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Research Article

Effect of *Agnikarma* in the Pain Management of *Janu-Sandhigata Vata (*Knee-Osteoarthritis) W.S.R to Inflammatory Biomarkers (hs-CRP, TNF-α and IL6)-An Open Labelled Clinical Trial

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ABSTRACT

Background: Globally, Osteoarthritis (OA) is the most common cause of disability. The concept that OA is an inflammatory disease has experienced an enormous shift in the last several years. Research indicates that proinflammatory cytokines (TNF-α, IL-6, and hs-CRP) are important mediators in the pathophysiology of osteoarthritis. *Janu-Sandhigata Vata*, in which *Shleshma avrata vata* is primarily responsible for excruciating pain in the knee joint, is correlated with knee OA. **Objectives:** To evaluate the effect of *Agnikarma* on inflammatory biomarkers in the pain management of Osteoarthritis. **Materials and Methods:** The study was an open labelled clinical trial with a pre and post design. For the study, a total of 15 patients with knee osteoarthritis (*Janusandhigata vata*) who met the inclusion criteria were enrolled. The patients were treated with a single Agnikarma on the 2) most tender point of affected knee joint. Systemic venous blood was collected before the Agnikarma procedure, after 24 hr and after 1 week of the procedure to assess the changes in the inflammatory biomarkers by ELISA method. Parameters like VAS, VDS scale, Crepitus, Tenderness, Range of movements were assessed on baseline, immediately after the procedure, after 24 hr, 3rd day and after 1 week. Statistical analysis was done with Wilcoxon Matched Pair test, dependent '*t*' test and one way ANOVA. **Results:** Comparing baseline to various time periods yielded significant results ($p<0.0001$) in all evaluated parameters. **Conclusion:** *Agnikarma* was found effective on inflammatory biomarkers and in the pain management of knee osteoarthritis.

Keywords: *Agnikarma*, Inflammatory Biomarkers, Inflammatory mediators, *Janusandhigata vata*, Osteoarthritis, Pain management, Para surgical procedure, TNF-α, IL-6, hs-CRP.

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INTRODUCTION

According to a number of sources, osteoarthritis is a degenerative, inflammatory joint disease that typically affects older people.[1] In India, the most common OA condition is knee OA, which affects 22% to 39% of people, compared to men, women are more likely to develop OA.[2] According to the World Health Organization (WHO), OA affects 18.0% of women over 60 and 9.6% of men worldwide.[2] An uncomfortable sensation that makes it difficult for a person to go about his daily business is pain.[3] It has been proposed that osteoarthritis and pain have an inflammatory component.[3] Evidence has been presented that inflammatory factor, including interleukin 6, C-Reactive Protein (CRP), and Tumour Necrosis Factor alpha (TNF-α), are important mediators in the pathophysiology of Osteoarthritis (OA).[4]

Vata Dosha, which causes symptoms like *Shopha* (joint swelling) and *Vedana* (ache in joint movement), is the root cause of *Sandhigata Vata.*[5] Several treatment techniques, including *Snehana, Upanaha, Agnikarma, Raktamoksana*, and others, are recommended for *Vatavyadhis* in *Ayurvedic literature.*[5] As *aatyayeka chikitsa, Agnikarma* is considered one of the most important practices in Janu sandhigatavata because of its *Ushna, Suksma*, and *Asukari guna*, which eliminates *Srotavarodha* and pacifies the *Vata Kapha Dosha*.[6] Studies have demonstrated that *agnikarma* is a nonpharmacological treatment that benefits *Sandhigata Vata* patients by reducing pain.[6] Currently, no researches are carried out to correlate the relation between pain reduction by *Agnikarma* and changes occurring in the inflammatory biomarkers. Hence the clinical trial aims to

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evaluate the effect of *Agnikarma* in Knee OA and its impact on inflammatory biomarkers.

MATERIALS AND METHODS

Patients presenting with knee joint pain as the primary complaint at the OPD and IPD departments of *Shalyatantra* of KAHER's Shri B.M.K Ayurveda Institute, Belagavi, were recruited for the proposed study. Prior to recruitment, the patient provided written informed consent. The study's results were reported in accordance with the CONSORT statement's guidelines. The study was approved by the Institutional Ethics Committee (Reference: BMK/20/PG/ST/3, KAHER BMK Ayurveda Mahavidyalaya Belagavi, CTRI registration number: CTRI/2021/11/038093). The period of data collection was September 2022-June 2023. Throughout the study period, the patients were systematically recorded and monitored for any adverse events.

