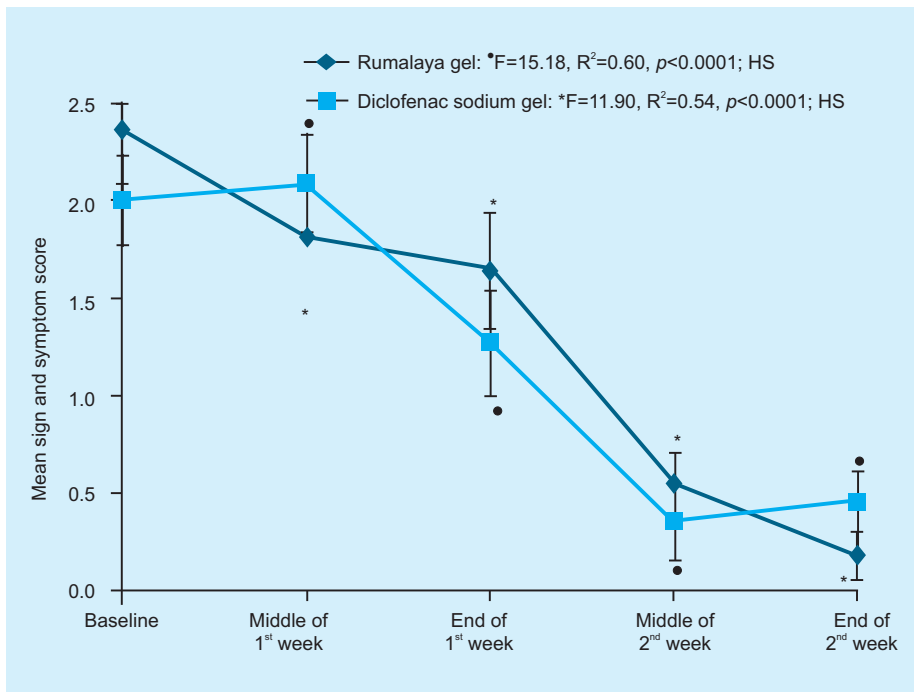
Soft tissue injuries and inflammatory disorders lead to a compromised quality of life and commonly prescribed systemic NSAIDs are causally associated with numerous short- and long-term adverse events. Therefore, there is a felt need for a safer, effective and affordable topical formulation for long-term use. Diclofenac sodium gel is one of the frequently used, potent NSAID, for the management of soft tissue injuries and inflammatory disorders.

This study observed a highly significant reduction in the mean scores of pain intensity at the involved area, pain intensity at the adjacent area, swelling and tenderness at the involved area and overall functional improvement in the local/joint mobility, in both the groups. 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.

The active constituents of *Mentha arvensis* are menthol, monoterpenes and sesquiterpene hydrocarbons.<sup>6</sup> 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.<sup>6</sup> *Cinnamomum zeylanicum* contains L-



**Figure 6: The mean sign and symptom scores in patients with DeQueryain's tenosynovitis in both the groups**



**Figure 7: The mean sign and symptom scores in patients with Tendoachilles tendonitis/bursitis in both the groups**

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 (trihydroxy-dimethoxy-epoxyllignan).<sup>7</sup> 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,<sup>8</sup> and a flavone (vitexicarpin).<sup>9</sup> The principle constituents *Boswellia serrata* are acetyl keto-beta boswellic acid, keto beta-boswellic acid, acetyl beta-boswellic acid and beta-boswellic acid.<sup>10</sup> The principal constituents of *Zingiber officinalis* are zingiberene (A and B), and zingiberol.<sup>11</sup>

*Mentha arvensis*, *Gaultheria fragrantissima*,<sup>12</sup> *Cedrus deodara*,<sup>13</sup> *Vitex negundo*,<sup>14</sup> and *Boswellia serrata*,<sup>4</sup> have potent analgesic activity. Hence, Rumalaya gel depresses the cutaneous sensory pain receptors and acts directly to diminish or obliterate pain.

*Mentha arvensis*, *Gaultheria fragrantissima*,<sup>15</sup> *Pinus roxburghii*,<sup>16</sup> *Cedrus deodara*, *Vitex negundo*, *Boswellia serrata*,<sup>17</sup> and *Zingiber officinalis* have potent anti-inflammatory activities. Rumalaya gel penetrates superficial inflamed tissues, increases blood flow to the affected area, and inhibits the release of proinflammatory chemomediators. Thereby, Rumalaya gel reduces swelling associated with inflammatory conditions, shortens the recovery time and increases the mobility of the affected joints.

*Mentha arvensis*,<sup>18</sup> *Gaultheria fragrantissima*,<sup>19</sup> *Pinus roxburghii*,<sup>20</sup> *Cinnamomum zeylanicum*,<sup>21</sup> *Vitex negundo*,<sup>22</sup> and *Zingiber officinalis*<sup>23</sup> are potent antioxidants and the antioxidant activity of above ingredients adds synergism to the anti-inflammatory property of Rumalaya gel.

Glycosaminoglycans are amorphous gels, which attach specifically to linking proteins in the extracellular matrix, and provide the structural support to the body. Boswellic acids from *Boswellia serrata* prevent the catabolism of GAGs.<sup>24</sup>

*Cinnamon zeylanicum* increases the hydroxyproline content in tissues, which is reduced in chronic

inflammatory diseases,<sup>25</sup> and thus 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*, *Cedrus 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 fragrantissima*, *Pinus roxburghii*, *Cinnamomum zeylanicum*, *Vitex negundo*, and *Zingiber officinalis*), glycosaminoglycan building activity (of *Boswellia serrata*), and the cartilage healing property (of *Cinnamomum zeylanicum*). Thus, Rumalaya gel has analgesic, anti-inflammatory, antioxidant, counterirritant, glycosaminoglycan building and cartilage healing properties. Rumalaya gel induces vasodilation of the cutaneous vasculature, which increases 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.

## CONCLUSION

Topical analgesic preparations are preferred for their clinical efficacy, short- and long-term safety, convenience, compliance, and affordability. This comparative clinical trial was conducted to evaluate the efficacy and safety of Rumalaya gel with Diclofenac sodium gel, in certain soft tissue injuries and inflammatory musculoskeletal disorders.

This study observed a highly significant reduction in the mean scores of pain intensity at the involved area, pain intensity at the adjacent area, swelling and tenderness at the involved area and

overall functional improvement of the local/joint mobility, in both the groups. Also, there were no clinically significant adverse events and the overall compliance to the treatment was excellent.

These excellent beneficial actions of Rumalaya gel are due to its analgesic, anti-inflammatory, antioxidant, GAG building activities, and the cartilage healing property.

Thus, it can be concluded that Rumalaya gel is as effective and safe as Diclofenac sodium gel and is without any adverse effects and has excellent tolerability profile in the treatment of soft tissue injuries and inflammatory musculoskeletal disorders.

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