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Clinical study on Sandhigata Vata w.r.s. to Osteoarthritis and its management by comparing the efficacy of Samananga Sneha and Samananga Sneha with Shadanga Guggulu

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ABSTRACT

Sandhigata Vata is a disease seen commonly both in developing and developed countries. The disease causes mild, moderate or severe degree of morbidity and rarely mortality. The occurrence of problems is increasingly prevalent now a day due to change in lifestyle, food habits and social and cultural changes as well as travelling. Sandhishula, Sandhishotha, Sandhigraha and Atopa are the important clinical features of Sandhigata Vata. According to WHO, Osteoarthritis is the 2nd commonest problem in the world population i.e. 30%. The major risk factors associated with Kneejoint Osteoarthritis are Age, female sex, obesity, occupational Knee bending. Osteoarthritis is the most common articular disorder that begins asymptomatically and is extremely common by age 70. Almost all people by the age 40 have some pathologic change in weight bearing joints. 25% females and 16% males have symptomatic OA. To study the efficacy of Shamananga Sneha in Sandhigata Vata w.s.r. to Osteoarthritis knee. To compare (study) the efficacy of Shamananga Sneha with Shadanga Guggulu in Janu Sandhigata Vata. To compare the results of the two clinical groups. The study was comparative trial and 30 patients with Janu Sandhigata Vata. All the patients were randomly assigned into two groups namely A and B. Group A receive Shamananga Sneha (Guggulu Tiktaka Ghrita) for 30 days, and Group B receive Shamananga Sneha (Guggulu Tiktaka Ghrita) along with Shadanga Guggulu for 30 days. The patients were clinically evaluated and observations were recorded as in the case performa. Shamananga Sneha (Guggulu Tiktaka Ghrita) along with Shadanga Guggulu i.e. group B was more beneficial in relieving the symptoms than Shamananga Sneha i.e. group A (Guggulu Tiktaka Ghrita).

Key words: Janu Sandhigata Vata, Guggulu Tiktaka Ghrita, Shadanga Guggulu.

INTRODUCTION

Osteoarthritis is a degenerative joint disorder characterized by breakdown of joint cartilage.

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Osteoarthritis or Degenerative Joint Disease (DJD) may first appear without symptoms between 20 to 30 years of age. The symptoms, such as pain and inflammation will be noticed in the middle age. Till the age of 55 it occurs equally in both sexes; after 55 the incidence is higher in women. It is estimated that approximately 4 out of 100 people are affected by this disease. The incidence of osteoarthritis in India is as high as 12%. According to WHO Osteoarthritis is the 2nd commonest problem in the world population i.e. 30%. The major risk factors associated with Knee joint are Age, female sex, obesity, occupational Knee bending. This makes an important cause of disability. Osteoarthritis, the most common articular disorder begins asymptomatically in the 2nd and 3rd decades and is extremely common by the age of 70. Almost all

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persons by age 40 have some pathologic change in weight bearing joint. 25% females and 16% males have symptomatic Osteoarthritis.

In the conventional svstem of medicine. administration of pain killers like NSAID's (non steroidal anti inflammatory drugs), Narcotics, Corticosteroids, intra articular injections etc. which gives temporary relief and lastly surgery (Knee replacement), which are quite expensive, need hospitalization and also causes adverse effects constitute usual line of treatment. Where as such type of conditions can be better treatable by the management mentioned in Ayurvedic classics.

Acharya Charaka was the first person who described the disease separately as "Sandhigata Anila".[1] General line of treatment for Vata Vyadhis has been described by Acharya Charaka i.e. repeated use of Snehana and Swedana, Basti and Mrudu Virechana. Acharya Charaka has also been recommended drugs comprising of Tikta Dravya and Ghrita as treatment for Asthyashritha Vata^[2] and Sandhigata Vata in Charaka Samhita. Asthi and Majja are chief components of Sandhi which are affected. However, Guggulu is a Sroto-Shodhaka and proved to have both anti-inflammatory an anti-arthritic properties by various research workers.^[3] Here one group is treated with Guggulutiktaka Ghrita. In another group Guggulutiktaka Ghrita with Shadanga Guggulu. Because Guggulu has got Vatashamaka properties.