Subjects

Total 15 patients diagnosed with knee osteoarthritis as per inclusion criteria were enrolled in the study.

Inclusion Criteria

The patients with classical features of *Sandhigatavata* and either sex with age 45 to 70 years and *Yogya* for *Agnikarma* were included in the study.

Exclusion Criteria

Patients with a history of osteoarthritis caused by secondary illnesses such as tuberculosis, syphilis, AIDS, leprosy, and autoimmune disorders such as RA, as well as a history of knee joint surgery, were excluded. Patients suffering from a metabolic disease such as diabetes and a major systemic illness such as severe anaemia, Parkinson's disease, paralysis, or cancer. Patients taking opioids, anticoagulants, or antiplatelet drugs, as well as those with a febrile condition or who are classically contraindicated for Agnikarma, were excluded.[6]

Screening Methods

According to the inclusion and exclusion criteria, patients with knee joint pain were screened. Patients who met the study's requirements were enlisted and shown as a consort chart (Figure 1).

Research Design

Subjects were enrolled as a single group in this open-label clinical trial, which had a pre- and post-test design. The information was methodically documented and subjected to suitable statistical techniques for analysis. 15 patients having a diagnosis of *Janu Sandhigata Vata* were enrolled in accordance with the study's research proforma.

Intervention

Agnikarma was carried out in compliance with the *Ayurvedic* hospital norms and procedures set forth by NABH. Prerequisites for the intervention included prior planning and postoperative care protocols. On the day of enrollment, the *Agnikarma* intervention was carried out just once (Figure 2). Patients were informed about the study's purpose and design, and their informed consent was acquired. To measure inflammatory biomarkers, systemic venous blood was extracted from the median cubital vein prior to therapy, 24 hr later, and a week later.

Standard operative procedure for *Agnikarma*

Pre-operative Procedure

Collection of instruments-Hole towel (1), Surgical gloves (2 pairs), Gauze piece, Pad, Povidine iodine solution, Bandage cutting scissor (1), Sponge holding forceps (1), Thermo regulated *Agnikarma* instrument, and *Shatadhauta ghrita*.

Preparation of the patient

Well informed consent was taken.

Part preparation.

Monitoring of vitals-Record pulse and Blood pressure with time and date done.

Operative Procedure

Position-Supine or prone position, as comfortable for the patient. Thermoregulated *Agnikarma* (Figures 1 and 2) instrument is set at the required temperature 200°C.

Agnikarma was done at most tender points at knee joint with average time of application of instrument ranging from 1-2 sec.

Monitoring the vitals of patient after procedure.

Post-operative Procedure

After *Agnikarma* the sites were anointed with *Shatadhauta ghrita* (Figure 2).

Vitals were monitored and VAS and VDS scale of pain noted.

Procedure for Inflammatory Biomarkers Assessment

The inflammatory Biomarkers Assessment was done by ELISA Reader; venous blood was drawn from the cubital vein before procedure, after 24 hr and after 1 week of procedure. Blood was centrifuged; serum was separated and collected in cryotubes by proper coding and stored at-80°C at Basic Science Research Centre (BSRC), Belagavi. The Samples analysis was done at BSRC by ELISA method after following proper SOP provided by the Biomarkers Kit manual. The readings were documented properly and results were drawn and evaluated by qualified professionals at the KLE Basic Scientific Research Centre in Belagavi to confirm

its accuracy. The detailed procedure of inflammatory biomarkers is provided as supplementary material.

Criteria for Assessment

Pain was measured using the Visual Analogous Scale (VAS) and Verbal Descriptive Scale (VDS) prior to, immediately following and at several points in time, such as 24 hr, 3 days, and 7 days after the day of enrollment. Grades were used to measure the Knee joint tenderness, crepitus and goniometry were used to measure the range of flexion and extension. The ELISA method was used to measure the inflammatory biomarkers hs-CRP, TNF-α, and IL6.

Statistical Methods

Using the Wilcoxon match paired test, the changes in the VAS and VDS scales as well as the grades of tenderness and crepitus were compared from baseline to various time intervals, including just after the procedure, 24 hr later, on the third day, and on the seventh day (Table 1). Using the dependent '*t*' test, the changes in flexion and extension were compared from baseline to several time intervals, including just after the procedure, 24 hr later, on the third day, and on the seventh day. Using a one-way ANOVA test, the changes in the levels of the inflammatory biomarkers hs-CRP, IL-6, and TNF-α were compared from baseline to various time intervals, such as 24 hr and 1 week later. All tests were deemed statistically significant at $p<0.05$ and values were presented as mean±standard deviation.

