Clinical Trial Report (Draft version V.2)

(As per Appendix-I to Schedule Y -Format for submission of Clinical Trial Reports)

1. *Title of the trial :*

   "***Evaluation of Contrapain Lepa and Oil (topical application) for Analgesic and anti-inflammatory activities in Musculoskeletal Disorders – Clinical Study***"

2. *Name of the investigator and institution:*

   Clinical Study Site: KAHER's Shri B M K Ayurveda Mahavidyalaya & KLE Ayurveda Hospital & MRC, Belagavi, Karnataka 590003

   Investigators:

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Sponsor: MB Life Sciences Pvt. Ltd. New Delhi

3. *Objectives of the trial :*

To assess the analgesic and anti-inflammatory effect of CONTRAPAIN – LEPA & OIL topical application in Patients of Musculoskeletal Disorders

4. *Design of study: (open, single-blind or double-blind, non-comparative or comparative; parallel group or crossover.)*

Open Labelled, Non-comparative Clinical Study with Four sub groups of Musculo-Skeletal Disease (MSD) viz. Osteo Arthritis(OA), Rheumatoid Arthritis (RA), Spondylitis & Sprain

Single centric, Single Group (Stratified as Four Sub Groups with clinical conditions of pain and inflammation) with Pretest and Posttest design

5. *Number of patients, with criteria for selection and exclusion; whether written informed consent, was obtained.*

No. of patients :

Eighty (80) patients with Musculo-Skeletal Disease

Inclusion Criteria:

- Patients with musculoskeletal pain & swelling, fulfilling the diagnostic criteria of MSD
- Male and female Patients with age between 20-70 years
- Mild, moderate cases of MSD

- Willing to give consent for participating in the study
- Patients who are currently on analgesics / NSAID, will be given a washout period of 7 days prior to recruitment

Exclusion Criteria:

- Patients having severe MSD
- Those who are suffering from dermatitis or had a history of dermatitis
- Pregnant and lactating women
- Any other conditions which in the opinion of investigator will place the subject at risk or will influence the conduct of study or interpretation of results

Assessment Criteria:

Parameters at screening:

RA, CRP, Serum Uric acid

Subjective parameters: (0, 7th 15th & 30th Day)

Pain (VAS), Tenderness, Shotha (Swelling/Inflammation), Stabdata (Stiffness), Physician Global Assessment

Objective parameters: (0, 7th 15th & 30th Day)

Range of Motion (Goniometer)

Safety Parameters: (0 and 7th day)

CBC, LFT, RFT (Only 50% of Patients)

Whether Informed Consent was obtained:

YES, Informed Consent was obtained from all participants of the study.

6. *Treatments given: drugs and dosage forms: regimens; method of allocations of patients to the treatments; method of verifying compliance, if any.*

Drug :

Contrapain (Lepa) powder with lukewarm water as paste & Contrapain oil.

Doasge Forms & Dose :

1. Contrapain Powder (5gm) mixed with leukwarm water (15ml) to make paste

2. Contrapain Oil (sos)

Regimen:

► Trial medication: Applied externally at the site of pain Twice in a Day for a period of 7 Days

1. Contrapain Lepa – Contrapain powder (5gm) mixed with sufficient lukewarm water (15ml approximately) made as a paste, was applied at the site of pain and left it for 30 - 60 minutes.

2. Applied Paste (Lepa) removed with running water and allowed it to dry.

3. This was followed by application of Contrapain oil at the site of pain.

► Assessment done on 0, 7th day as well as Post-treatment follow-up assessment was done on 15th & 30th day

Method of allocation of patients to treatments:

After clinical screening, Patients who fulfil Diagnostic criteria, inclusion criteria and signing informed consent, were allocated in to the study. Based on clinical and laboratory diagnosis, Patients were allocated to their respective subgroup i.e. OA, RA, Spondylitis or Sprain

Method of verifying compliance:

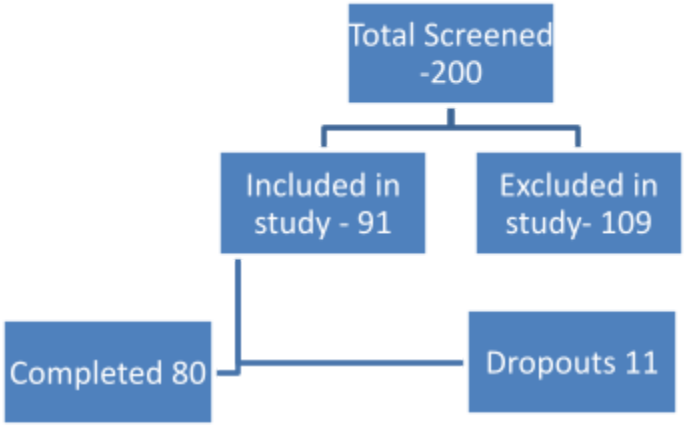
All the included patients were administered the treatment in hospital only. For outstation patients, day stay along with meals was provided in research ward of the hospital to provide treatment in the morning and evening.

7. *Observations made before, during and at the end of the treatment, for efficacy and safety , with methods used.*

Study Design:

Open Labelled, Non-comparative Clinical Study with Four sub groups of Musculo-Skeletal Disease (MSD) viz. Osteo Arthritis(OA), Rheumatoid Arthritis (RA), Spondylitis & Sprain

Single centric, Single Group (Stratified as Four Sub Groups with clinical conditions of pain and inflammation) with Pretest and Posttest design



Duration of Study and Follow-Up:

Therapy: 7 days

Follow up: on 15th and 30th day after treatment period.

Safety:

Incidence of adverse events (AEs) will be reported and if necessary clinical investigator will make the appropriate clinical management.

Changes in following parameters between day 0 day 7 day (in 50% of Patients)

- CBC, LFT, RFT

Efficacy:

Before and after the treatment period of 7 days, on 15th and 30th days

Changes in following parameters between day 0, day 7, day 15 & day 30:

- Pain (VAS),
- Tenderness,
- Shotha (Swelling/Inflammation),
- Stabdata (Stiffness),
- Physician Global Assessment
- Range of Motions (Goniometer)

Parameters at screening:

RA, CRP, Serum Uric acid

Subjective parameters:

Pain (VAS), Tenderness, Shotha (Swelling/Inflammation), Stabdata (Stiffness), Physician Global Assessment

Objective parameters:

Range of Motion (Goniometer)

Safety Parameters:

CBC, LFT, RFT (base line and 7th day) (Only 50% of Patients)

8. ***Results:*** *exclusions and dropouts, if any, with reasons; description of patients with initial comparability of groups where appropriate; clinical and laboratory observations on efficacy and safety; adverse drug reactions.*

Summary of Recruitment

No. of screened subjects: 200

No. of Included subjects: 91

No. of excluded subjects: 109

During screening at OPDs those who have not fulfilled inclusion criteria, who are were coming under exclusion criteria and who does not want to participate in study or not willing for Informed consent were excluded from study.

No. of Dropouts: 11

Reasons for Dropouts:

Out of 11 patients, 6 patients didn't turn up for the treatment as well as for the laboratory investigations, and 5 patients didn't come for the follow up.

No of Completed Subjects: 80

Description of patients with initial comparability of groups where appropriate:

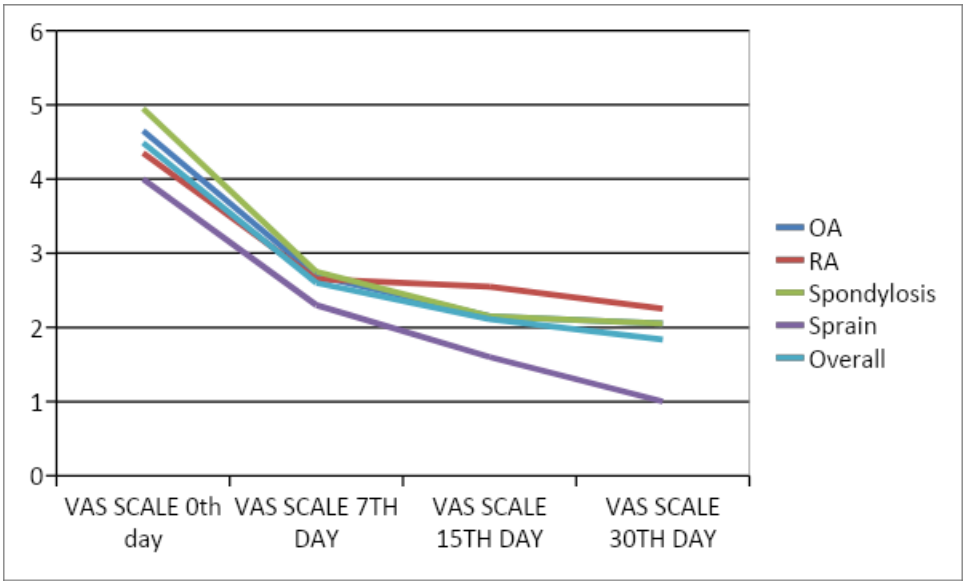
At baseline in each subgroup all assessment parameters are comparable.

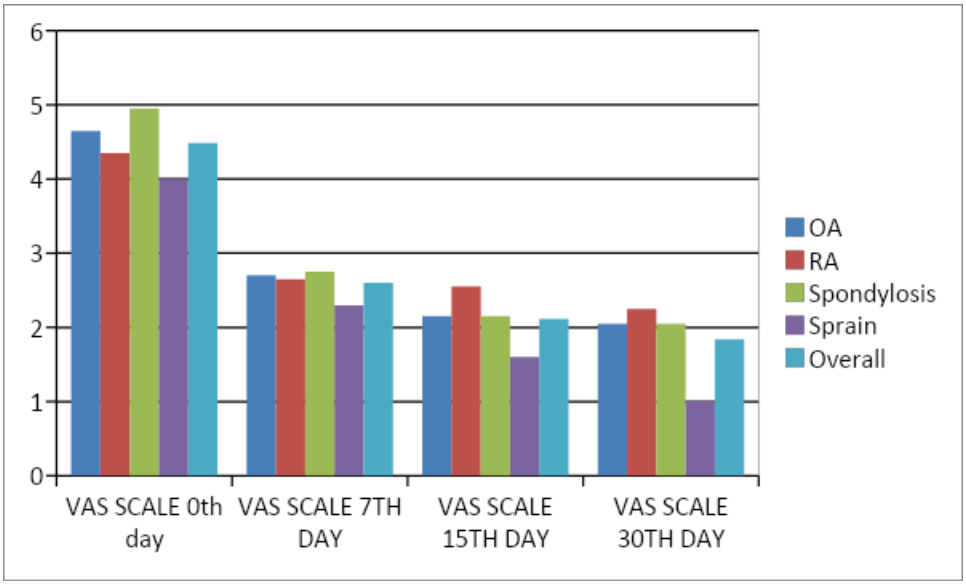
Clinical observations on efficacy:

1. Effect of Test drug on Pain (Visual Analogue Scale) – on Total subjects (N=80) & on four clinical MSD conditions (Mean scores)

diagnosis	VAS SCALE 0th day	VAS SCALE 7TH DAY	VAS SCALE 15TH DAY	VAS SCALE 30TH DAY
OA	4.65	2.7	2.15	2.05
RA	4.35	2.65	2.55	2.25
Spondylosis	4.95	2.75	2.15	2.05
Sprain	4	2.3	1.6	1
Overall	4.4875	2.6	2.1125	1.8375

Pain measured by VAS has been reduced in all the trial subjects as well as in each of the four clinical conditions of Musculoskeletal disease when compared with before treatment to after treatment on 7th day as well as on follow up days of 15th and 30th days. The study also observed that pain reduced is sustained through follow ups on 15th and 30th days.

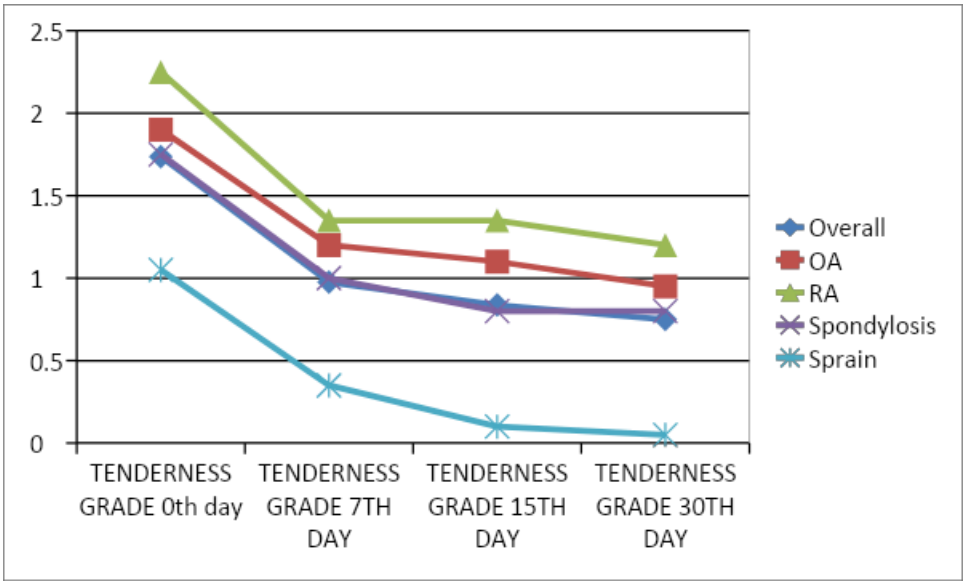


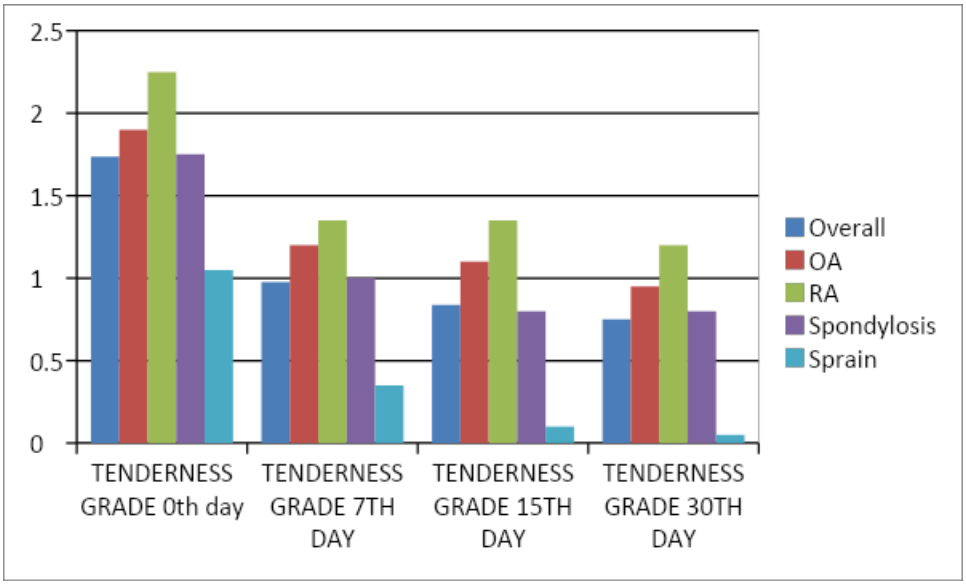


2. Effect on Tenderness (Mean Scores)

Diagnosis	**TENDERNESS GRADE 0th day**	**TENDERNESS GRADE 7TH DAY**	**TENDERNESS GRADE 15TH DAY**	**TENDERNESS GRADE 30TH DAY**
OA	1.9	1.2	1.1	0.95
RA	2.25	1.35	1.35	1.2
Spondylosis	1.75	1	0.8	0.8
Sprain	1.05	0.35	0.1	0.05
Overall	1.7375	0.975	0.8375	0.75

Study showed that Tenderness is reduced in Overall subjects as well as in each MSD condition when compared from before study Average Grades of Tenderness to after study and after Follow up period. Reduction in tenderness in sustained even during follow up period.