AIMS AND OBJECTIVES

- 1. To study the efficacy of *Shamananga Sneha* in *Sandhigata Vata* w.s.r. to Osteoarthritis knee.
- 2. To compare (study) the efficacy of Shamananga Sneha with Shadanga Guggulu in Janu Sandhigata Vata.
- 3. To compare the results of the two clinical groups.

MATERIAL AND METHODS

Patients, suffering from Osteoarthritis, were selected from O.P.D and I.P.D of RAMC College, Ramagondhanahalli, Yelahanka, Bengaluru.

Inclusion Criteria

Patients presenting with classical signs and symptoms of *Janu Sandhigata Vata* (Osteoarthritis knee joint) like;

- Patients with Pratyatmalaksana of Sandhigata Vata.^[4]
- Patients age group 40 to 70 years irrespective of sex, religion and socioeconomic status will be taken.
- Patients who are fit for Shamanagasneha and are willing to sign the informed consent will be included in the study.

Exclusion Criteria

- Patients having systemic disorder which might interfere with the treatment.
- Patients who are not fit for the *Shamanagasneha*.
- Patients with infective Neoplastic and traumatic condition of knee joint.

Grouping

Group A: Patient given *Guggulutiktaka Ghrita* 10 ml twice a day for 30 days.

Group B: Patient given *Guggulutiktaka Ghrita* 10 ml + *Shadanga Guggulu* 3gms twice a day for 30 days.

OBSERVATIONS

Total 30 patients were registered (group A-15 & group B-15), amongst them all patients were completed the treatment, no drop out.

Table 1: Status wise distribution of 30 patients ofSandhigata Vata.

Status	Number of p	oatients	Total	%
	Group A	Group B		
Completed	15	15	30	100
Drop out	0	0	0	0
Total	15	15	30	100

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In this study, maximum 43.4% patients were found in 51-10 years of age group, 66.7% females, 50% were muslims, 33.3% were manual labor and house wives each, 40% were middle class and lower class each, 90% were married, 50% were sub urban population, 36.7% subjects were high school educated, 50% were *Vata Pitta Prakriti,* 70% were mixed diet, 66.7% were having no habits, 66.7% were having *Madhayama Ahara - Abhyavaharana Shakti,* 63.3% were having

Madhyama Ahara - Jarana Shakti, 50% were having Samagni, 53.3% were having Madhyama Kostha, 56.7% were having Madhyama Vyayama Shakti, 63.3% were having sound sleep, over 70% were having 0-2 years of Chronicity.

Over 56.7% were having normal weight, almost all the patients 100% were having both the joints involvement.

Table 2: Showing Individual study of the Subjective and Objective parameters in Group A.

Parameter	Mean			%	S. D	S. E	Df	t-value	p-value	Remarks
Sandhi Shoola	0 th	3			0.93	0.24	14		1	
	15 th	2.93	0.07	2.33	0.80	0.21		0.5641	>0.05	NS
	30 th	1.4	1.6	53.33	1.12	0.29		6.807	<0.001	HS
Sandhi Graha	0 th	2.6			1.06	0.27	14			
	15 th	2.27	0.33	12.69	0.96	0.25		2.091	>0.05	NS
	30 th	1	1.6	61.53	1	0.26		6.807	<0.001	HS
Sandhi Shotha	0 th	0.8			1.15	0.3	14			
	15 th	0.6	0.2	25	0.83	0.21		1.8708	>0.05	NS
	30 th	0.33	0.47	58.75	0.49	0.13		2.4318	<0.05	S
Sandhi	0 th	1.33			0.49	0.13	14	4		
Sphutana	15 th	1.27	0.07	4.511	0.59	0.15		0.5641	>0.05	NS
	30 th	1.13	0.2	15.03	0.64	0.17		1.3817	>0.05	NS
ROM	0 th	1.47				0.17	14			
	15 th	1.2	0.27	18.36	0.68	0.17		2.256	<0.05	S
	30 th	0.4	1.07	72.78	0.51	0.13		6.959	<0.001	HS

Table 3: Showing Individual study of the Subjective and Objective parameters in Group B.