RESULTS

There were no dropouts and 15 patients finished the study. There were no adverse results during the research.

Subject Characteristics

Age-60% of the patients belonged to the age group of 51 to 60, 20% from 45 to 50 and 20% from 61 to 70 groups.

Sex-Out of 15 patients 26.67% of the patients was male and 73.33% were female.

Occupation-46.67 % of the patients were housewives and 20 % were farmers and 33.33% were doing other jobs like Tailoring, office work etc.

Site of tenderness-Most tenderness points were observed at medial patella and medial joint line area and remaining were at lateral patella, lateral joint line area, superior lateral, superior medial, patellar tendon zone and quadriceps tendon zone.

Primary Outcomes

Localized Pain

In both VDS and VAS parameters, the Agnikarma procedure had a significant result ($p=0.0007$) in lowering pain immediately, following the procedure, and at various time intervals ($p=0.0007$) (Table 1).

Tenderness and Crepitus

The Agnikarma procedure significantly reduced crepitus ($p=0.02$) and tenderness ($p=0.001$ and 0.0007) both immediately following the procedure and at various time points (Table 2).

Extension and Flexion

In both the Flexion and Extension parameters, the Agnikarma technique significantly reduced range of motions immediately, after the operation, and at various time intervals ($p=0.0001$) (Table 3).

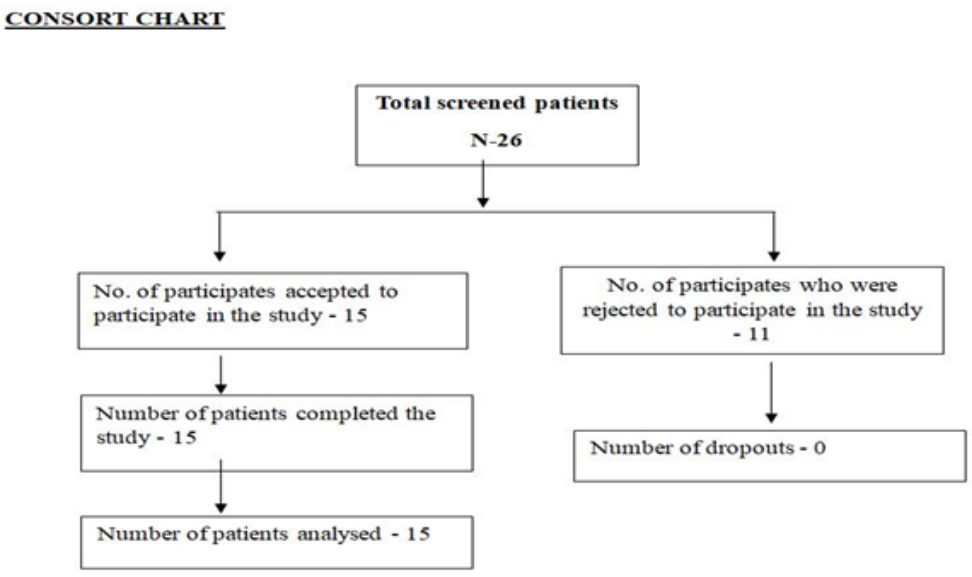

Figure 1: Consort chart.

Table 1: Comparison of different treatment time points with VAS and VDS by Wilcoxon matched pairs test.

	Time points	Mean	SD	Mean Diff.	SD Diff.	% of change	Z-value	*p*-value
VAS	Baseline	7.07	1.03	4.33	0.72	61.32	3.4078	0.0007*
	Immediate	2.73	1.10					
	Baseline	7.07	1.03	4.73	1.10	66.98	3.4079	0.0007*
	24 hr	2.33	1.59					
	Baseline	7.07	1.03	4.73	0.80	66.98	3.4079	0.0007*
	Day 3	2.33	1.23					
	Baseline	7.07	1.03	4.60	0.83	65.09	3.4078	0.0007*
	Day 7	2.47	0.83					
VDS	Baseline	7.00	1.20	4.27	0.88	60.95	3.4078	0.0007*
	Immediate	2.73	0.96					
	Baseline	7.00	1.20	4.60	1.12	65.71	3.4079	0.0007*
	24 hr	2.40	1.59					
	Baseline	7.00	1.20	4.53	1.06	64.76	3.4078	0.0007*
	Day 3	2.47	1.36					
	Baseline	7.00	1.20	4.60	1.35	65.71	3.4079	0.0007*
	Day 7	2.40	0.83					