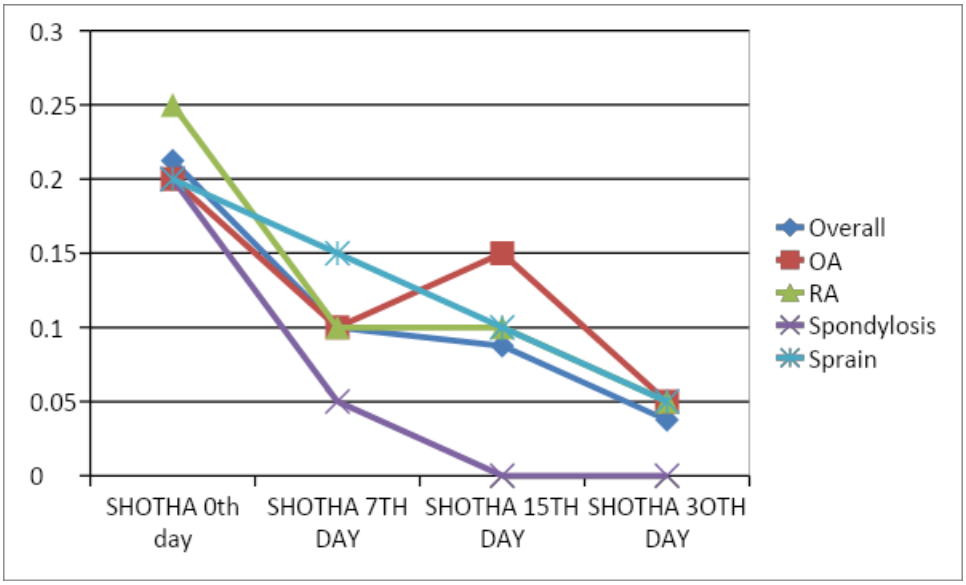


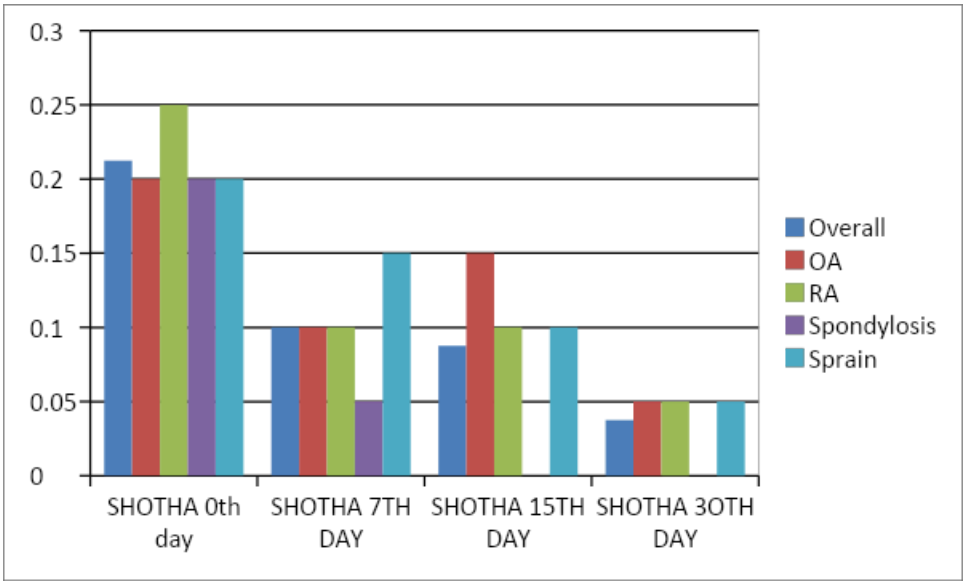
3. Effect on Shotha (Swelling) (Mean Scores)

diagnosis	SHOTHA 0th day	SHOTHA 7TH DAY	SHOTHA 15TH DAY	SHOTHA 3OTH DAY
OA	0.2	0.1	0.15	0.05
RA	0.25	0.1	0.1	0.05
Spondylosis	0.2	0.05	0	0
Sprain	0.2	0.15	0.1	0.05

Overall	0.2125	0.1	0.0875	0.0375

Study showed that Sotha (swelling) has reduced in overall subjects as well as in each condition of MSD in average values of grading when compared from before to after treatment and during followup peiod. And sustenance of effect in reducing swelling is observed during followup of 15 and 30 days.

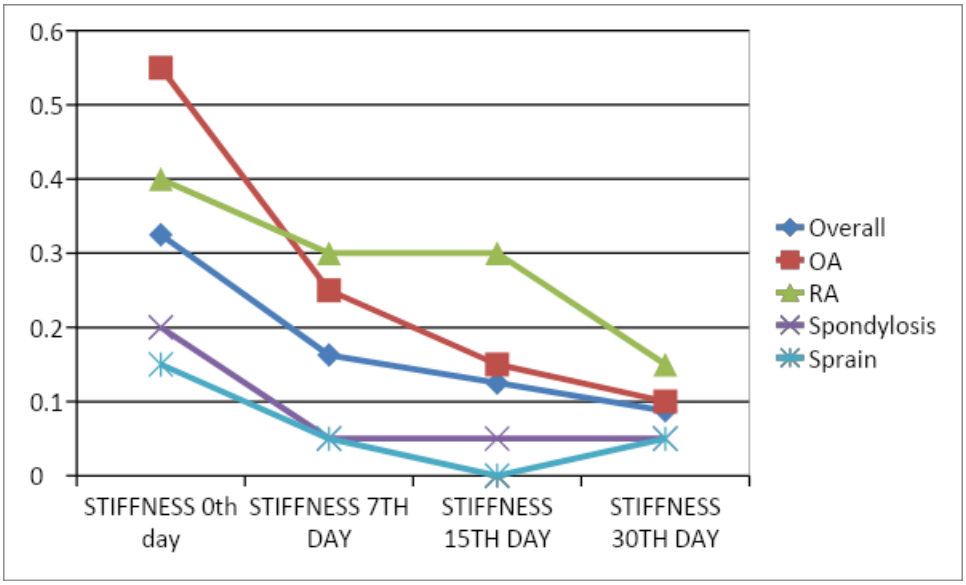


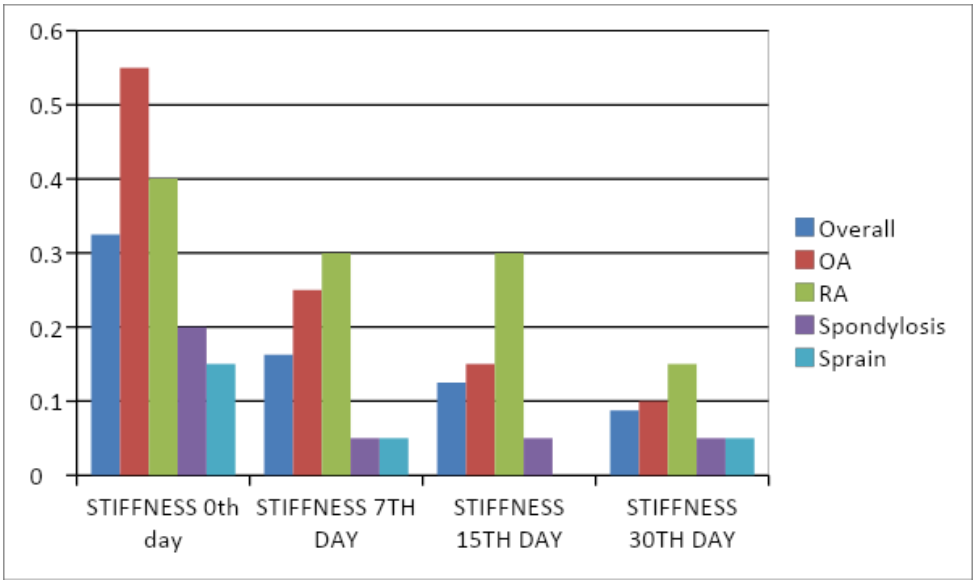


4. Effect on Stiffness (Mean scores)

diagnosis	STIFFNESS 0th day	STIFFNESS 7TH DAY	STIFFNESS 15TH DAY	STIFFNESS 30TH DAY
OA	0.55	0.25	0.15	0.1
RA	0.4	0.3	0.3	0.15
Spondylosis	0.2	0.05	0.05	0.05
Sprain	0.15	0.05	0	0.05
Overall	0.325	0.1625	0.125	0.0875

Study showed that stiffness has reduced in overall subjects as well as in each condition of MSD in average values of grading when compared from before to after treatment and during followup period. And sustenance of effect in reducing stiffness is observed during followup of 15 and 30 days.

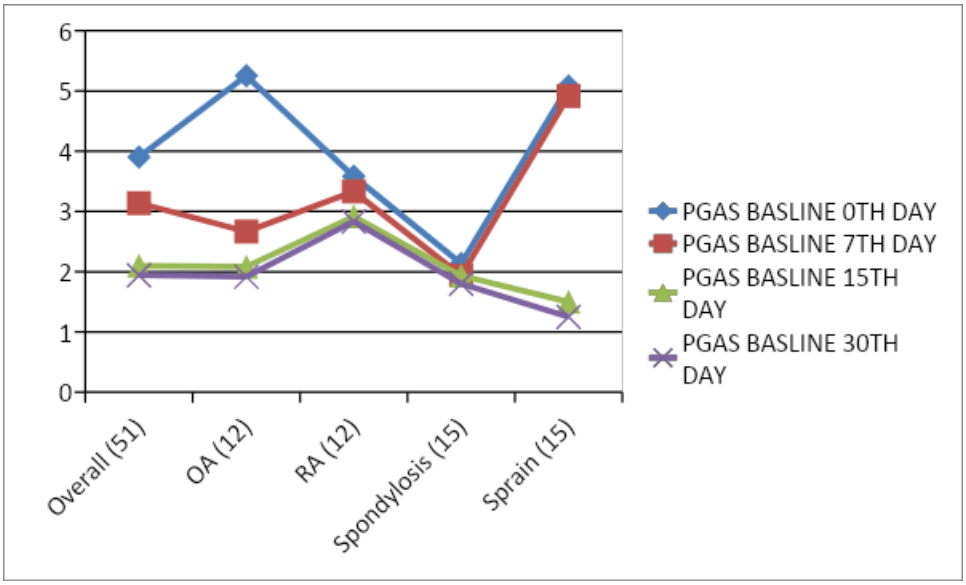


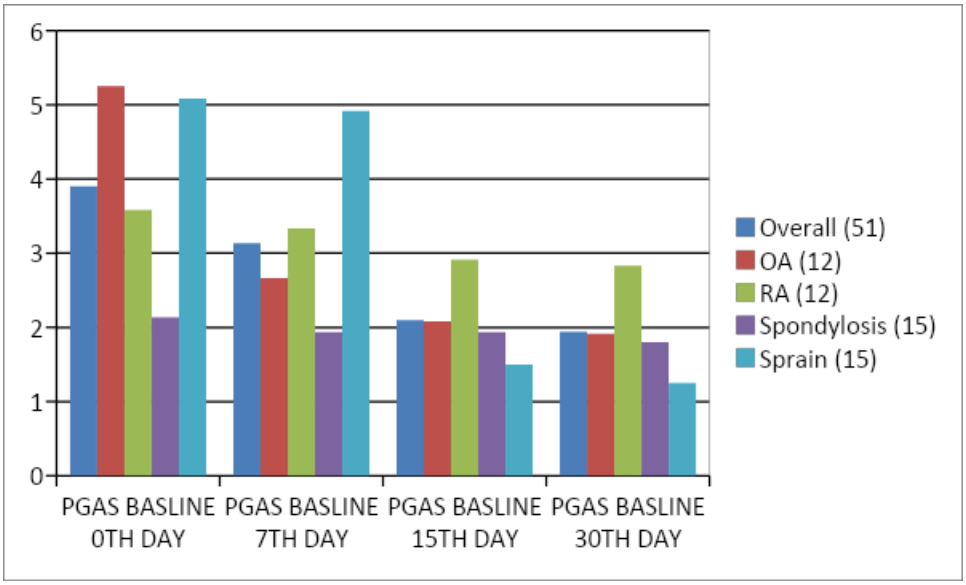


6. Efficacy based on Physician Global Assessment Score (PGAS) (Mean score)

diagnosis (Number of subjects)	**PGAS BASLINE 0TH DAY**	**PGAS BASLINE 7TH DAY**	**PGAS BASLINE 15TH DAY**	**PGAS BASLINE 30TH DAY**
OA (12)	5.25	2.667	2.083	1.916
RA (12)	3.583	3.333	2.916	2.833
Spondylosis (15)	2.133	1.933	1.933	1.8
Sprain (15)	5.083	4.916	1.5	1.25
Overall (51)	3.901961	3.137255	2.098039	1.941176

Physician Global Assessment Scale scoring in the study showed that PGAS has decreased from baseline to after treatment and as well as in follow up period.


6
5
4
3
2
1
0
Overall (51)
OA (12)
RA (12)
Spondylosis (15)
Sprain (15)
PGAS BASLINE 0TH DAY
PGAS BASLINE 7TH DAY
PGAS BASLINE 15TH DAY
PGAS BASLINE 30TH DAY


6
5
4
3
2
1
0
PGAS BASLINE 0TH DAY
PGAS BASLINE 7TH DAY
PGAS BASLINE 15TH DAY
PGAS BASLINE 30TH DAY
Overall (51)
OA (12)
RA (12)
Spondylosis (15)
Sprain (15)

Results & Statistics:

Table: Comparison of four diagnoses with respect to **VAS scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	4.65	1.18	2.70	1.42	2.15	0.88	2.05	0.76	1.95	0.94	2.50	0.83	2.60	0.88
RA	4.35	1.50	2.65	1.63	2.55	1.70	2.25	1.33	1.70	1.34	1.80	1.15	2.10	1.02
Spondylosis	4.95	1.32	2.75	1.29	2.15	1.42	2.05	1.47	2.20	1.06	2.80	1.32	2.90	1.41
Sprain	4.00	1.84	2.30	1.03	1.60	1.27	1.00	1.26	1.70	1.30	2.40	1.35	3.00	1.75
% of change in OA									41.94%#, p=0.0002*		53.76%#, p=0.0001*		55.91%#, p=0.0001*	
% of change in RA									39.08%#, p=0.0005*		41.38%#, p=0.0003*		48.28%#, p=0.0001*	
% of change in Spondylosis									44.44%#, p=0.0002*		56.57%#, p=0.0001*		58.59%#, p=0.0001*	

% of change in Sprain					42.50%#, p=0.0004*	60.00%#, p=0.0001*	75.00%#, p=0.0001*
H-value	7.5800	1.1400	2.9890	11.4870	4.2740	7.9990	5.1560
P-value	0.0560	0.7670	0.3930	0.0090*	0.2330	0.0460*	0.1610
Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.5609	p=0.6750	p=0.7557	p=0.8498	p=0.5250	p=0.0468*	p=0.1441
OA vs Spondylosis	p=0.3235	p=0.7455	p=0.7868	p=0.5609	p=0.3942	p=0.4735	p=0.5518
OA vs Sprain	p=0.0935	p=0.5609	p=0.2287	p=0.0077 *	p=0.2793	p=0.4652	p=0.4989
RA vs Spondylosis	p=0.1636	p=0.5338	p=0.5609	p=0.5250	p=0.2085	p=0.0186*	p=0.0699
RA vs Sprain	p=0.3235	p=0.8924	p=0.1441	p=0.0074 *	p=0.8182	p=0.2184	p=0.0834
Spondylosis vs Sprain	p=0.0193	p=0.3369	p=0.3369	p=0.0256 *	p=0.0699	p=0.2134	p=0.9892

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to VAS scores at different time points

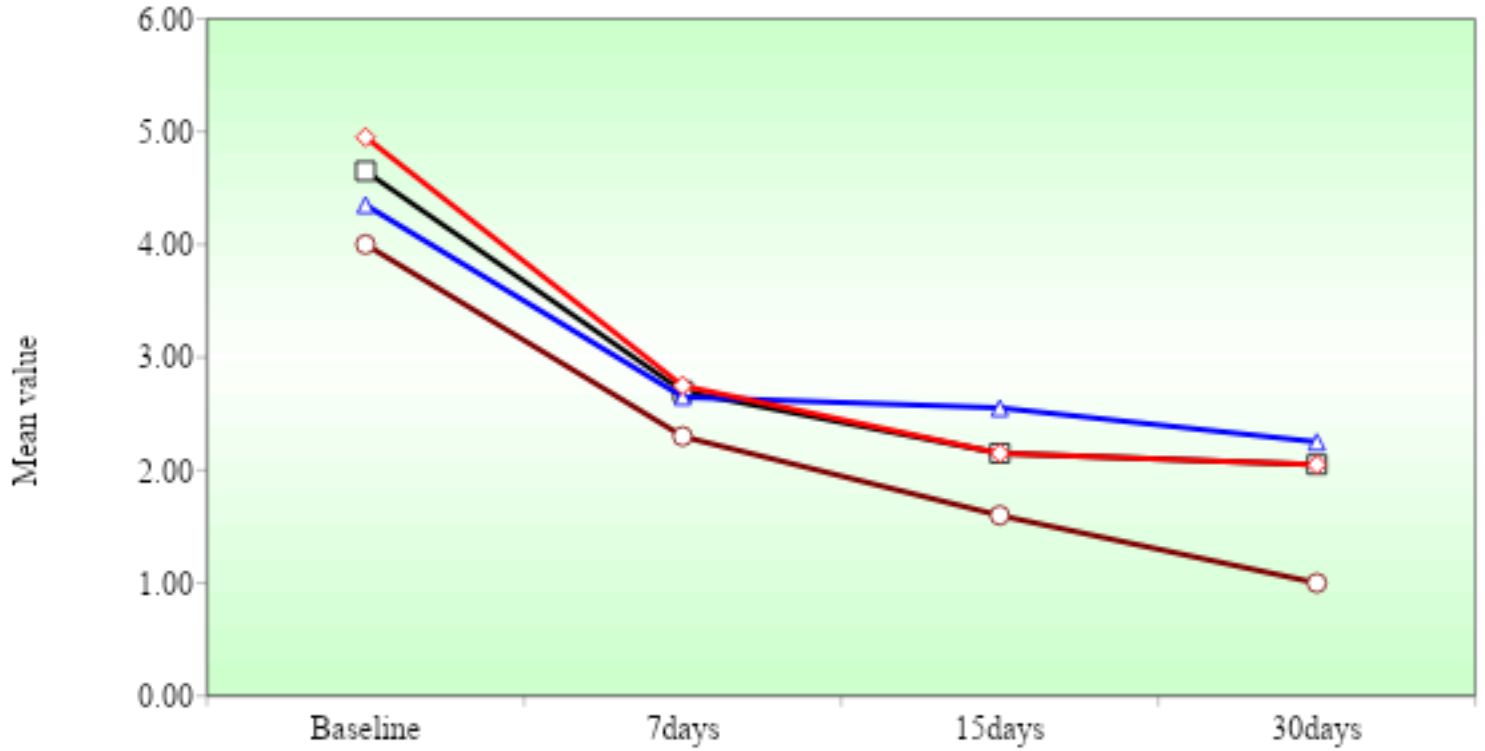


Table: Comparison of four diagnoses with respect to **swelling scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	0.2	0.4	0.1	0.3	0.2	0.4	0.1	0.2	0.1	0.4	0.1	0.4	0.2	0.4
RA	0.3	0.4	0.1	0.3	0.1	0.3	0.1	0.2	0.2	0.4	0.2	0.4	0.2	0.4
Spondylosis	0.2	0.4	0.1	0.2	0.0	0.0	0.0	0.0	0.2	0.4	0.2	0.4	0.2	0.4
Sprain	0.2	0.4	0.2	0.4	0.1	0.3	0.1	0.2	0.1	0.2	0.1	0.3	0.2	0.4
% of change in OA									50.00%#, p=0.3613		25.00%#, p=0.5930		75.00%#, p=0.1088	
% of change in RA									60.00%#, p=0.1088		60.00%#, p=0.1088		80.00%#, p=0.0679	
% of change in Spondylosis									75.00%#, p=0.1088		100.00%#, p=0.0679		100.00%#, p=0.0679	
% of change in Sprain									25.00%#, p=0.9990		50.00%#, p=0.9990		75.00%#, p=0.1088	
H-value	0.2210		1.0970		2.9370		1.0260		1.0950		1.7460		0.3420	
P-value	0.9740		0.7780		0.4010		0.7950		0.7780		0.6270		0.9520	