Parameter	Mean		%	S. D	S. E	Df	t-value	p-value	Remarks	
Sandhi Shoola	0 th	2.93			0.96	0.25	14			
	15 th	2.73	0.20	6.825	0.80	0.21		1.8708	>0.05	NS
	30 th	0.93	2	68.25	0.7	0.18		11.832	<0.001	HS
Sandhi Graha	0 th	2.47			1.25	0.32	14			

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	15 th	1.80	0.67	27.12	1.08	0.28		4.1833	<0.001	HS
	30 th	0.47	2	80.97	0.64	0.17		7.746	<0.001	HS
Sandhi Shotha	0 th	0.47			0.64	0.17	14			
	15 th	0.27	0.20	42.55	0.59	0.15		1.8708	>0.05	NS
	30 th	0.07	0.40	85.10	0.26	0.07		2.4495	<0.05	S
Sandhi	0 th	1.40			0.51	0.13	14			
Sphutana	15 th	1.33	0.07	5	0.62	0.16		1	>0.05	NS
	30 th	1.20	0.20	14.28	0.68	0.17		1.8708	>0.05	NS
ROM	0 th	1.53			0.64	0.17	14			
	15 th	0.93	0.6	39.21	0.7	0.18		4.582	<0.001	HS
	30 th	0.27	1.26	82.35	0.46	0.12		8.264	<0.001	HS

Table 4: Comparative effect of treatment between the group A & B (subjective and objective parameter)

Parameter	Assessment	Group	Mean	S.D	S.E	PSE	t-value	p-value	Remarks
Sandhi Shoola	15 th	А	2.93	0.80	0.21	0.292	0.6857	>0.05	NS
		В	2.73	0.80	0.21				
	30 th	А	1.40	1.12	0.29	0.342	1.3653	>0.05	NS
		В	0.93	0.70	0.18				
Sandhi Graha	15 th	А	2.27	0.96	0.25	0.374	1.2486	>0.05	NS
		В	1.80	1.08	0.28				
	30 th	А	1	1	0.26	0.307	1.7398	>0.05	NS
		В	0.47	0.64	0.17				
Sandhi Shotha	15 th	А	0.60	0.83	0.21	0.263	1.2671	>0.05	NS
		В	0.27	0.59	0.15				
	30 th	А	0.40	0.63	0.16	0.176	1.8898	>0.05	NS
		В	0.07	0.26	0.07				
Sandhi	15 th	А	1.27	0.59	0.15	0.221	0.3015	>0.05	NS
Sphutana		В	1.33	0.62	0.16				
	30 th	А	1.13	0.64	0.17	0.240	0.2774	>0.05	NS
		В	1.20	0.68	0.17				
ROM	15 th	А	1.2	0.68	0.17	0.252	1.0583	>0.05	NS

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	В	0.93	0.70	0.18				
30 th	А	0.40	0.51	0.13	0.176	0.7559	>0.05	NS
	В	0.27	0.46	0.12				

Comparative analysis of t-test for *Sandhi Shoola* was 53.3% improvement in Group A and 68.25% improvement in Group B, *Sandhi Graha* was 61.53% improvement in Group A and 80.97% improvement in Group B, *Sandhi Shotha* was 58.75% improvement in Group A and 85.10% improvement in Group B, *Sandhi Sphutana* was 15.03% improvement in Group A, 14.28% improvement in Group B, Range of Movements was 72.78% improvement in Group A and 82.35% improvement in Group B respectively.