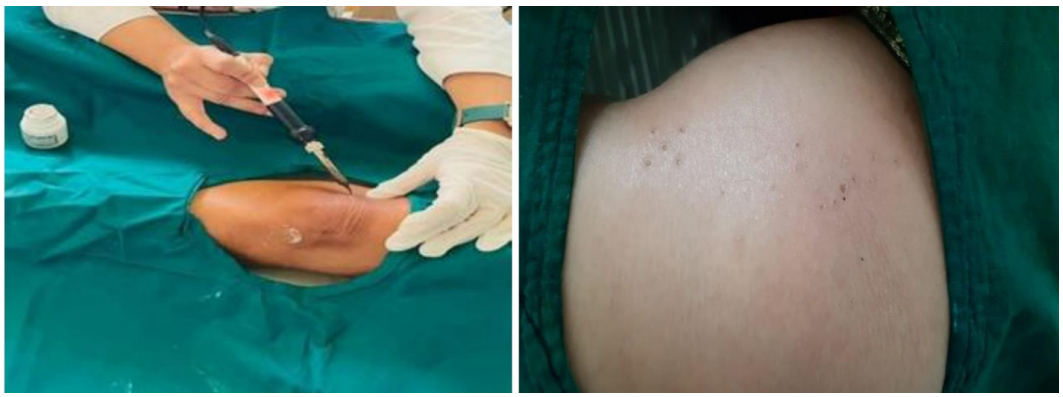

Figure 2: Agnikarma at Knee joint.

Inflammatory Biomarkers

hs-CRP-*Agnikarma* procedure showed significant result (p=0.02) in reducing hs-CRP immediately after 24 hr and 1 week (Tables 4A and 4B).

TNF-α-*Agnikarma* procedure did not showed significant result immediately after 24 hr but significant result was obtained after 1 week (p=0.0001) (Table 4A and 4B).

IL 6- *Agnikarma* procedure did not show significant result immediately after 24 hr but significant result was obtained after 1 week (p=0.0159) (Tables 4A and 4B).

DISCUSSION

Osteoarthritis of the knee is a complicated joint disease that affects a patient's quality of life and produces excruciating pain.[7] Although a number of theories have been put forth, the aetiology and natural history remain unclear.[7] There are numerous therapies available, each with unique drawbacks, but they all seek to lessen discomfort, improve function, and delay the need for joint replacement surgery.[7]

Pain and tenderness

Significant results were obtained in the pain parameter assessed using VAS and VDS. The *ushna guna* produced by *Agnikarma* soothes the *sheet guna* of the *Vata-Kapha Dosha* and alleviates pain.[8,9] *Agnikarma* can be used in managing the pain derived from *Twak, mamsa, sira, snayu, sandhi*, and *asthi*, as well as the specially used word *atyugraruja* (intense pain), which indicates the presence of free nerve endings from the superficial layer of the skin, muscle, arterial walls, periosteum, and joint surface.[8,9] Local therapeutic heat (*Agnikarma*) relieves pain and painful muscle spasms by inducing an inflammatory response in the area,

Table 2: Comparison of different treatment time points with Crepitus and Tenderness by Wilcoxon matched pairs test.

	Time points	Mean	SD	Mean Diff.	% of change	Z-value	*p*-value
Crepitus	Baseline	1.3	0.5	0.3	21.05	1.8257	0.0679
	Immediate	1.0	0.0				
	Baseline	1.3	0.5	0.7	52.63	2.8031	0.0051*
	24 hr	0.6	0.5				
	Baseline	1.3	0.5	0.5	36.84	2.3664	0.0180*
	Day 3	0.8	0.4				
	Baseline	1.3	0.5	0.4	31.58	2.2014	0.0277*
	Day 7	0.9	0.4				
Tenderness	Baseline	1.8	0.8	1.1	59.26	3.2958	0.0010*
	Immediate	0.7	0.6				
	Baseline	1.8	0.8	1.4	77.78	3.4078	0.0007*
	24 hr	0.4	0.5				
	Baseline	1.8	0.8	1.5	81.48	3.4078	0.0007*
	Day 3	0.3	0.5				
	Baseline	1.8	0.8	1.5	81.48	3.0594	0.0022*
	Day 7	0.3	0.5				

Table 3: Comparison of different treatment time points with FLEXION (in degree) by dependent *t* test.