#applied Wilcoxon matched pairs test

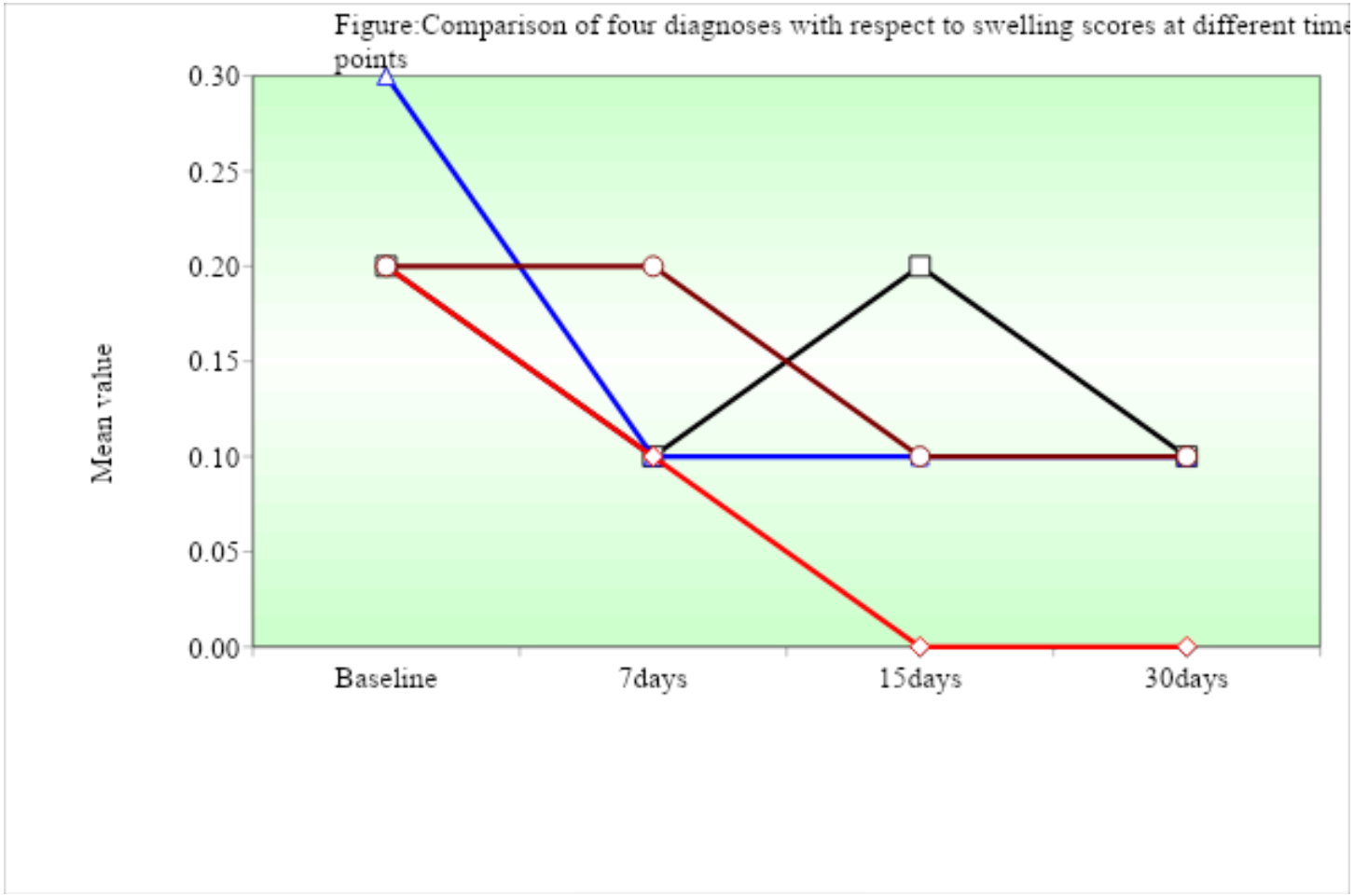


Figure:Comparison of four diagnoses with respect to swelling scores at different time points
Mean value
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Baseline
7days
15days
30days

Table: Comparison of four diagnoses with respect to **Tenderness scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	1.90	0.72	1.20	0.62	1.10	0.55	0.95	0.51	0.70	0.66	0.80	0.70	0.95	0.69
RA	2.25	0.44	1.35	0.75	1.35	0.75	1.20	0.52	0.90	0.79	0.90	0.79	1.05	0.69
Spondylosis	1.75	0.79	1.00	0.56	0.80	0.52	0.80	0.52	0.75	0.55	0.95	0.76	0.95	0.83
Sprain	1.05	0.51	0.35	0.49	0.10	0.31	0.05	0.22	0.70	0.57	0.95	0.51	1.00	0.46
% of change in OA									36.84%#, p=0.0022*		42.11%#, p=0.0015*		50.00%#, p=0.0004*	
% of change in RA									40.00%#, p=0.0010*		40.00%#, p=0.0015*		46.67%#, p=0.0004*	
% of change in Spondylosis									42.86%#, p=0.0010*		54.29%#, p=0.0007*		54.29%#, p=0.0011*	
% of change in Sprain									66.67%#, p=0.0021*		90.48%#, p=0.0003*		95.24%#, p=0.0002*	

H-value	32.7740	23.6850	38.4400	40.2720	0.6680	0.7600	0.6340
P-value	0.0001*	0.0001*	0.0001*	0.0001*	0.8810	0.8590	0.8890
Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.0787	p=0.5700	p=0.4171	p=0.2393	p=0.4989	p=0.5885	p=0.5609
OA vs Spondylosis	p=0.6168	p=0.3577	p=0.1677	p=0.4735	p=0.7455	p=0.6168	p=0.8817
OA vs Sprain	p=0.0005 *	p=0.0004 *	p=0.0001 *	p=0.0001 *	p=0.7660	p=0.4570	p=0.6456
RA vs Spondylosis	p=0.0256 *	p=0.1556	p=0.0385 *	p=0.0659	p=0.6949	p=0.9353	p=0.6750
RA vs Sprain	p=0.0001 *	p=0.0002 *	p=0.0001 *	p=0.0001 *	p=0.6750	p=0.9461	p=0.8077
Spondylosis vs Sprain	p=0.0032 *	p=0.0028 *	p=0.0004 *	p=0.0001 *	p=0.9892	p=0.8182	p=0.8077

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to Tenderness scores at different time poin

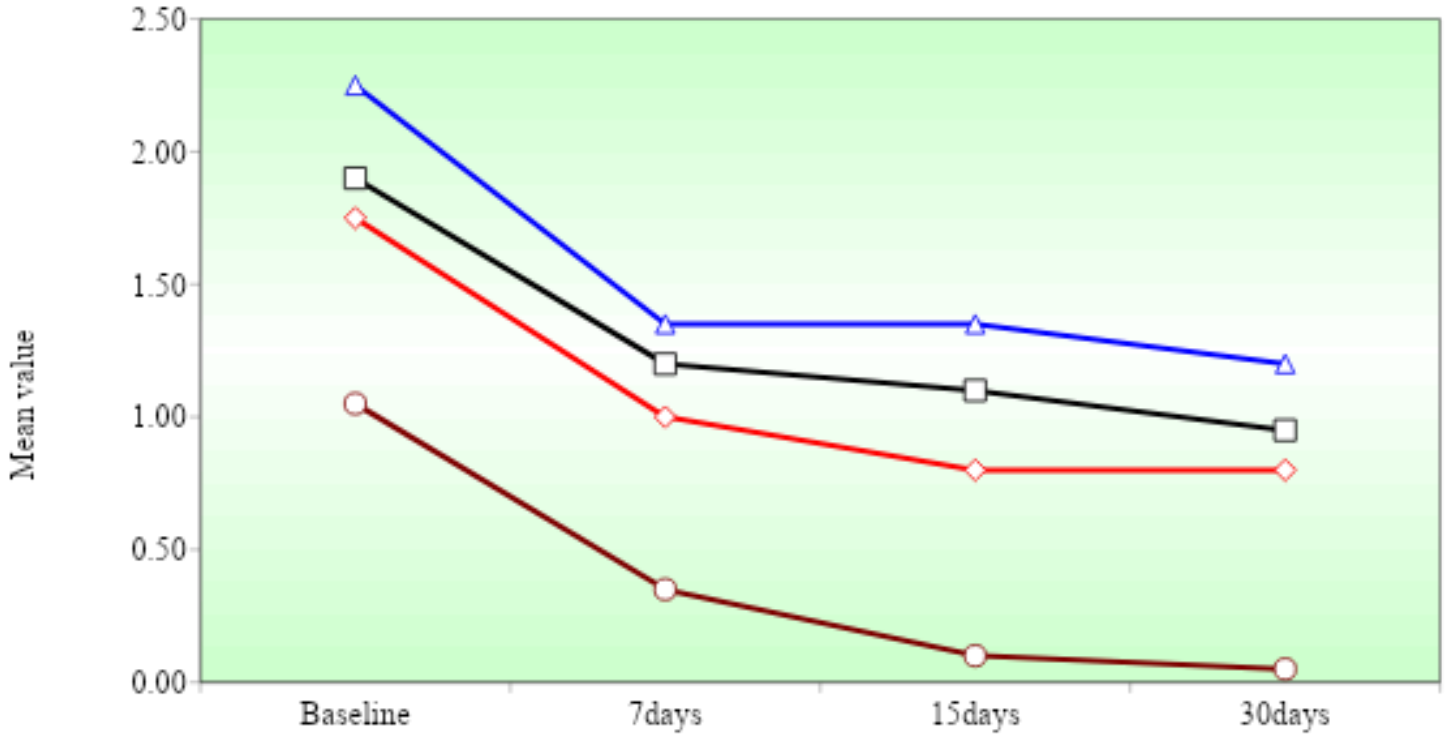


Table: Comparison of four diagnoses with respect to **Stiffness scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	0.6	0.5	0.3	0.4	0.2	0.4	0.1	0.3	0.3	0.5	0.4	0.5	0.5	0.5
RA	0.4	0.5	0.3	0.5	0.3	0.5	0.2	0.4	0.1	0.4	0.1	0.4	0.3	0.4
Spondylosis	0.2	0.4	0.1	0.2	0.1	0.2	0.1	0.2	0.2	0.4	0.2	0.4	0.2	0.4
Sprain	0.2	0.4	0.1	0.2	0.0	0.0	0.1	0.2	0.1	0.3	0.2	0.4	0.1	0.3
% of change in OA									54.55%#, p=0.0277*		72.73%#, p=0.0117*		81.82%#, p=0.0077*	
% of change in RA									25.00%#, p=0.3613		25.00%#, p=0.3613		62.50%#, p=0.0431*	
% of change in Spondylosis									75.00%#, p=0.1088		75.00%#, p=0.1088		75.00%#, p=0.1088	
% of change in Sprain									66.67%#, p=0.9999		100.00%#, p=0.1088		66.67%#, p=0.9999	

H-value	9.2280	7.5280	9.4800	1.7010	3.2650	5.8390	7.8390
P-value	0.0260*	0.0570	0.0240*	0.6370	0.3530	0.1200	0.0490*
Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.4171	p=0.7868	p=0.4171	p=0.7868	p=0.3169	p=0.1298	p=0.2793
OA vs Spondylosis	p=0.0583	p=0.2793	p=0.5885	p=0.7868	p=0.4171	p=0.1762	p=0.1046
OA vs Sprain	p=0.0305 *	p=0.2793	p=0.4171	p=0.7868	p=0.2793	p=0.1762	p=0.0500*
RA vs Spondylosis	p=0.2793	p=0.1762	p=0.1762	p=0.5885	p=0.8182	p=0.8182	p=0.5885
RA vs Sprain	p=0.1762	p=0.1762	p=0.1046	p=0.5885	p=0.9784	p=0.8182	p=0.4171
Spondylosis vs Sprain	p=0.7868	p=1.0000	p=0.7868	p=1.0000	p=0.7868	p=1.0000	p=0.7868

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to Stiffness scores at different time points

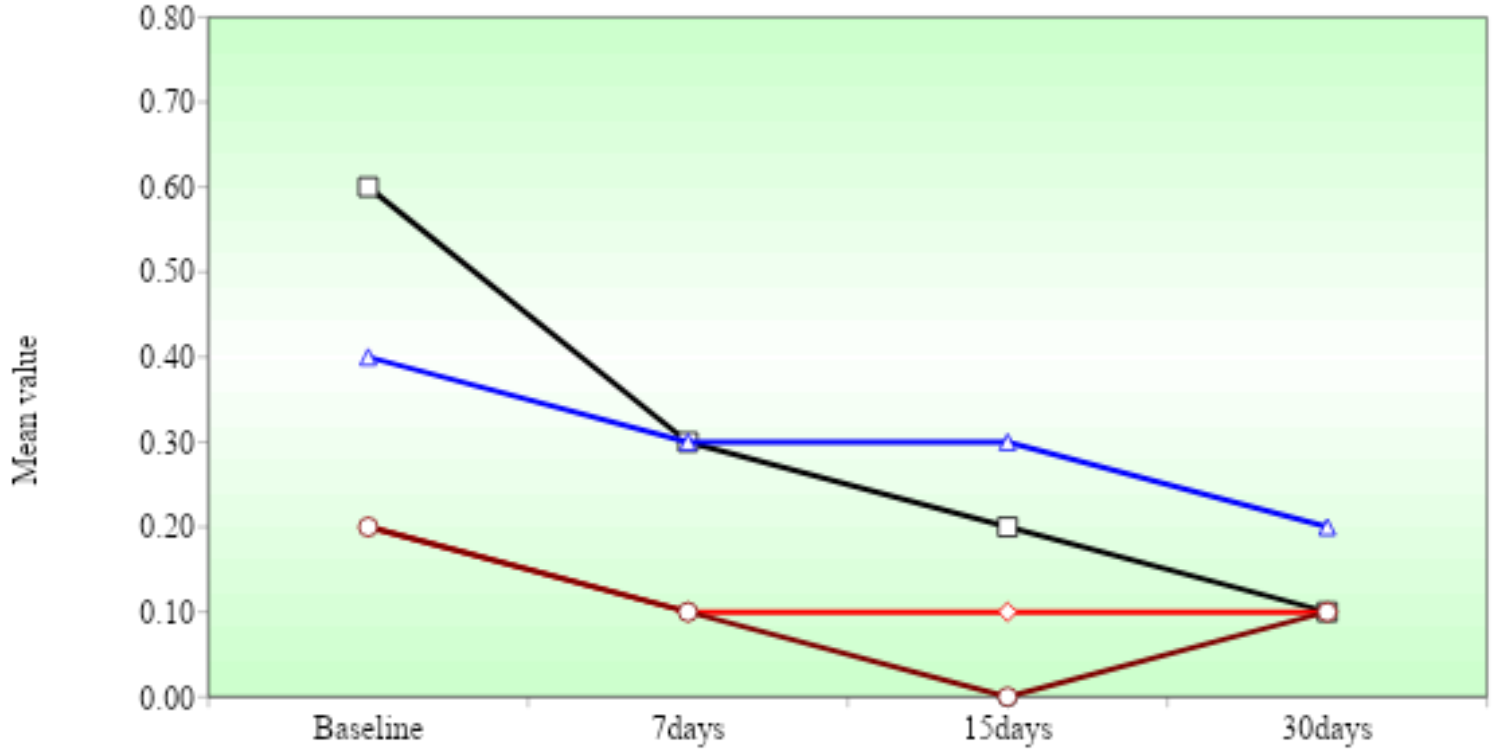


Table: Comparison of four diagnoses with respect to **left knee joint flexion** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	45.0	56.6	45.6	57.4	47.2	59.5	47.1	59.3	-0.6	2.3	-2.2	5.2	-2.1	5.2
RA	27.5	50.7	26.5	48.7	26.5	48.7	26.9	49.0	1.0	4.5	1.0	4.5	0.6	4.9
Spondylosis	59.5	55.6	60.0	55.8	60.0	55.8	60.3	56.0	-0.5	4.9	-0.5	4.9	-0.8	5.1
Sprain	16.5	40.3	16.5	40.3	16.5	40.3	16.5	40.3	0.0	0.0	0.0	0.0	0.0	0.0
% of change in OA									-1.33%#, p=1.0000		-4.89%#, p=0.0431*		-4.67%#, p=0.0679	
% of change in RA									3.64%#, p=1.0000		3.64%#, p=1.0000		2.18%#, p=1.0000	
% of change in Spondylosis									-0.84%#, p=1.0000		-0.84%#, p=1.0000		-1.35%#, p=0.7150	
% of change in Sprain									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	