Table 5: Total effect of therapy.

Grading	Group A		Group B	
	No of Patients	%	No of Patients	%
Complete Remission ≥ 75%	4	26.66	5	33.33
Marked Improvement ≥ 50%	6	40	9	60
Moderate Improvement ≥25%	5	33.33	1	6.6
No Improvement ≥ 0%	0	0	0	0

Comparative analysis of the overall effect of the treatments in both the groups was done statistically with unpaired t test. In the clinical trial, the result obtained regarding the overall assessment showed better result in Group B than Group A. In Group A among 15 subjects there was complete remission in 4 subjects (26.66%), marked improvement in 6 subjects (40%), moderate improvement in 5 subjects (33.33%). In Group B among 15 subjects 5 subjects (33.33%) reported complete remission, 9 subjects (60%) reported marked improvement, 1 subjects (6.6%) subjects reported moderate improvement. In case of

Sandhigata Vata Group A overall result is 52.28% and Group B overall result is 66.19%.

DISCUSSION

In this study 43.4% patients were found in 51-60 years of age group. *Sandhigata Vata* will be more in aged persons. According to sex 66.7% were female patients, which indicates that *Sandhigata Vata* is more common in female and here the lack of female hormone (oestrogen) in the pre-menopausal period also play an important role. Modern text also reflect the same type of prevalence, Osteoarthritis or Degenerative Joint Disease (DJD) may first appear without symptoms between 20 and 30 years of age.^[5] The symptoms, such as pain and inflammation, appear in middle age. Till the age of 55 it occurs equally in both sexes; after 55 the incidence is higher in women.^[6]

According to the different *Nidana* of the disease *Katu Rasa Atisevana* (53.3%), *Ati Rooksha Bhojana* (23.3%), *Ratri Jagarana* (63.3%). These *Nidana* plays an important role in aggravation of the *Vata* Dosha and thus causes *Sandhigata Vata*. In case of Chronicity 70% patients were having 0-2 years of chronicity.

Among the risk factors patients of female sex 66.7% and 73.3% were having *Ati Chinta* was found prevalent.

Among the chief complaints *Sandhi Shoola* is present in all patients. In *Sandhigata Vata* there will be aggravation of *Vata Dosha* which is responsible for any kind of *Shula*. *Sandhi Graha, Sandhi Shotha, Sandhi Sphutana* was found more in the patients, which occurs due to aggravation of *Vata Dosha* and *Kapha Kshaya*.

Guggulu Tiktaka Ghrita along with Shadanga Guggulu i.e. Group B has showed better relief in the disease Sandhigata Vata in the present study.

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In both the groups (A & B) i.e. 33.33% & 26.66% patients achieved complete remission, while 40% & 60% patients found in marked improvement and 33.33% & 3.3% were having moderate improvement. No patients found unchanged in both the groups.