	Time points	Mean	SD	Mean Diff.	SD Diff.	% of change	*t*-value	*p*-value
Flexion (in degree)	Baseline	48.67	15.75	-18.33	4.50	-37.67	-15.7835	0.0001*
	Immediate	67.00	15.33					
	Baseline	48.67	15.75	-33.33	7.24	-68.49	-17.8377	0.0001*
	24 hr	82.00	11.92					
	Baseline	48.67	15.75	-44.00	11.37	-90.41	-14.9873	0.0001*
	Day 3	92.67	12.66					
	Baseline	48.67	15.75	-51.00	8.49	-104.79	-23.2551	0.0001*
	Day 7	99.67	10.77					
Extension (in degree)	Baseline	12.87	2.13	4.20	1.37	32.64	11.8456	0.0001*
	Immediate	8.67	1.91					
	Baseline	12.87	2.13	5.87	1.25	45.60	18.2363	0.0001*
	24 hr	7.00	2.17					
	Baseline	12.87	2.13	7.80	1.61	60.62	18.7350	0.0001*
	Day 3	5.07	2.12					
	Baseline	12.87	2.13	10.73	1.16	83.42	35.7463	0.0001*
	Day 7	2.13	2.23					

increasing blood circulation and reducing metabolic waste that causes pain.[9]

Range of motions

The *vedana viseshas* of the *vata dosha* are *Sandhisphoorana* and *Toda*.[10] *Agnikarma* reduces the *vata* through its *ushna* and *ruksha guna*, which helps to control pain and thereby improves range of motion.[11] *Agnikarma's* possesses *ushna, tikshna*, and *sukshma gunas* which alleviate *avarana* and restore *vata's* normal *gati*, facilitating proper limb movement.[11] Pain reduction occurred immediately following the procedure and at various intervals, demonstrating its significant effects on improving the movements of knee joint.[12,13]

Table 4 A: Comparison of different treatment time points with hs-CRP values by one way ANOVA test.

RM one-way ANOVA Multiple comparisons	Time points	Mean	Mean Diff.	*p*-value	Significant
hs-CRP	Baseline	198.8	74.16	0.0241	Yes
	Immediate	124.6			
	Baseline	198.8	127.0	0.0075	Yes
	After 1 week	71.80			
	After 24 hr	124.6	52.81	0.0085	Yes
	After 1 week	71.80			
IL 6	Baseline	460.4	-114.9	0.6578	No
	Immediate	575.3			
	Baseline	460.4	211.3	0.0159	Yes
	After 1 week	249.2			
	After 24 hr	575.3	326.1	0.0039	Yes
	After 1 week	249.2			
TNF-α	Baseline	343.3	-77.23	0.1022	No
	Immediate	420.5			
	Baseline	343.3	129.5	0.0001	Yes
	After 1 week	213.8			
	After 24 hr	420.5	206.7	0.0001	Yes
	After 1 week	213.8			

Table 4 B: Comparison of different treatment time points with hs-CRP values by one way ANOVA test.

Parameters	RM one-way ANOVA Descriptive statistics	Mean	Std. Deviation	Std. Error of Mean	F Value	*p*-Value
hs-CRP	Baseline	198.8	154.4	41.26	12.66	0.0022
	After 24 hr	124.6	102.4	27.38		
	After 1 Week	71.80	73.86	19.74		
IL6	Baseline	460.4	380.6	98.27	13.38	0.0009
	After 24 hr	575.3	444.3	114.7		
	After 1 Week	249.2	152.0	39.25		
TNF-α	Baseline	343.3	168.7	43.55	23.28	<0.0001
	After 24 hr	420.5	163.4	42.19		
	After 1 Week	213.8	130.1	33.58		

Inflammatory Biomarkers-There was an increase in all three biomarkers before treatment which shows the association of these inflammatory mediators with the disease.

hs-CRP

The significant reduction in hs-CRP value after 24 hr could be due to the local Agnikarma reducing the systemic load of hs-CRP, and after 1 week could be due to reduced Il-6 synthesis (which is the key factor for CRP synthesis) or plasma half-life (which decreases if no triggering factors are present).[14] It has been established that C-reactive protein acts as a "acute phase reactant". The majority of CRP produced by hepatocytes is regulated by circulating cytokines. CRP plasma concentration is primarily determined by synthesis rate, with a circulating half-life of approximately 19 hr.[14] hs-CRP has been linked to knee OA[15] severity; in the current study, elevated levels of hs-CRP were found in all samples. *Agnikarma* is a procedure that transfers thermal energy from a higher concentration to a lower concentration via the skin.[9] As a result, thermal energy affects the larger diameter. A beta fibres close the physiological pain gate, suppressing pain signals sent by smaller diameter fibres (Aδ and C fibres).[9,16] As pain is reduced, hs-CRP levels may fall.[9,16] *Agnikarma* activates PANs in the form of TRPV1 (transient receptor potential vanniloid 1) at the site of injury, which causes tissue injury to produce a variety of excitatory

or inhibitory mediators.[9,16] Opioid peptides, endocannabinoids, and somatostatin are all inhibitive mediators. The Central Nervous System (CNS) naturally produces endogenous opioids, which are tiny molecules with a direct impact on pain relief.[9,16]