H-value	7.1560	7.5970	7.7790	7.7410	3.8480	10.8270	4.9090
P-value	0.0670	0.0550	0.0510	0.0520	0.2780	0.0130*	0.1790
Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.5162	p=0.3942	p=0.3302	p=0.3369	p=0.4328	p=0.1199	p=0.2915
OA vs Spondylosis	p=0.5338	p=0.7557	p=0.9784	p=0.9892	p=0.4652	p=0.1517	p=0.3369
OA vs Sprain	p=0.1517	p=0.1298	p=0.1105	p=0.1105	p=0.5885	p=0.1762	p=0.2793
RA vs Spondylosis	p=0.1762	p=0.1333	p=0.1333	p=0.1333	p=0.9892	p=0.9892	p=0.9784
RA vs Sprain	p=0.5338	p=0.5609	p=0.5609	p=0.5609	p=0.7868	p=0.7868	p=0.9990
Spondylosis vs Sprain	p=0.0659	p=0.0531	p=0.0422 *	p=0.0421 *	p=0.1521	p=0.0186*	p=0.0377*

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to left knee joint flexion scores at different time points

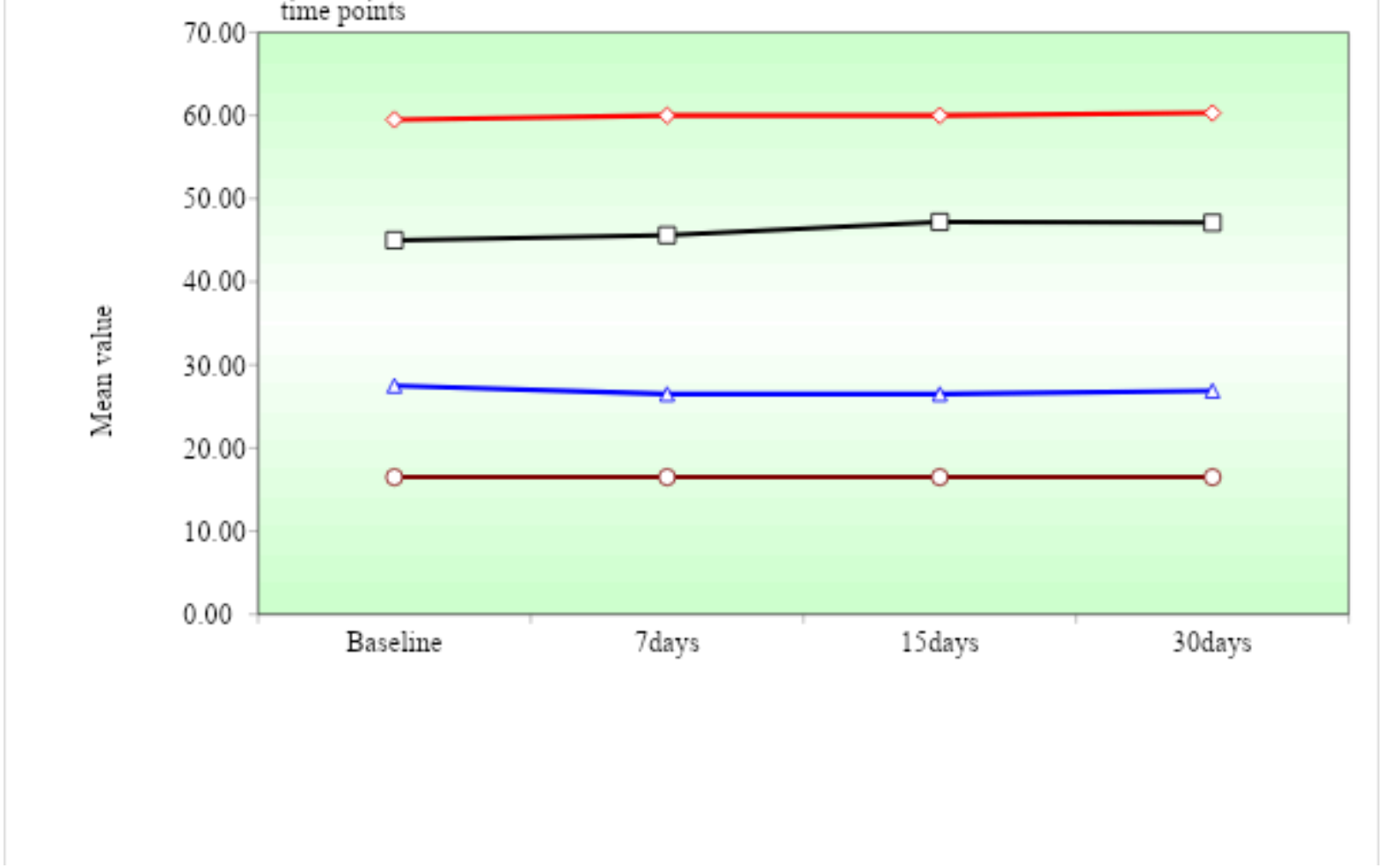


Table: Comparison of four diagnoses with respect to **left knee joint/extension** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	1.8	4.4	1.5	3.7	1.4	3.4	0.9	2.8	0.3	1.1	0.4	1.2	0.9	2.5
RA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Spondylosis	2.0	4.1	1.0	3.1	0.0	0.0	0.0	0.0	1.0	3.1	2.0	4.1	2.0	4.1
Sprain	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
% of change in OA									14.29%#, p=0.9999		20.00%#, p=0.9999		48.57%#, p=0.1088	
% of change in RA									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	
% of change in Spondylosis									50.00%#, p=1.0000		100.00%#, p=1.0000		100.00%#, p=0.7150	
% of change in Sprain									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	
H-value	7.8180		5.6880		9.2310		6.0760		3.8310		8.1160		8.0060	
P-value	0.0500		0.1280		0.0260*		0.1080		0.2800		0.0440*		0.0460*	
Pair wise comparisons by Mann-Whitney U test														
OA vs RA	p=0.4171		p=0.4171		p=0.4171		p=0.5885		p=0.7868		p=0.5885		p=0.4171	

OA vs Spondylosis	p=0.8287	p=0.7868	p=0.4171	p=0.5885	p=0.7660	p=0.5162	p=0.7049
OA vs Sprain	p=0.4171	p=0.4171	p=0.4171	p=0.5885	p=0.7868	p=0.5885	p=0.4171
RA vs Spondylosis	p=0.0374*	p=0.1520	p=0.0374*	p=1.0000	p=0.1520	p=0.0374*	p=0.0374*
RA vs Sprain	p=1.0000	p=1.0000	p=1.0000	p=1.0000	p=1.0000	p=1.0000	p=1.0000
Spondylosis vs Sprain	p=0.2793	p=0.5885	p=1.0000	p=1.0000	p=0.5885	p=0.2793	p=0.2793

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to left knee joint/extension scores at different time points

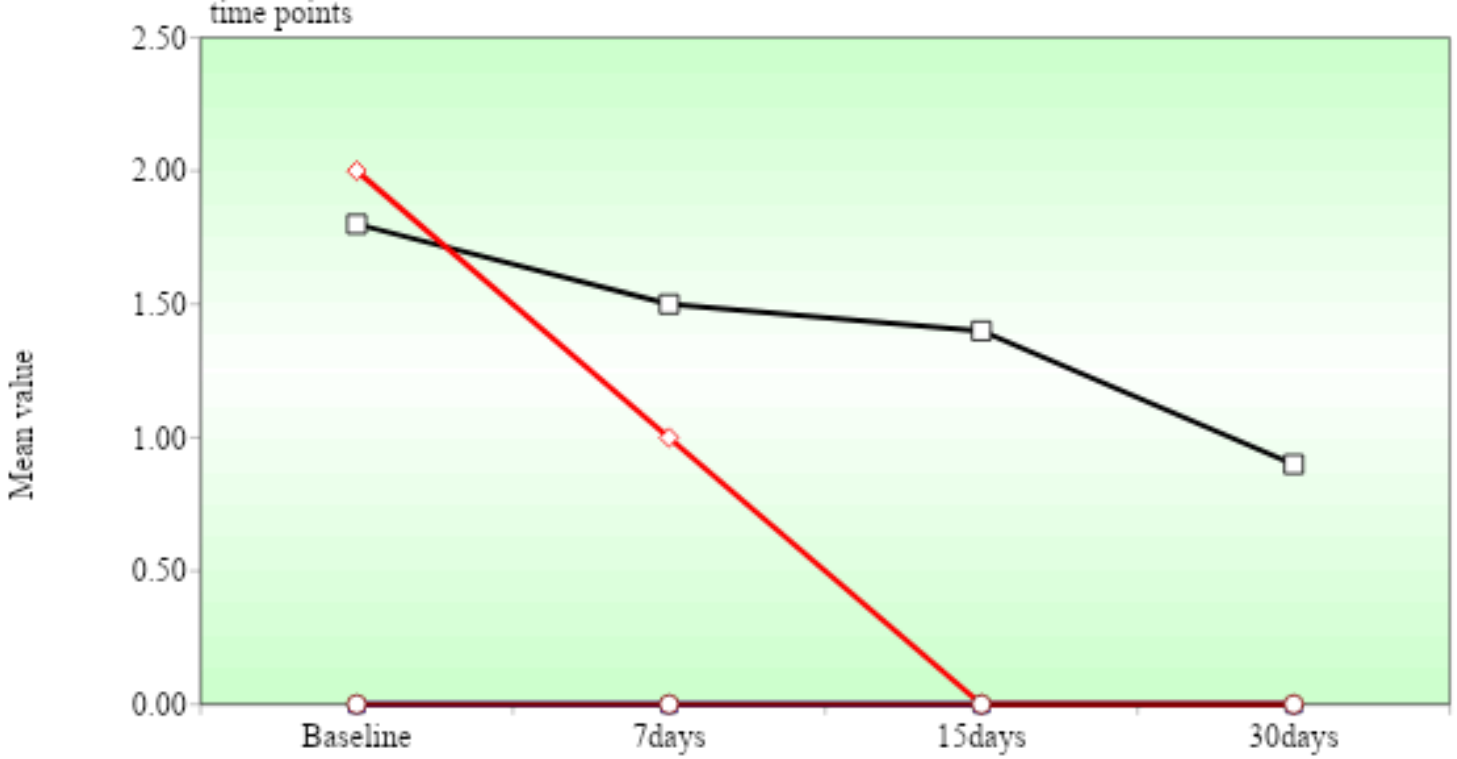


Table: Comparison of four diagnoses with respect to **right knee joint/flexion** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	39.85	55.78	39.50	55.30	41.50	58.25	40.90	57.43	0.35	1.18	-1.65	4.93	-1.05	5.58
RA	34.50	48.93	37.00	52.12	36.40	51.26	37.90	53.59	-2.50	7.86	-1.90	5.33	-3.40	11.41
Spondylosis	53.75	55.46	55.85	57.44	55.85	57.44	55.55	57.08	-2.10	5.41	-2.10	5.41	-1.80	5.84
Sprain	16.50	40.30	16.50	40.30	16.50	40.30	16.50	40.30	0.00	0.00	0.00	0.00	0.00	0.00
% of change in OA									0.88%#, p=1.0000		-4.14%#, p=0.1057		-2.63%#, p=0.4185	
% of change in RA									-7.25%#, p=1.0000		-5.51%#, p=0.1088		-9.86%#, p=0.1380	
% of change in Spondylosis									-3.91%#, p=0.1088		-3.91%#, p=0.1088		-3.35%#, p=1.0000	
% of change in Sprain									0.00		0.00		0.00	
H-value	5.4270		6.2540		6.0780		5.8640		8.0320		2.7940		1.7940	
P-value	0.1430		0.1000		0.1080		0.1180		0.0520		0.4240		0.6160	

#applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to right knee joint/flexion scores at different time points

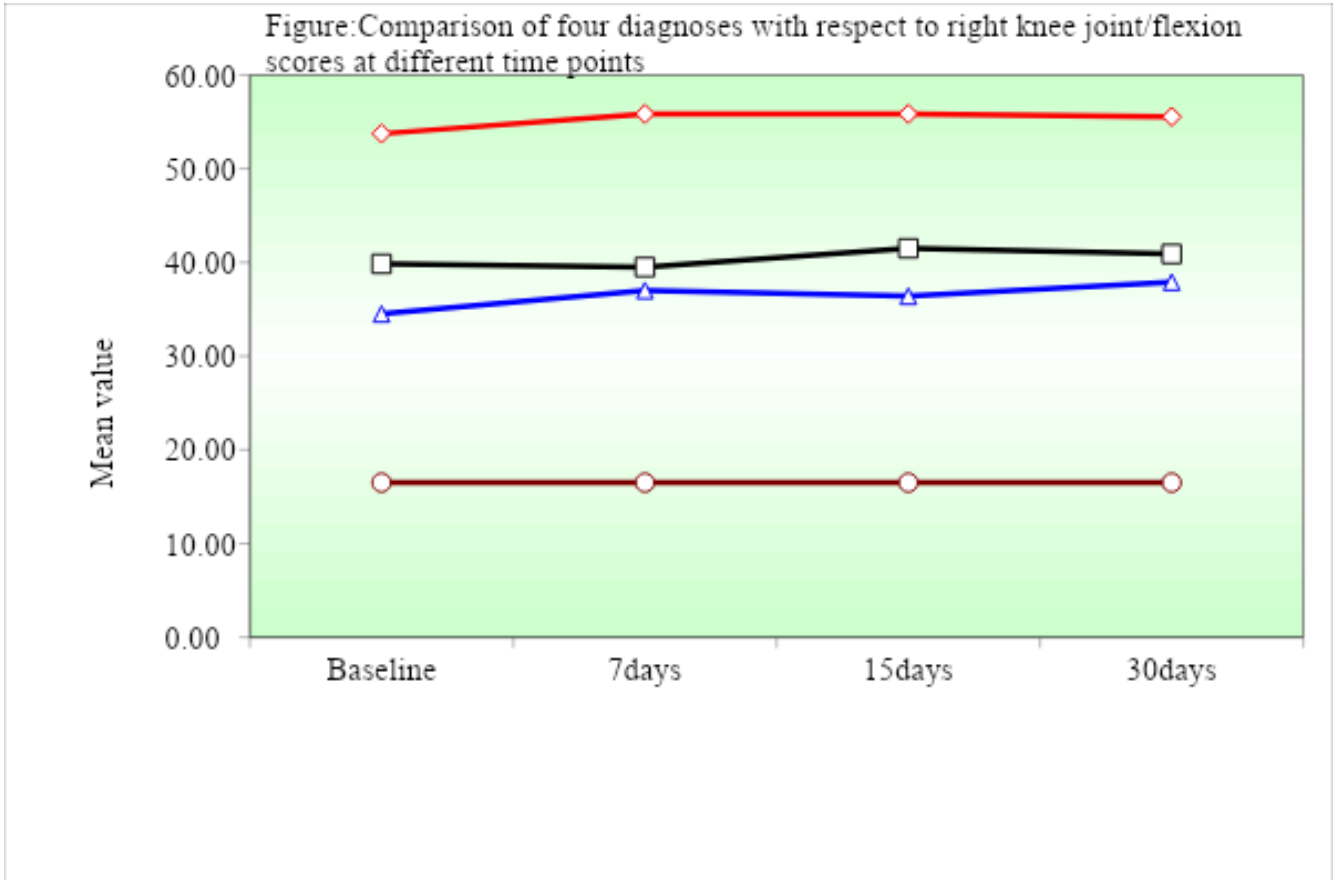


Table: Comparison of four diagnoses with respect to **right knee joint/extension** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	4.00	10.59	4.75	10.06	4.40	9.48	1.00	3.08	-0.75	3.73	-0.40	4.11	3.00	10.18
RA	2.00	6.96	3.00	7.85	2.25	5.50	1.50	4.62	-1.00	5.28	-0.25	6.38	0.50	5.36
Spondylosis	5.75	10.79	4.25	10.79	3.00	10.44	2.75	10.19	1.50	3.66	2.75	4.99	3.00	4.97
Sprain	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
% of change in OA									-18.75%#, p=0.4227		-10.00%#, p=0.8551		75.00%#, p=0.1088	
% of change in RA									-50.00%#, p=0.2851		-12.50%#, p=0.7150		25.00%#, p=0.7893	
% of change in Spondylosis									26.09%#, p=0.1088		47.83%#, p=0.0431*		52.17%#, p=0.0277*	
% of change in Sprain									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	

H-value	9.4530	5.3000	5.5500	2.1380	4.8600	6.1750	7.4590
P-value	0.0240*	0.1510	0.1360	0.5440	0.1820	0.1030	0.0590