IL-6-After 24 hr, there is likely an increase in IL-6, which could be the result of PAN activation or triggering in the nearby inflammatory or affected area. *Agnikarma* may have inhibited the triggering of pain, as evidenced by the significant reduction in IL-6 value observed after a week. A potential early predictor of the systemic inflammatory response has been identified as IL-6.[17] Primary sensory neuron cells are the primary site of TRPV1 expression.[18] Changes such as heat, acidity, and strain are detected by TRPV1.[18] Heat activates the transient receptor potential vannilloid 1, PKC, or protein kinase C enzyme, and the cAMP response element-binding protein, or CREB, signalling pathway in skeletal muscle cells to increase the production of IL-6.[19]

TNF-α-Increased TNF-α level after 24 hr may indicate PAN activation in the affected region. *Agnikarma* may have inhibited the triggering of pain, resulting in a significant reduction in TNF-α level after one week. TNF-α stimulates the production of IL-6, a secondary cytokine.[20-22] TNF-α level are higher in muscle soreness and areas with low tolerance to pressure.[20-22] *Agnikarma* causes inflammation at the site, leading to the production of pro-inflammatory cytokines like TNF- α and IL-6.[20-22]

LIMITATIONS OF THE STUDY

Single sitting of Agnikarma was performed and the follow up period was 1 week. Expenses towards the procurement of biomarker kit, storage of serum at -20º and the acceptability of the patients for repeated blood withdrawal made us choose small size.

STRENGTHS OF THE STUDY

The present research work is the first study which aimed to establish the relation between *Agnikarma* and inflammatory biomarkers. Standard protocol was followed for the *Agnikarma* procedure as per the NABH guidelines and standard procedure (ELISA) was followed for the assessment of inflammatory biomarkers.

CONCLUSION

The *Agnikarma* treatment in the management of *Sandhigatavata* was found to be safe and effective in all the assessed parameters immediately and at different times. *Agnikarma* inhibited pain triggering as it was administered for a single time in the present study. A single sitting of these methods may provide short relief because the pain was quickly reduced up until the seventh day and then increased in intensity on the tenth day. Since at least three sittings are frequently employed in clinical practice to relieve pain, an effort was undertaken in the current study to validate the reuse of procedures at a certain time period. To produce evidence-based results, several *Agnikarma* process sittings and biomarker assessments at different times are required. This is the first study of its kind to explain the connection between inflammatory biomarkers and the Para surgical Ayurveda treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

hs-CRP: High sensitivity C-reactive protein; **TNF-α:** Tumor necrosis factor alpha; **IL-6:** Interleukin 6; **OA:** Osteoarthritis; **ELISA:** Enzyme linked immune assay; **VAS:** Visual analogous scale; **VDS:** Visual descriptive scale; **CRP:** C-reactive protein; **TRPV1:** Transient receptor potential vannilloid 1; **PKC:** Protein kinase C; **cAMP:** Cyclic adenosine monophosphate; **CREB:** cAMP-response element binding protein; **NABH:** National Accreditation Board for hospitals and Health care providers.

ETHICAL APPROVAL

The study was conducted after the permission of the Institutional Ethical Committee. Protocol Id: BMK/20/PG/ST/3, CTRI registration number: CTRI/2021/11/038093).

SUMMARY

Osteoarthritis of the knee is chronic joint problem causing burden on the population and needs proper pain management. The study conducted by *Agnikarma* on painful knee joints has yielded good results and controlled the inflammation for a certain period. were assessed by ELISA method. Parameters like VAS, VDS scale, Crepitus, Tenderness, Range of movements along with Inflammatory biomarkers like hs-CRP, TNF-α and IL-6 were assessed on baseline, immediately after the procedure, after 24 hr, 3rd day and after 1 week. Significant results were obtained in all the assessed parameters; by this we can conclude that *Agnikarma* is found effective on inflammatory biomarkers and in pain management.

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