*p<0.05, #applied Wilcoxon matched pairs test

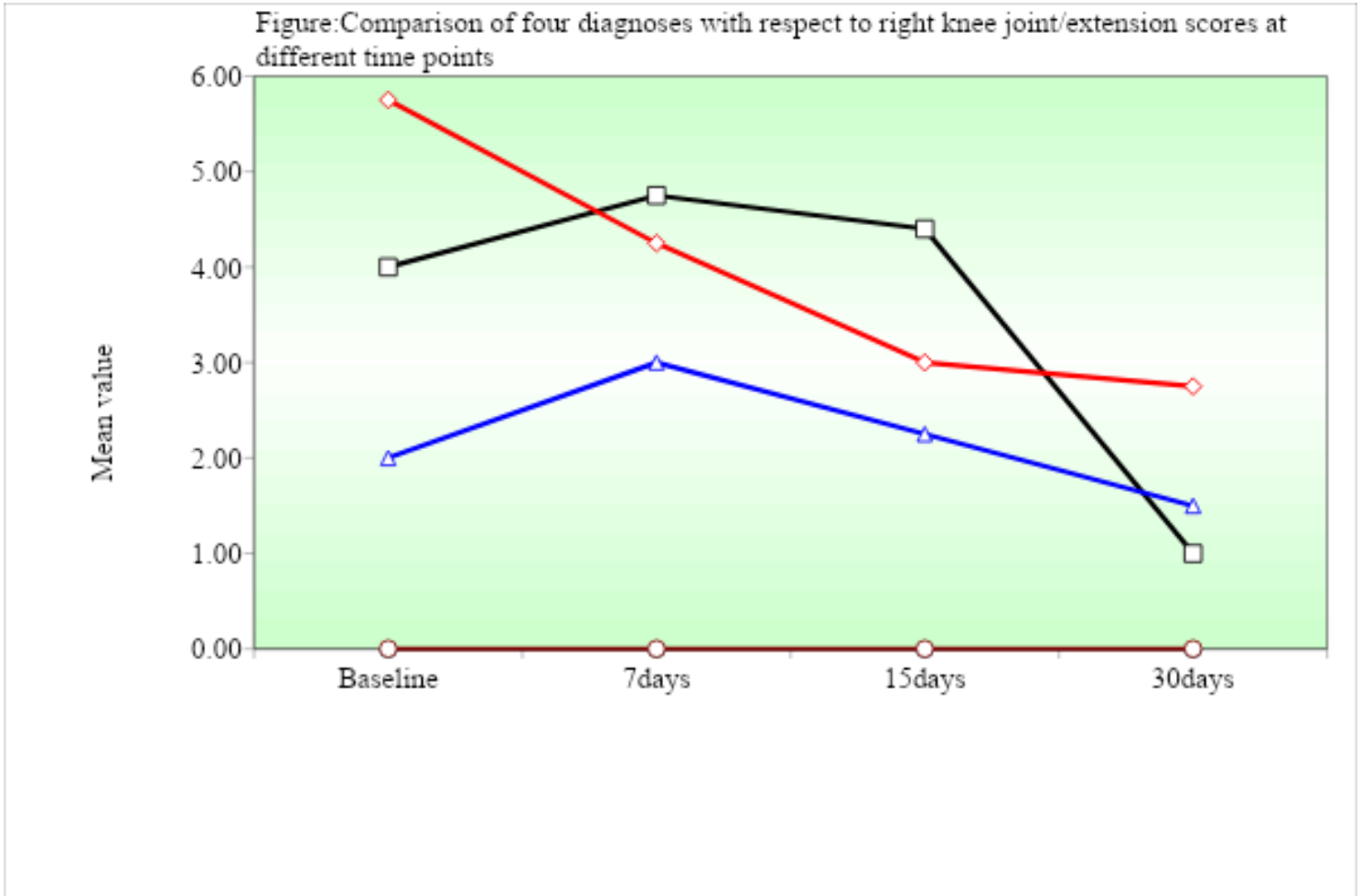


Table: Comparison of four diagnoses with respect to **LUMBER FLEXION** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	37.00	17.73	38.25	18.37	37.85	18.26	38.35	18.03	-1.25	2.22	-0.85	2.76	-1.35	3.79
RA	26.00	25.11	24.50	25.54	26.75	25.25	25.50	23.73	1.50	5.64	-0.75	4.67	0.50	6.47
Spondylosis	15.75	22.02	15.75	22.02	15.75	22.02	15.75	22.02	0.00	0.00	0.00	0.00	0.00	0.00
Sprain	11.25	19.99	11.25	19.99	11.25	19.99	11.25	19.99	0.00	0.00	0.00	0.00	0.00	0.00
% of change in OA									-3.38%#, p=0.0431		-2.30%#, p=0.1508		-3.65%#, p=0.0796	
% of change in RA									5.77%#, p=1.0000		-2.88%#, p=1.0000		1.92%#, p=0.6002	
% of change in Spondylosis									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	
% of change in Sprain									0.00%#, p=1.0000		0.00%#, p=1.0000		0.00%#, p=1.0000	
H-value	12.9540		15.7940		14.6110		15.1190		15.4520		3.0740		4.6220	
P-value	0.0050*		0.0010*		0.0020*		0.0020*		0.0010*		0.3800		0.2020	

Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.3712	p=0.1177	p=0.2819	p=0.2135	p=0.0078*	p=0.3261	p=0.1345
OA vs Spondylosis	p=0.0155*	p=0.0038*	p=0.0068*	p=0.0068*	p=0.1762	p=0.4171	p=0.4171
OA vs Sprain	p=0.0023*	p=0.0007*	p=0.0012*	p=0.0012*	p=0.1762	p=0.4171	p=0.4171
RA vs Spondylosis	p=0.1719	p=0.2733	p=0.1719	p=0.1719	p=0.5885	p=1.0000	p=0.5885
RA vs Sprain	p=0.0679	p=0.1199	p=0.0679	p=0.0679	p=0.5885	p=1.0000	p=0.5885
Spondylosis vs Sprain	p=0.5885	p=0.5885	p=0.5885	p=0.5885	p=1.0000	p=1.0000	p=1.0000

*p<0.05, #applied Wilcoxon matched pairs test

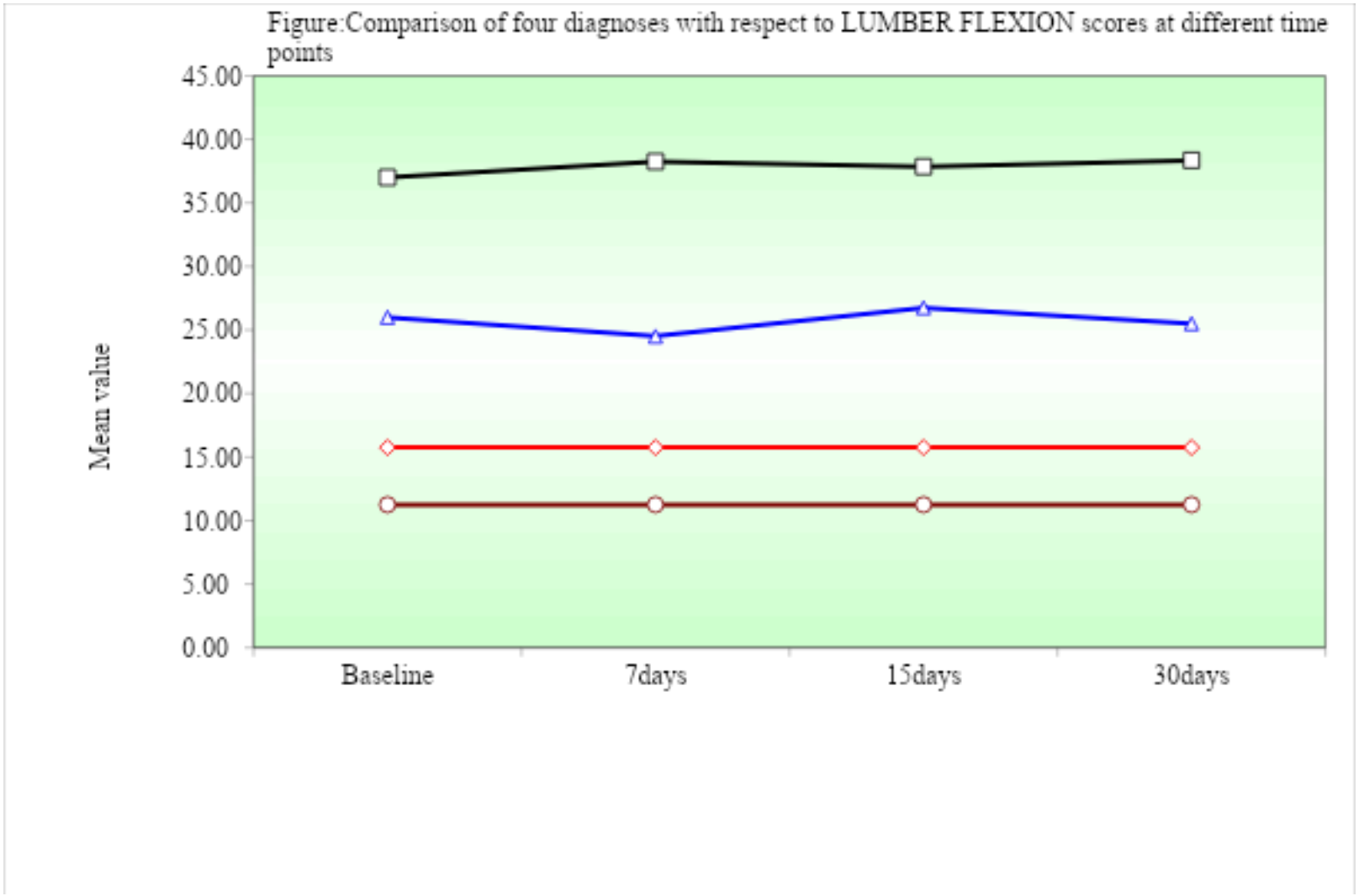


Figure:Comparison of four diagnoses with respect to LUMBER FLEXION scores at different time points
Mean value
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Baseline
7days
15days
30days

ble: Comparison of four diagnoses with respect to **LUMBER EXTENSION** scores at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	20.00	9.03	19.85	9.11	20.65	9.40	21.00	9.45	0.15	2.39	-0.65	2.30	-1.00	3.61
RA	13.00	12.29	15.00	14.60	13.50	12.58	12.85	12.04	-2.00	6.96	-0.50	2.76	0.15	3.07
Spondylosis	7.75	11.06	8.00	11.40	8.50	11.93	8.50	11.93	-0.25	1.12	-0.75	2.45	-0.75	2.45
Sprain	5.75	10.29	5.85	10.45	6.25	11.11	6.25	11.11	-0.10	0.45	-0.50	1.54	-0.50	1.54
% of change in OA									0.75%#, p=0.8927		-3.25%#, p=0.2807		-5.00%#, p=0.2361	
% of change in RA									-15.38%#, p=1.0000		-3.85%#, p=0.4227		1.15%#, p=0.6858	
% of change in Spondylosis									-3.23%#, p=1.0000		-9.68%#, p=1.0000		-9.68%#, p=1.0000	
% of change in Sprain									-1.74%#, p=1.0000		-8.70%#, p=1.0000		-8.70%#, p=1.0000	

H-value	16.2710	14.1640	14.3030	15.6650	2.1310	0.5670	2.1210
P-value	0.0010*	0.0030*	0.0030*	0.0010*	0.5460	0.9040	0.5480
Pair wise comparisons by Mann-Whitney U test							
OA vs RA	p=0.1636	p=0.6456	p=0.1298	p=0.0256*	p=0.4328	p=0.6554	p=0.3302
OA vs Spondylosis	p=0.0031*	p=0.0077*	p=0.0068*	p=0.0049*	p=0.6168	p=0.8182	p=0.7764
OA vs Sprain	p=0.0008*	p=0.0016*	p=0.0019*	p=0.0015*	p=0.6359	p=0.7868	p=0.7251
RA vs Spondylosis	p=0.1850	p=0.1298	p=0.2559	p=0.3867	p=0.7660	p=0.8077	p=0.4570
RA vs Sprain	p=0.0787	p=0.0453*	p=0.1199	p=0.1762	p=0.7660	p=0.8287	p=0.4652
Spondylosis vs Sprain	p=0.5351	p=0.4913	p=0.5530	p=0.5530	p=0.9714	p=0.9585	p=0.9585

*p<0.05, #applied Wilcoxon matched pairs test

Figure:Comparison of four diagnoses with respect to LUMBER EXTENSION scores at different time points

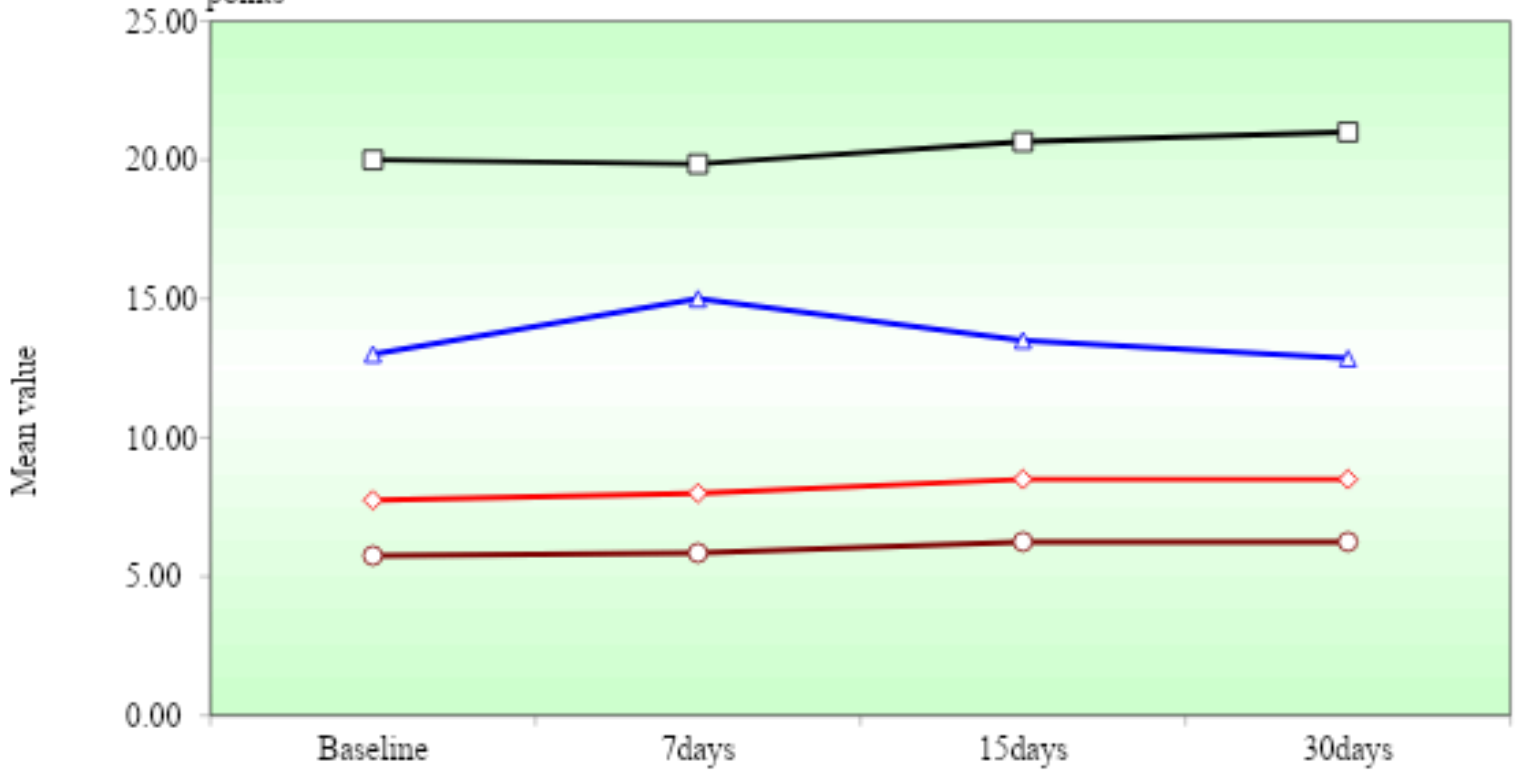


Table: Comparison of four diagnoses with respect to **various parameters** scores at different time points by Kruskal Wallis ANOVA (numbers are only yes status)

Parameters	Time	OA		RA		Spondylosis		Sprain		H-value	p-value
		Present	%	Present	%	Present	%	Present	%		
Neck flexion	Baseline	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	7day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	15day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	30day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
Neck extension	Baseline	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	7day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	15day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	30day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500

Neck rotation	Baseline	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	7day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	15day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
	30day	2	10.00	1	5.00	5	25.00	1	5.00	5.3160	0.1500
Lateral bending left side	Baseline	2	10.00	1	5.00	2	10.00	1	5.00	0.7120	0.8700
	7day	2	10.00	1	5.00	4	20.00	1	5.00	3.2920	0.3490
	15day	2	10.00	1	5.00	4	20.00	1	5.00	3.2920	0.3490
	30day	2	10.00	1	5.00	4	20.00	1	5.00	3.2920	0.3490
Lateral bending right side	Baseline	1	5.00	0	0.00	4	20.00	1	5.00	6.4050	0.0930
	7day	1	5.00	0	0.00	4	20.00	1	5.00	6.4050	0.0930
	15day	1	5.00	0	0.00	4	20.00	1	5.00	6.4050	0.0930

	30day	0	0.00	0	0.00	4	20.00	1	5.00	9.0590	0.0290
Right wrist joint flexion	Baseline	1	5.00	0	0.00	0	0.00	4	20.00	9.0590	0.0290
	7day	1	5.00	0	0.00	0	0.00	4	20.00	9.0590	0.0290
	15day	1	5.00	0	0.00	0	0.00	4	20.00	9.0590	0.0290
	30day	1	5.00	0	0.00	0	0.00	4	20.00	9.0590	0.0290
Right wrist joint extension	Baseline	1	5.00	0	0.00	0	0.00	2	10.00	3.7620	0.2880
	7day	0	0.00	0	0.00	0	0.00	3	15.00	9.2340	0.0260
	15day	1	5.00	0	0.00	0	0.00	4	20.00	9.0590	0.0290
	30day	0	0.00	0	0.00	0	0.00	4	20.00	12.4740	0.0060
Right wrist joint ulnar deviation	Baseline	0	0.00	0	0.00	0	0.00	2	10.00	6.0770	0.1080
	7day	2	10.00	0	0.00	1	5.00	3	15.00	3.5590	0.3130

	15day	1	5.00	0	0.00	1	5.00	4	20.00	6.4050	0.0930
	30day	1	5.00	0	0.00	1	5.00	4	20.00	6.4050	0.0930
Right wrist joint radial deviation	Baseline	0	0.00	0	0.00	0	0.00	2	10.00	6.0770	0.1080
	7day	2	10.00	0	0.00	1	5.00	2	10.00	2.3170	0.5090
	15day	1	5.00	0	0.00	1	5.00	4	20.00	6.4050	0.0930
	30day	1	5.00	0	0.00	1	5.00	4	20.00	6.4050	0.0930
Left shoulder joint/abduction	Baseline	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	7day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	15day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	30day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
Right shoulder joint abduction	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880

	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
Left shoulder joint adduction	Baseline	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	7day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	15day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	30day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
Right shoulder joint adduction	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880

Flexion/ left shoulder joint	Baseline	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	7day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	15day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	30day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
Flexion/ right shoulder joint	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
Extention/ left shoulder joint	Baseline	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	7day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	15day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880

	30day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
Extention/ right shoulder joint	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
External rotation/ left shoulder joint	Baseline	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	7day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	15day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
	30day	1	5.00	0	0.00	2	10.00	0	0.00	3.7620	0.2880
External rotation/ right shoulder joint	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880

	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
Internal rotation/ left shoulder joint	Baseline	0	0.00	0	0.00	2	10.00	0	0.00	6.0770	0.1080
	7day	0	0.00	0	0.00	2	10.00	0	0.00	6.0770	0.1080
	15day	0	0.00	0	0.00	2	10.00	0	0.00	6.0770	0.1080
	30day	0	0.00	0	0.00	2	10.00	0	0.00	6.0770	0.1080
Internal rotation/ right shoulder joint	Baseline	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	7day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	15day	0	0.00	1	5.00	2	10.00	0	0.00	3.7620	0.2880
	30day	0	0.00	1	5.00	3	15.00	0	0.00	6.2370	0.1010
Plantar flexion	Baseline	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010

	7day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
	15day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
	30day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
Dorsi flexion	Baseline	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
	7day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
	15day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
	30day	0	0.00	1	5.00	0	0.00	3	15.00	6.2370	0.1010
Right elbow joint flexion	Baseline	1	5.00	1	5.00	0	0.00	4	20.00	6.4050	0.0930
	7day	1	5.00	1	5.00	0	0.00	4	20.00	6.4050	0.0930
	15day	1	5.00	1	5.00	0	0.00	4	20.00	6.4050	0.0930
	30day	1	5.00	1	5.00	1	5.00	4	20.00	4.1740	0.2430

Right elbow joint extention	Baseline	0	0.00	0	0.00	0	0.00	0	0.00	0.0000	1.0000
	7day	0	0.00	0	0.00	0	0.00	0	0.00	0.0000	1.0000
	15day	0	0.00	0	0.00	0	0.00	0	0.00	0.0000	1.0000
	30day	0	0.00	0	0.00	0	0.00	0	0.00	0.0000	1.0000
	RA 0TH	2	10.00	0	0.00	0	0.00	0	0.00	6.0770	0.1080
	CRP 0TH	0	0.00	0	0.00	0	0.00	0	0.00	0.0000	1.0000

Table: Comparison of four diagnoses with respect to **PGAS scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	3.15	6.66	1.60	1.70	1.25	1.52	1.15	1.79	1.55	5.61	1.90	5.50	2.00	5.32
RA	2.15	3.57	2.00	3.54	1.75	3.58	1.70	3.60	0.15	0.49	0.40	0.75	0.45	0.83
Spondylosis	1.60	1.19	1.45	1.10	1.45	1.10	1.35	0.93	0.15	0.49	0.15	0.49	0.25	0.64
Sprain	3.05	9.68	2.95	9.69	0.90	1.07	0.75	1.16	0.10	0.31	2.15	8.92	2.30	8.89
% of change in OA									49.21%#, p=0.1088		60.32%#, p=0.0431*		63.49%#, p=0.0051*	
% of change in RA									6.98%#, p=1.0000		18.60%#, p=0.0431*		20.93%#, p=0.0431*	
% of change in Spondylosis									9.38%#, p=1.0000		9.38%#, p=1.0000		15.63%#, p=0.1088	

% of change in Sprain								3.28%#, p=1.0000	70.49%#, p=0.0679	75.41%#, p=0.0277*
H-value	2.1050		2.6310		3.0110		4.8490	0.5950	2.1000	5.7500
P-value	0.5510		0.4520		0.3900		0.1830	0.8980	0.5520	0.1240

*p<0.05, #applied Wilcoxon matched pairs test

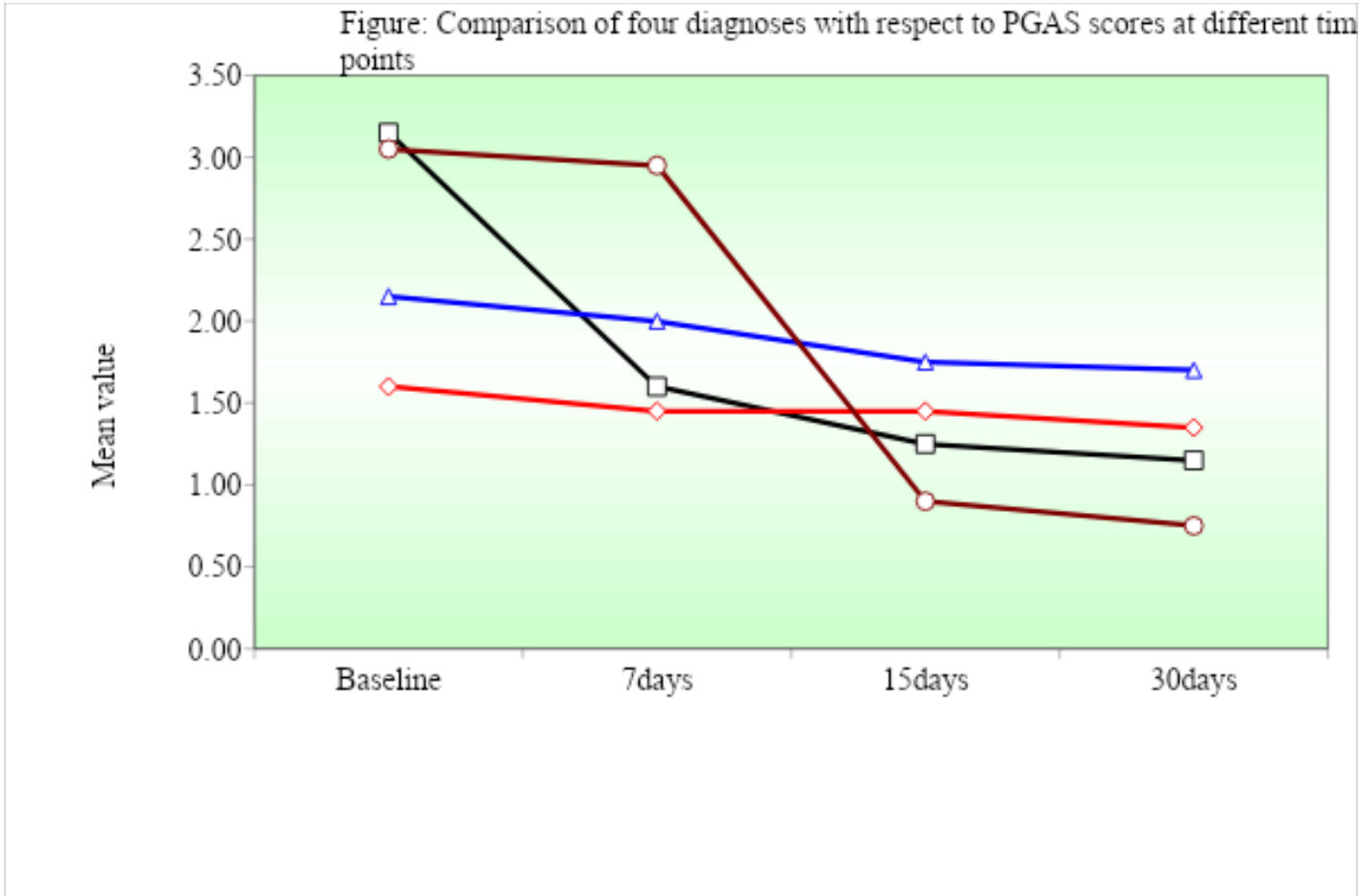


Table: Comparison of four diagnoses with respect to **TOTAL PAINFUL JOINTS scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	2.85	6.20	1.45	1.50	1.05	1.15	1.05	1.54	1.40	5.58	1.80	5.46	1.80	5.28
RA	1.80	3.47	1.80	3.47	1.55	3.50	1.50	3.52	0.00	0.00	0.25	0.55	0.30	0.66
Spondylosis	1.45	1.05	1.30	0.92	1.30	0.92	1.30	0.92	0.15	0.49	0.15	0.49	0.15	0.49
Sprain	1.80	4.81	1.75	4.82	0.70	0.80	0.45	0.83	0.05	0.22	1.10	4.46	1.35	4.42
% of change in OA									49.12%#, p=0.1088		63.16%#, p=0.0277*		63.16%#, p=0.0051*	
% of change in RA									0.00%#, p=1.0000		13.89%#, p=0.0679		16.67%#, p=0.0679	
% of change in Spondylosis									10.34%#, p=1.0000		10.34%#, p=1.0000		10.34%#, p=1.0000	
% of change in Sprain									2.78%#, p=1.0000		61.11%#, p=0.1088		75.00%#, p=0.0117	
H-value	3.6850		3.4560		4.2490		8.3750		3.6800		3.0110		8.9100	

P-value	0.2980	0.3270	0.2360	0.0390*	0.2980	0.3900	0.0310*

*p<0.05, #applied Wilcoxon matched pairs test

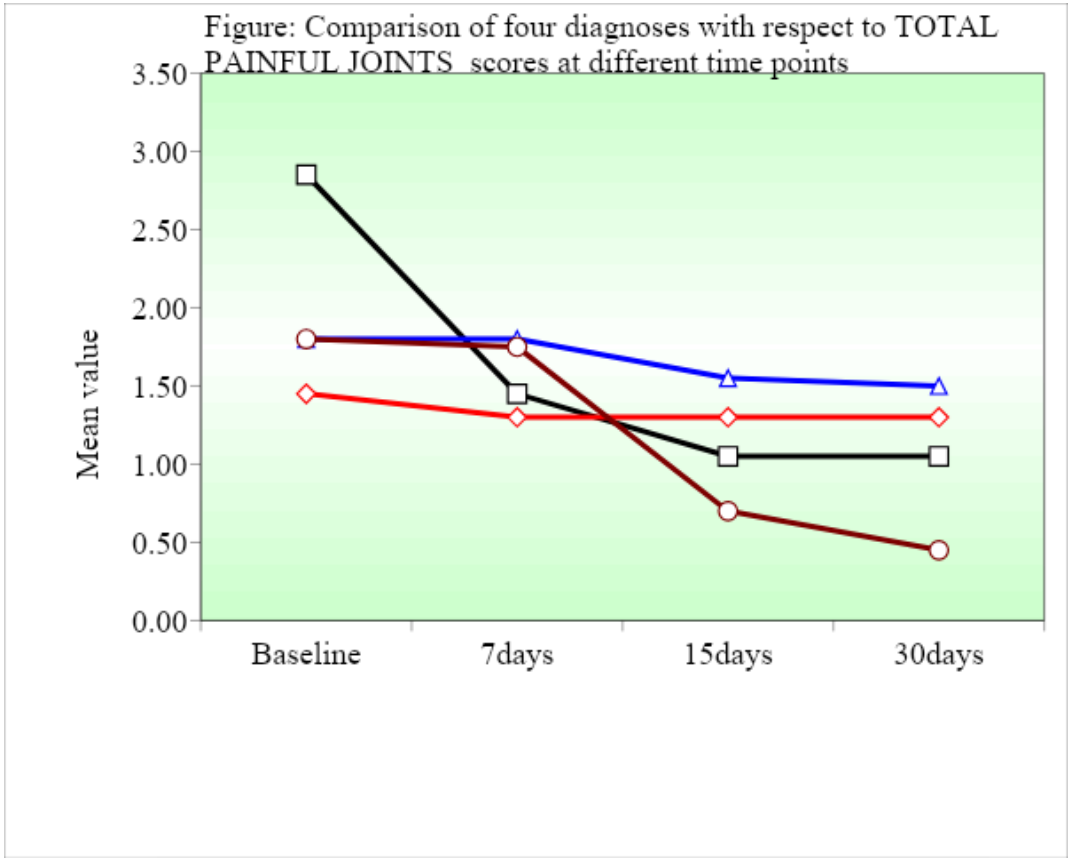
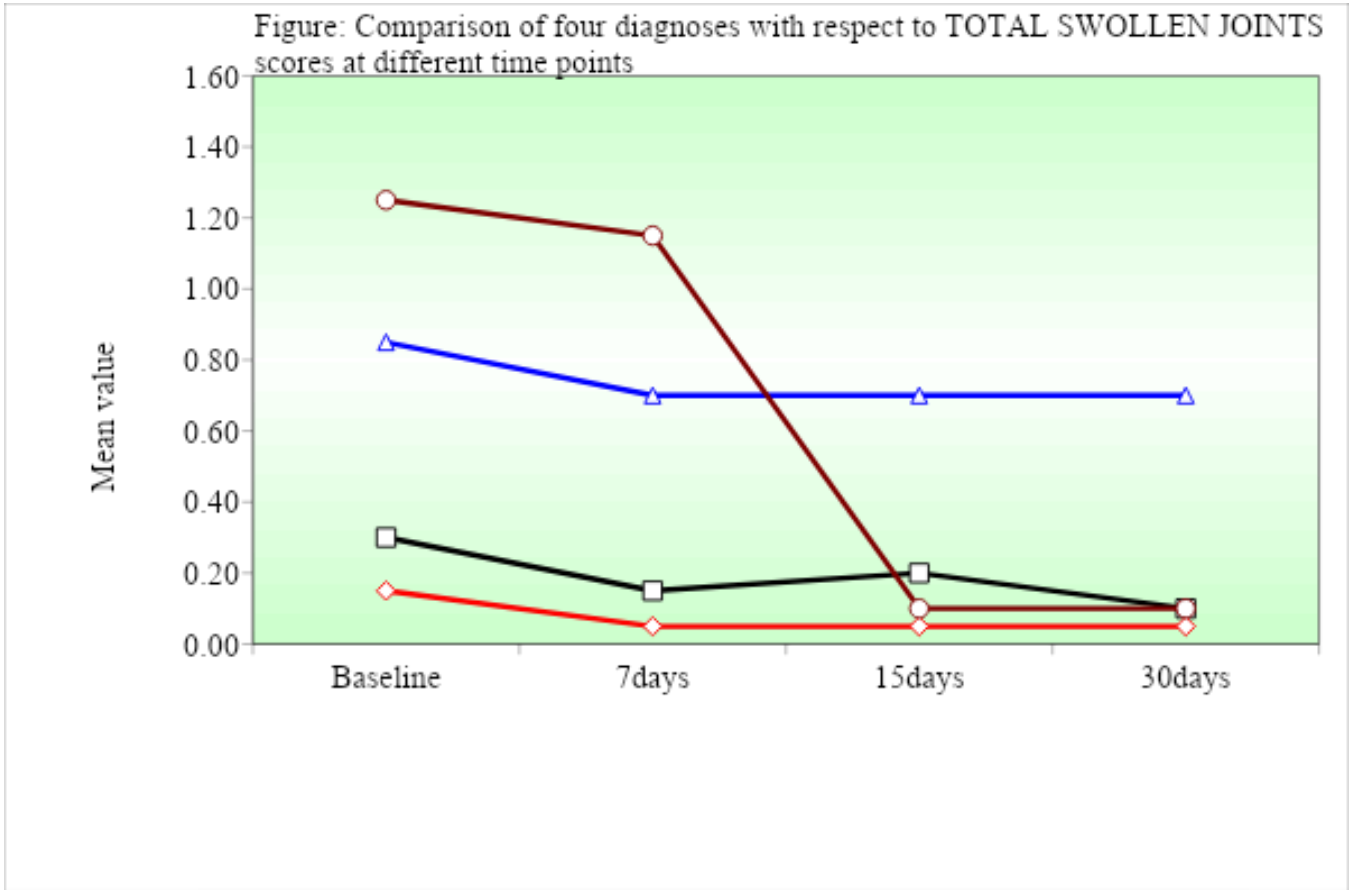


Table: Comparison of four diagnoses with respect to **TOTAL SWOLLEN JOINTS scores** at different time points by Kruskal Wallis ANOVA

Diagnosis	Baseline		7days		15days		30days		Changes from Baseline to					
									7days		15days		30days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
OA	0.30	0.80	0.15	0.49	0.20	0.52	0.10	0.45	0.15	0.67	0.10	0.72	0.20	0.70
RA	0.85	2.28	0.70	2.27	0.70	2.27	0.70	2.27	0.15	0.49	0.15	0.49	0.15	0.49
Spondylosis	0.15	0.49	0.05	0.22	0.05	0.22	0.05	0.22	0.10	0.45	0.10	0.45	0.10	0.45
Sprain	1.25	4.90	1.15	4.91	0.10	0.45	0.10	0.45	0.10	0.31	1.15	4.45	1.15	4.45
% of change in OA									50.00%#, p=1.0000		33.33%#, p=1.0000		66.67%#, p=1.0000	
% of change in RA									17.65%#, p=1.0000		17.65%#, p=1.0000		17.65%#, p=1.0000	
% of change in Spondylosis									66.67%#, p=1.0000		66.67%#, p=1.0000		66.67%#, p=1.0000	

% of change in Sprain									8.00%#, p=1.0000	92.00%#, p=0.0679	92.00%#, p=0.0679
H-value	1.8600		1.2660		2.2880		2.3150		0.5930	3.7980	2.2070
P-value	0.6020		0.7370		0.5150		0.5100		0.8980	0.2840	0.5310

#applied Wilcoxon matched pairs test



SAFETY PARAMETERS (Haematology, LFT, RFT)

Table: Normality of change scores from baseline to 7 days of different parameters by Kolmogorov Smirnov test

Parameters	Z-value	p-value
Hb%	**1.2240**	**0.1000**
WBC count	**0.6580**	**0.7800**
Neutrophils	**0.6050**	**0.8580**
Lymphocytes	1.9420	0.0010*
Eosinophils	**1.0790**	**0.1950**
Monocytes	1.7110	0.0060*
ESR	2.0680	0.0001*
S.Bilirubin Total	2.3440	0.0001*
S Bilirubin Direct	3.2980	0.0001*
SGPT	1.8890	0.0020*
SGOT	1.8380	0.0020*
S total Protein	1.3910	0.0420*
S albumin	2.3320	0.0001*
A/G Ratio	2.6140	0.0001*
S. alkaline Phosphatase	1.5320	0.0180*
Creatinine	1.5130	0.0210*
Urea	1.8960	0.0020*
Uric Acid	1.2320	0.0960*

*$p<0.05$

Note: Change in Hb%, WBC count, Neutrophils and Eosinophils from baseline to 7 days not follows a normal distribution, the parametric paired t test was applied and rest of the parameters the non-parametric tests i.e. Wilcoxon matched pairs test was applied

Table: Comparison of baseline and 7 days time points with respect to Hemetology parameters by paired t test and Wilcoxon matched pairs test

Parameters	Time	Mean	Std.Dv.	Mean Diff.	SD Diff.	% of change	Paired t / Z-value	P-value
Hb%	Baseline	11.58	2.19					
	7 day	11.84	1.90	-0.25	0.88	-2.17	-2.0256	0.0483*
WBC count	Baseline	7296.00	1971.11					
	7 day	7570.00	1762.91	-274.00	1067.48	-3.76	-1.8150	0.0756
Neutrophils	Baseline	60.98	6.36					
	7 day	62.40	6.46	-1.42	4.44	-2.33	-2.2636	0.0281*
Lymphocytes	Baseline	32.04	10.35					
	7 day	29.50	6.76	2.54	11.31	7.93	1.8464	0.0648
Eosinophils	Baseline	6.80	1.44					
	7 day	6.66	1.60	0.14	1.53	2.06	0.6490	0.5194
Monocytes	Baseline	1.40	0.49					
	7 day	1.44	0.50	-0.04	0.73	-2.86	0.3429	0.7317
ESR	Baseline	33.47	16.99					
	7 day	28.61	15.47	4.86	12.75	14.51	3.2734	0.0011*

*p<0.05

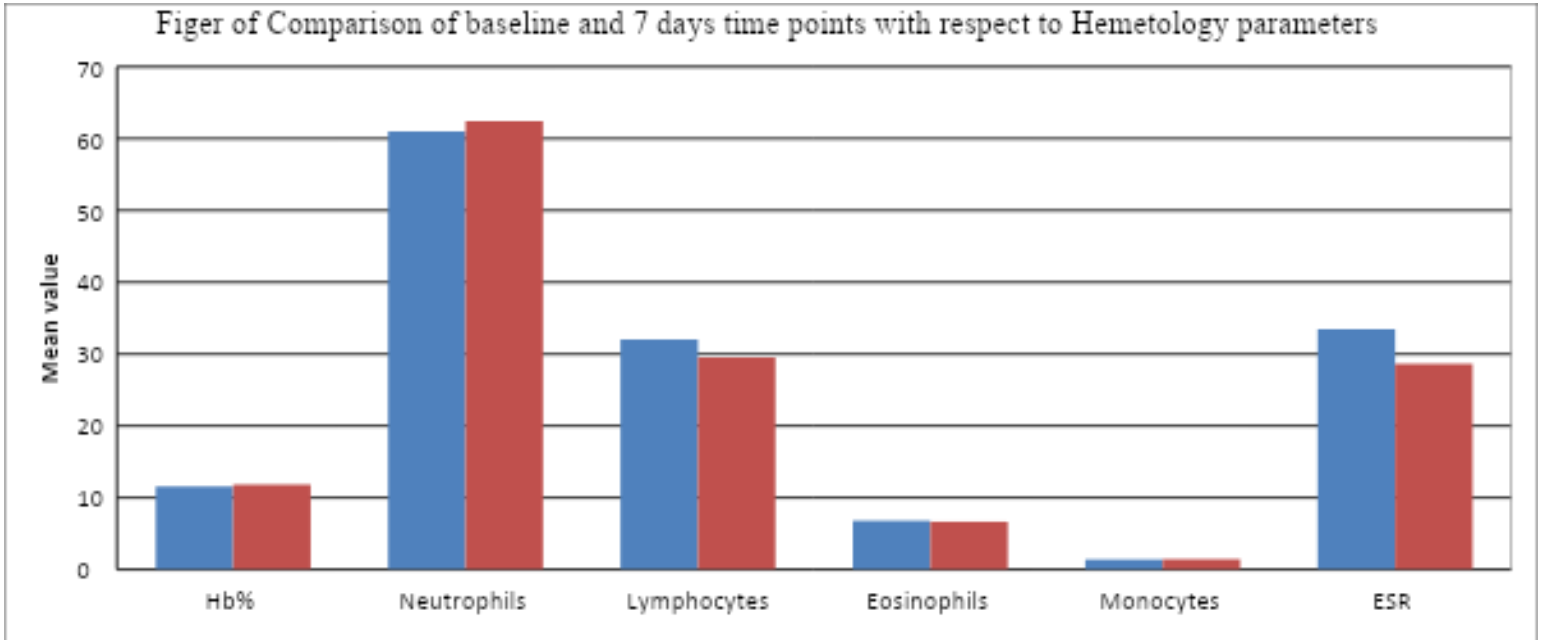
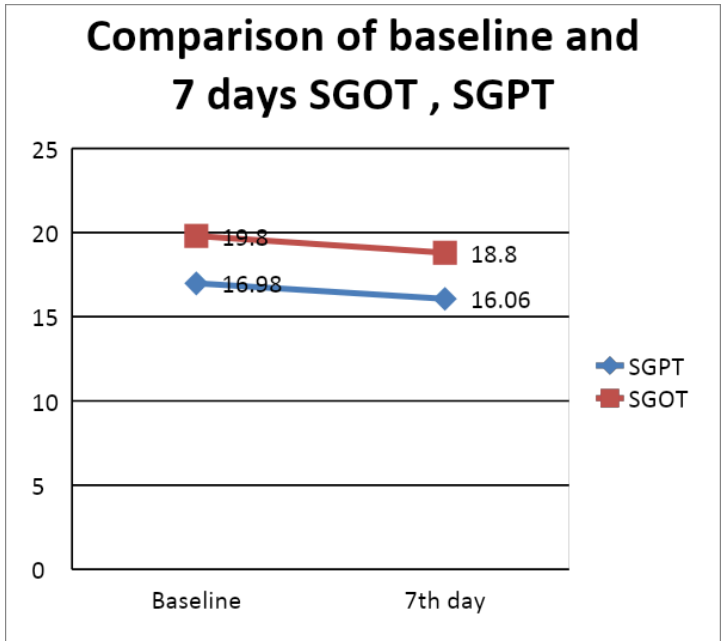
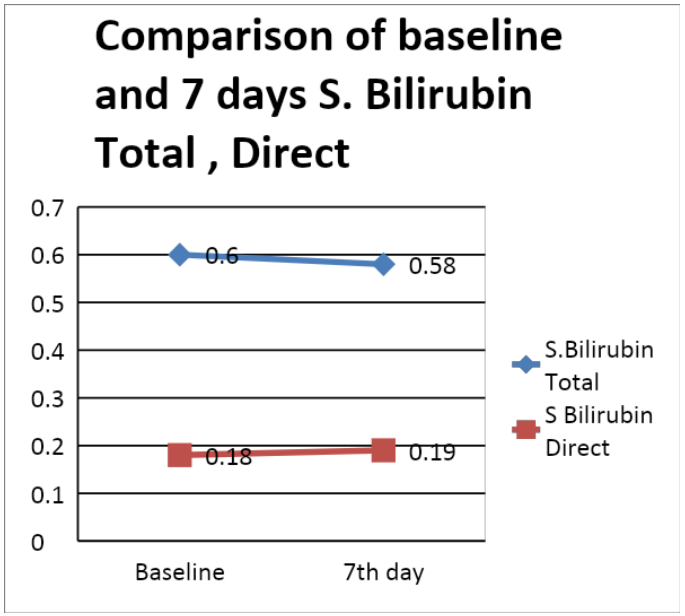

Figer of Comparison of baseline and 7 days time points with respect to Hemetology parameters
Mean value
70
60
50
40
30
20
10
0
Hb%
Neutrophils
Lymphocytes
Eosinophils
Monocytes
ESR

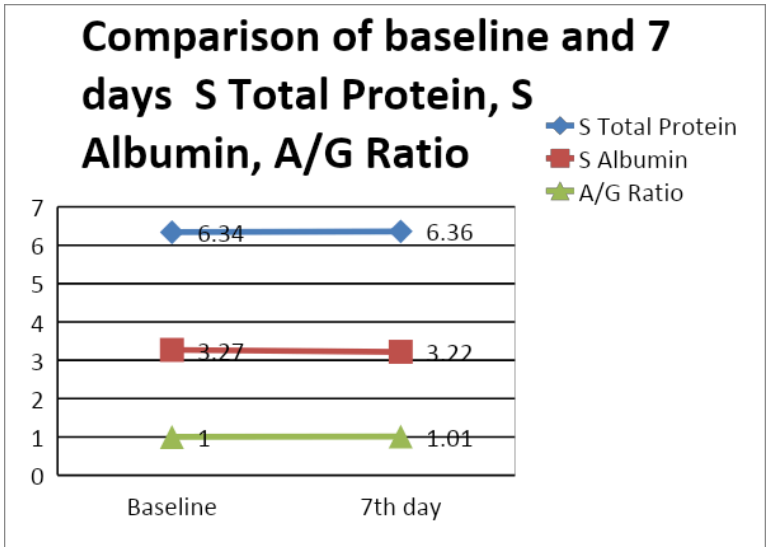
Table: Comparison of baseline and 7 days' time points with respect to LFT parameters by Wilcoxon matched pairs test

Parameters	Time	Mean	Std.Dv.	Mean Diff.	SD Diff.	% of change	Z-value	P-value
S.Bilirubin Total	Baseline	0.60	0.12					
	7 day	0.58	0.09	0.03	0.08	4.64	1.8293	0.0674
S Bilirubin Direct	Baseline	0.18	0.04					
	7 day	0.19	0.18	-0.01	0.18	-6.82	1.1893	0.2343
SGPT	Baseline	16.98	3.52					
	7 day	16.06	2.41	0.92	2.47	5.42	2.5606	0.0105*
SGOT	Baseline	19.80	3.47					
	7 day	18.80	2.86	1.00	2.87	5.05	2.4219	0.0154*
S Total Protein	Baseline	6.34	0.28					
	7 day	6.36	0.24	-0.02	0.19	-0.28	0.3017	0.7629
S Albumin	Baseline	3.27	0.25					
	7 day	3.22	0.51	0.06	0.51	1.77	0.4996	0.6174
A/G Ratio	Baseline	1.00	0.13					
	7 day	1.01	0.13	-0.01	0.13	-1.00	0.3878	0.6982
S. Alkaline Phosphatase	Baseline	78.28	9.99					
	7 day	75.16	9.08	3.12	8.08	3.99	3.0868	0.0020*

*$p<0.05$


Comparison of baseline and 7 days SGOT , SGPT
25
20
15
10
5
0
19.8
18.8
16.98
16.06
Baseline
7th day
SGPT
SGOT


Comparison of baseline and 7 days S. Bilirubin Total , Direct
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.6
0.58
0.18
0.19
Baseline
7th day
S.Bilirubin Total
S Bilirubin Direct


Comparison of baseline and 7 days S Total Protein, S Albumin, A/G Ratio
7
6
5
4
3
2
1
0
6.34
6.36
3.27
3.22
1
1.01
Baseline
7th day
S Total Protein
S Albumin
A/G Ratio

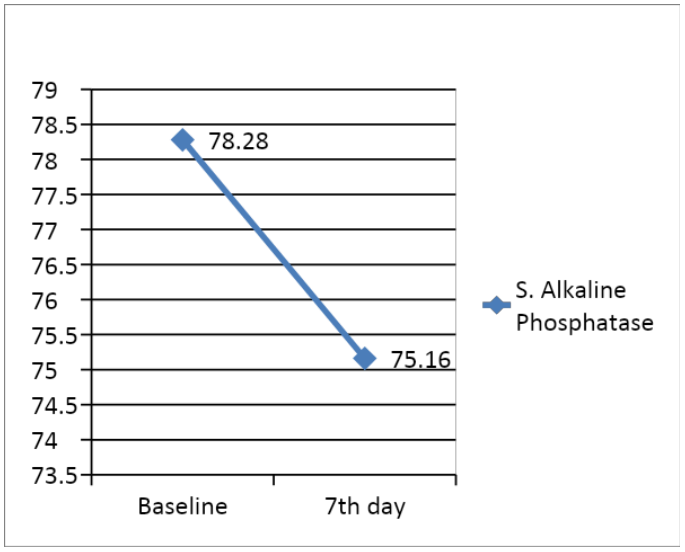
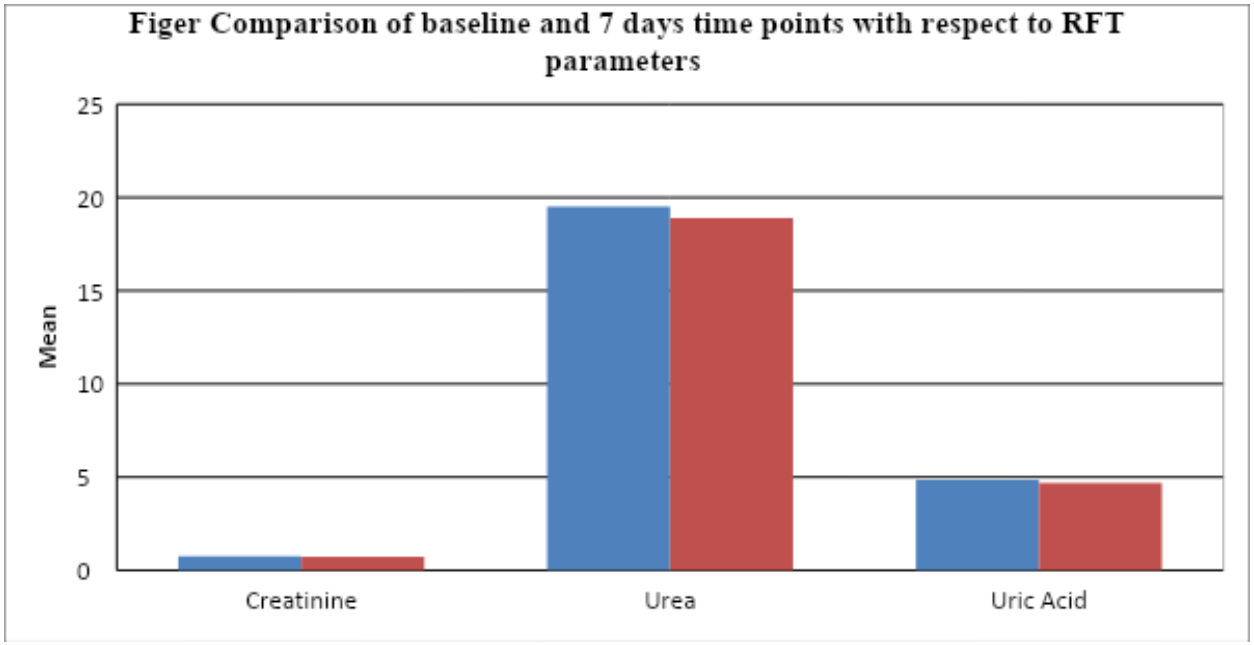

79
78.5
78
77.5
77
76.5
76
75.5
75
74.5
74
73.5
78.28
75.16
Baseline
7th day
S. Alkaline Phosphatase

Table: Comparison of baseline and 7 days time points with respect to RFT parameters by Wilcoxon matched pairs test

Parameters	Time	Mean	Std.Dv.	Mean Diff.	SD Diff.	% of change	Z-value	P-value
Creatinine	Baseline	0.75	0.09					
	7 day	0.72	0.08	0.03	0.10	4.52	2.9003	0.0037*
Urea	Baseline	19.52	3.34					
	7 day	18.90	2.50	0.62	2.91	3.18	0.9071	0.3644
Uric Acid	Baseline	4.85	0.63					
	7 day	4.70	0.57	0.15	0.42	3.14	2.0773	0.0378*

*$p<0.05$



Significant improvement observed in VAS scoring in all groups on 7th , 15th and 30th day.

No significant changes were observed in swelling in all groups on all assessment days.

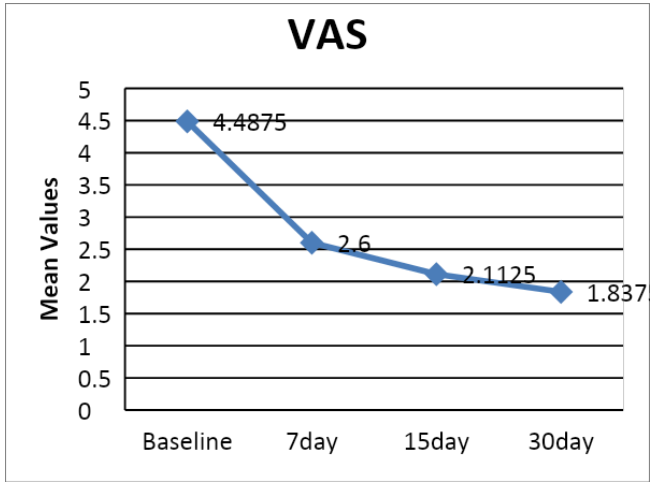
Significant changes were observed in all groups on all assessment days in tenderness score.

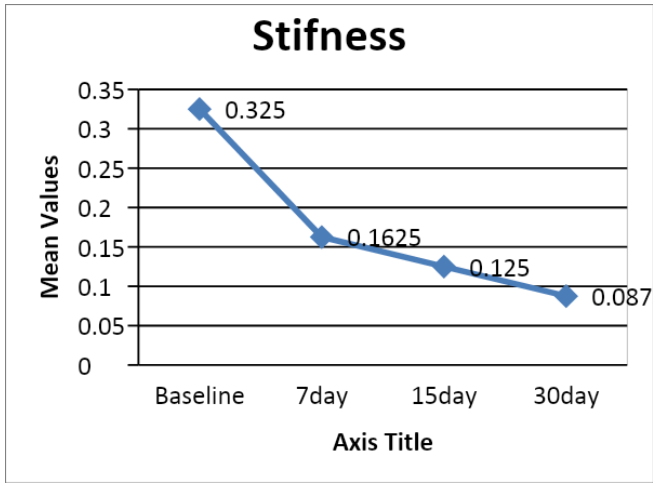
Significant changes were seen on stiffness in all groups.

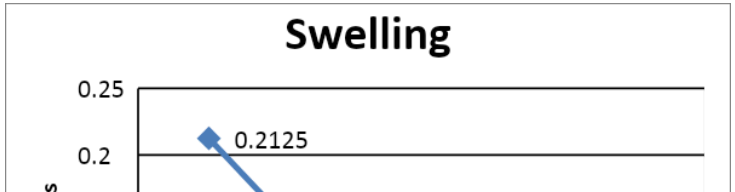
Although changes were seen in the haematological values like lymphocytes, monocytes, ESR, serum bilirubin, SGPT, SGOT, total protein, creatinin, urea, uric acid, the said changes were negligible, as they lie in the normal limits.

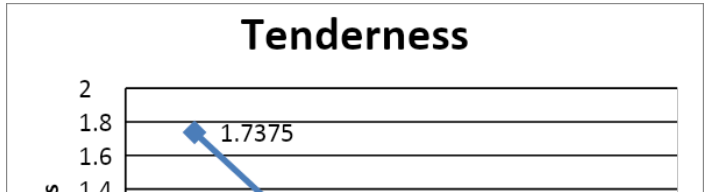
Table of Overall assessment **(Single Group Including four subgroups)**

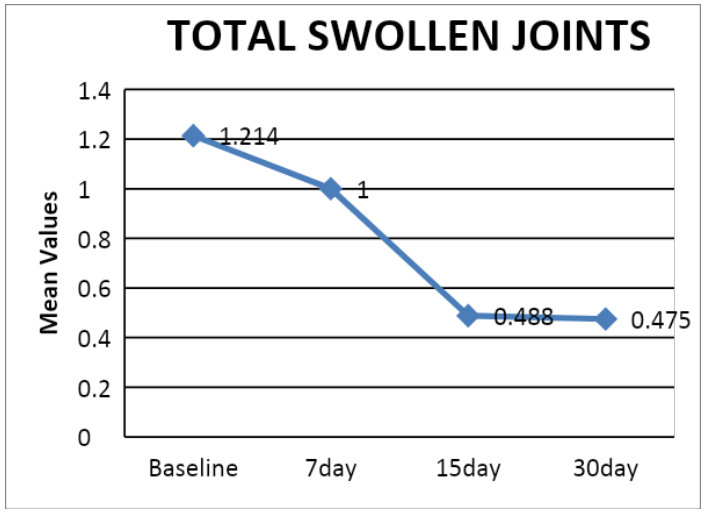
	Baseline	**7day**	**15day**	**30day**
VAS	4.4875±2.9	2.6±1.35	2.1125±1.37	1.8375± 1.31
Swelling	0.2125± 0.41	0.1± 0.3	0.0875± 0.28	0.0375 ± 0.19
Tenderness	1.7375± 0.76	0.975± 0.71	0.8375± 0.72	0.75± 0.63
Stiffness	0.325± 0.47	0.1625± 0.37	0.125± 0.33	0.0875± 0.28
PGAS	3.901± 7.27	3.137± 6.24	2.098± 2.27	1.98± 2.41
Total Painful Joints	3.098±5.03	2.47± 3.52	1.804± 2.16	1.72± 2.33
Total Swollen Joints	1.214± 3.69	1± 3.73	0.488± 1.61	0.475± 1.66

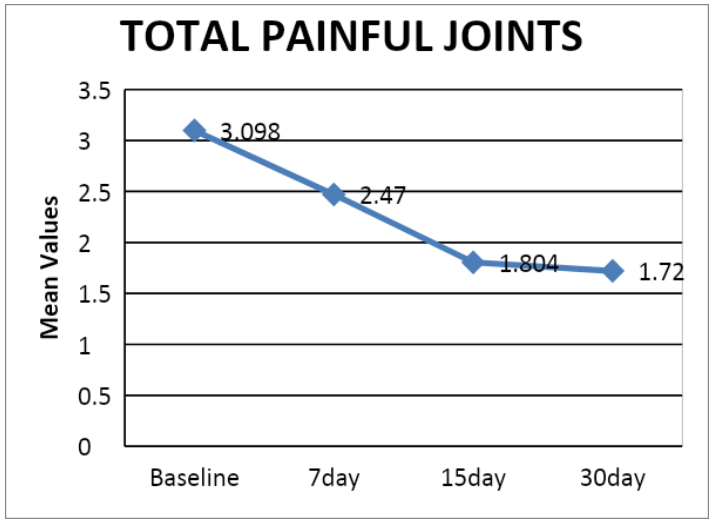


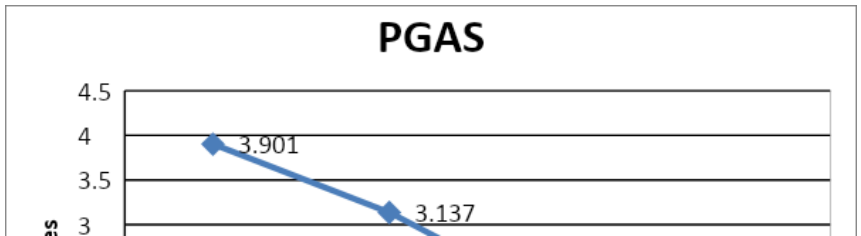







TOTAL SWOLLEN JOINTS
Mean Values
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.214
1
0.488
0.475
Baseline
7day
15day
30day


TOTAL PAINFUL JOINTS
Mean Values
3.5
3
2.5
2
1.5
1
0.5
0
3.098
2.47
1.804
1.72
Baseline
7day
15day
30day


PGAS
4.5
4
3.5
3
3.901
3.137

Laboratory observations on efficacy:

NOT APPLICABLE

Clinical and laboratory observations on safety:

ADRs :

All the subjects were asked daily during treatment and at followup period to report any Adverse Event.

Two ADRs were reported. Redness and Skin rash were observed which were relieved in few hours without medication. Subjects continued in the study.

Even though Trial Drug is a topical application, for assessing safety – CBC, ESR, Liver Function Tests and Renal Function Tests were done in half of the total subjects, before and after treatment.

Adverse drug reactions : TWO

AE 1:

Subject no : CP17

Age: 40yrs

Sex:Female

AE: **Skin Rash (Redness, swelling) at the site of Test drug Apllication**

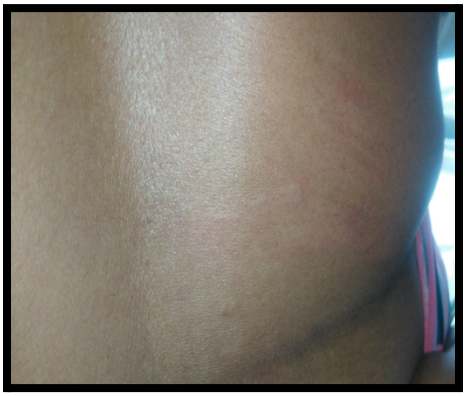
Past History: No any significant history

Prakriti : Kapha-pittja

Probable cause: Due to pitta vitiation.

Rx given: Shatdhouta ghrita application

Rechallange : next day no symptoms seen and pt continue treatment



AE 2:

Subject no : CP33

Age: 35yrs

Sex: Female

AE: **Skin Rash (Redness, swelling) at the site of Test drug Apllication**

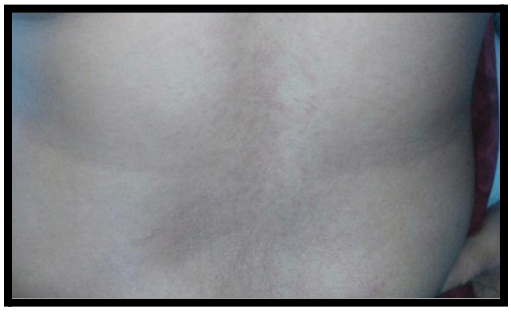
H/O : No any significant history

Prakriti : Vata-pittaja

Probable cause: pitta prakopa

Rx given: NIL

Rechallange : next day no symptoms seen and pt continue treatment



Results on safety parameters: All the lab parameters (CBC, ESR, LFT & RFT) are within the limits before and after the trial drug administration indicating the safety of the product.

9. ***Discussions of results:*** *relevance to objectives, correlation with other reports data, if any; guidance for further study, if necessary:*

Pain measured by VAS has been reduced in all the trial subjects as well as in each of the four clinical conditions of Musculoskeletal disease when compared with before treatment (4.4875) to after treatment on 7th day (2.6) as well as on follow up days of 15th (2.1125) and 30th days (1.8375), which are statistically significant (p). The ingredients in contrapain lepa and oil are Ushna (Punarnava, Kunduru, Rasna Daruharidra, Shunti Devadaru Nirgundi Eranda Tila Yavani Tailaparna) and Kapha Vatahara. Pain being one of the cardinal sign of aggravated vata dosha. Lepa and taila subside vata dosha, so it is helpful in reduction of pain. Nirgundi inhibits prostaglandins with the help of flavonoids present in it, which in turn

decreases the pain[0]. Hence combined effect of these modalities is better in pain and tenderness.

Study showed that Tenderness is reduced in Overall subjects as well as in each MSD condition when compared from before treatment (1.7375) study Average Grades of Tenderness to after study and after Follow up days of 7th day (0.975), 15th (0.8375), 30th days (0.75). Lepa dravya namely punarnava, chitraka, shigru, rasna, lodhra devadaru are shotha hara. Also the procedure of lepa has peedana effect on part applied which has helped in the reduction of swelling Also the ingredients of oil such as Nirgundi decreases the vata and kapha dosha hence it reduces Shotha. Nirgundi will do the inhibition of Prostaglandins with the help of flavonoids present in it, which in turn decreases the inflammation and Vitex negundo leaf oil shows significantly inhibits COX-1 Pathways hence it is having anti-inflammatory effect.

Study showed that Sotha (swelling) has reduced in overall subjects as well as in each condition of MSD in average values of grading when compared from before intervention (0.2125) to after treatment and during follow-up period of 7th day (0.1), 15th (0.0875), 30th days (0.0375).

Study showed that stiffness has reduced in overall subjects as well as in each condition of MSD in average values of grading when compared from before treatment (0.325) to after treatment and during followup period. And sustenance of effect in reducing stiffness is observed during follow-up of 7th day (0.1625), 15th day(0.125) and 30th days(0.0875). Sthamba is a symptom produced due to sheetaguna of vata and kapha. The contents of contrapain lepa and oil due to their ushna guna and kaphavatahara property counteract the sheetaguna and counteract the stiffness in joints

Physician Global Assessment Scale scoring in the study showed that PGAS has decreased from baseline (3.901961) to after treatment and as well as in follow up period of 7th day (2.098039), 15th day (0.125) and 30th days (1.941176).

Pila sebaceous Uptake:

When a Lepa is applied over the surface of skin to the direction of hairs on it, through a proper base, the active principles of the ingredients of Lepa are released into that base. After that, this combination enters the Romakupa & further gets absorbed through the swedavahi srotas & siramukha. However, it should be kept in mind that the pila sebaceous uptake i.e.

absorption of Lepa differs as per the site variation, skin condition & more important is the base through which it is applied.

Cutaneous Biotransformation:

Thereafter it the viable epidermis starts off the catabolic degradation of the absorbed material with the help of essential enzymes. In due course of the above transformation, some new metabolites might be forming which pacifies the provocated Doshas locally & thus breaks the local pathogenesis cycle leading to the alleviation in the signs and symptoms. The physic-chemical properties of a drug in a topical dosage form affect that drug's trans-dermal delivery and topical bioavailability. The molecules of the formulation after penetrating through the stratum conium and into viable epidermis and dermis produces its characteristic pharmacological response through receptors even before the blood and lymph circulations remove it, in which case it may set in a cascade of systemic effects though the horny layer is very impermeable to most chemicals, contributing the rate.

Most of the ingredients present in Contrapain lepa and liniment possess ushna guna Kapha Vata hara , pachana, amadosha hara, shotha hara properties due to which there is stanika pachana of doshas , reduction of shotha, shoola and stamba which are common presentations in musculoskeletal disorders. The oils presents in the Contrapain liniment namely Menthol, Karpura, Thymol, Tailparna, Gandhapura, Gandhatruna, Katuveera, Dalchini, Lavanga oil possess counter irritant properties which causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints and viscera distal to the site of application limiting step in trans-dermal absorption because of its high diffusion resistance, providing a small fractional area of 0.1 % only as permeable appendage shunt route. Besides this route the drug molecules may penetrate through thehair follicles and sebaceous glands or through sweat ducts also and thus helps to remove or neutralize the toxins in initial stage only

*10. **Summary and conclusion**:*

Study Design:

Open Labelled, Non-comparative Clinical Study with Four sub groups of Musculo- Skeletal Disease (MSD) viz. OA, RA, Spondylitis & Sprain

Single centric, Single Group (Four clinical conditions having pain and inflammation) with Pretest and Posttest design

200 Subjects were screened in OPD of Panchakarma, KLE Ayurveda Hospital & MRC, KAHER's Shri B M K Ayurved Mahavidyalaya, Belagavi. Among them 91 were included and 109 were excluded from study. All the participants have signed the informed consent. 80 subjects have completed the study and 11 subjects were dropouts.

Trial drug Contrapain Lepa & oil was applied externally twice daily for 7 days. Assessment was done on baseline, 7th day , 15th day and 30th day. Half of the subjects were screened for safety paremeters (CBC, LFT and RFT) at baseline and 7th day.

Results:

Single Group Assessment (including 4 subgroups)

Pain assessed by (Visual Analogue Scale)VAS has reduced from mean score of 4.4875±2.9 at baseline to 2.6±1.35 on 7th day, 2.1125±1.37 on 15th day and 1.8375±1.31 on 30th day.

Swelling has reduced from mean score of 0.2125±0.41 at baseline to 0.1±0.3 on 7th day, 0.00875±0.28 on 15th day and 0.0375±0.19 on 30th day.

Tenderness has reduced from mean score of 1.7375±0.76 at baseline to 0.975±0.71 on 7th day, 0.8375±0.72 on 15th day and 0.75±0.63 on 30th day.

Stiffness has reduced from mean score of 0.325±0.47 at baseline to 0.1625±0.37 on 7th day, 0.0125±0.33 on 15th day and 0.0875±0.28 on 30th day.

PGAS has reduced from mean score of 3.910±7.27 at baseline to 3.137±6.24 on 7th day, 2.098±2.27 on 15th day and 1.98±2.41 on 30th day.

Total Painful Joints has reduced from mean score of 3.098±5.03 at baseline to 2.47±3.52 on 7th day, 1.804±2.16 on 15th day and 1.72±2.33 on 30th day.

Total Swollen Joint has reduced from mean score of 1.214±3.69 at baseline to 1±3.73 on 7th day, 0.488±1.61 on 15th day and 0.475±1.66 on 30th day.

Sub Group wise assessment

Study has showed efficacy of Trial drug Contrapain Lepa & Oil external application at the site of pain in Musculoskeletal Disease conditions viz. Osteoarthritis, Rhemuatoid

Arthritis, Spondylosis and Sprain, by reducing pain, stiffness, tenderness and improving movements in affected joints.

Significant improvements were observed in VAS scoring in all groups on 7th , 15th and 30th day.

No significant changes were observed in swelling in all groups on all assessment days.

Significant changes were observed in all groups on all assessment days in tenderness.

PGAS showed significant decrease in OA and RA subgroups on 15th and 30th days, while in Sprian subgroup decrease was significant only on 30th day.

OA subgroup has showed statistically significant decrease in Total Painful Joints on 15th and 30th day.

Although changes were seen in the haematological values like lymphocytes, monocytes, ESR, serum bilirubin, SGPT, SGOT, total protein, creatinin, urea, uric acid, the said changes were negligible, as they lie in the normal limits.

Efficacy of treatment is sustainable as shown by follow up at 15th and 30th day observations.

Trial Product has also showed its safety as observed by minimal variations in Haematological parameters, LFT and RFT.

No severe ADRs were observed either during treatment period or during follow up period, except in two cases where mild rash with redness which was relieved on its own in few hours without medication and subjects have continued the treatment.

11. References:

1. AYUSH GCP
2. CDCSO GCP
3. Schedule Y of D&C Act

12. Annexures:

1. Protocol
2. Case Report Format
3. Informed Consent Form
4. Patient Information Sheet
5. Ethical Committee Permission Letter
6. CTRI Registration