Probable mode of action of Guggulu Tiktaka Ghrita

Sandhigata Vata is Madhyama Roga Margagata Vatika disorders in which vitiated Vata gets lodged in Sandhi. Hence to treat Sandhigata Vata drugs acting on both Vata and Asthi should be selected. According to Charaka, in Asthi Dhatu Dushti the treatment should be given Tikta Dravya Ghrita and Kshira. In Guaaulu Tiktaka Ghrita predominance of Tikta Rasa is there. Tikta Rasa has Vayu and Akasha Mahabhuta in dominance. Hence it has got affinity towards the body elements like Asthi having Vayu and Akasha Mahabhuta in dominance. Though, Tikta Rasa aggravates Vayu which may enhance the pathogenic process of Sandhigata Vata but, the main principle of Ayurvedic treatment is "Sthanam Jayate Purvam". The main site of Sandhigata Vata is Sandhi which is the site of Shleshaka Kapha. Most of ingredients of Guggulu Tiktaka Ghrita have Tikta Rasa, Ushna Virya and Madhura and Katu Vipaka. The Tikta Rasa increase the Dhatvagni (metabolic stage). As Dhatvagni increase, nutrition of all the Dhatus will be increased. As a result Asthi Dhatu, Majja Dhatu may get stable and Asthi Dhatu and Majja Dhatu Kshaya will be decreased. So degeneration in the Asthi Dhatu may not occur rapidly. It can be said, it slows down the degeneration processes. Tikta Rasa has got Deepana, Pachana and Rochana properties. So it helps in the improvement of the general condition of health and thus strengthen the whole body as well joints.^[7] On other hand Tikta Rasa possess as Lekhana property, so it helps in the weight reduction of the patients and helps in the management of Osteoarthritis.^[8] *Tikta Rasa* is also has got Jwaraghna and Daha Prashamana properties that it may act as anti-inflammatory agent and can reduce the pain and swelling of the joints. Ghrita is Vata-Pittashamaka. Balya, Agnivardhaka, Madhura, Saumya, Sheetavirya, Shula, Jwarahara, Vrishya and

Vayasthapaka also.^[9] Thus, it pacifies *Vata*, improve the general condition of the body and acts as a rejuvenator of the body. Thus, helps in the *Samprapti Vighatana* of the *Sandhigata Vata*. *Ghrita* is having property like *Yogavahi* which is helpful in increasing bio-availability of other drugs without loosing its own property. *Ghrita* also contains vitamin D which plays an important role to utilize calcium and phosphorous in blood and bone building.^[10]

Due to the Ushna property of Guggulu, it is one of the major Vatashamaka Dravya. Due to its Ruksha and Vishada Guna it acts as a Medohara. Due to its Katu Rasa it acts as a Deepana. Thus help in the improvement of general condition of the patient. Purana Guggulu also acts as a Rasayana which may help to prevent the any degenerative change in the body. Pharmacologically Guggulu has got the properties of anti-inflammatory, immunomodulatory and anti-lipidaemic action. On the overall effect of the Panchatikta Ghrita Guggulu, it has been found that drug is predominant in Ushna Virya which helps in pacification of aggravated Vata and subside the pain.

Probable mode of action of Shadanga Guggulu

Shadanga Guggulu contains One part each of Rasna, Guduci, Erandamula, Devdaru, Sunthi and Sarvasambhaga of Shuddha Guggulu and Gritha, ingredients which have various types of actions in the body. Most of these ingredients are having Tikta Rasa, Ushna Virya and Madhura and Katu Vipaka. According to Sushruta Samhita, Guggulu has pleasant odour, subtle, penetrating, light, hot in potency, pungent/bitter in taste, Katu Vipaka, laxative, good for heart unctuous and slimy. When fresh, it is stoutening and aphrodisiac, while old one causes thinning of the body, by its penetration and Ushna Veerya. It mitigates Kapha and Vata, being laxative it eliminates feces and mitigates Pitta by its pleasant smell. It relives bad smell of the abdomen, by its subtleness it kindles digestive fire. Sandhigata Vata is a Madhyama Roga Margagata Vatika disorders in which vitiated Vata gets lodged in Sandhi. Hence to treat Sandhigata Vata drugs acting on both Vata and

Asthi should be selected. According to Charaka, in Asthi Dhatu Dushti the treatment given should be Tikta Dravyasadhita Ghrita and Kshira. In Shadanga Guggulu predominance of Tikta Rasa is there and Gritha also there. Gritha is having Vatahara and Rasayana property, prevents further Dhutukshaya and nourishes body, It is also having Deepana property so maintains Agni of the body which keeps body healthy. Tikta Rasa is having Lekhana property, so it helps in the weight reduction of the patients and helps in the management of Osteoarthritis. Tikta Rasa is also having Jwaraghna and Daha Prashamana properties. Thus it acts as anti inflammatory agent and can reduce the pain and swelling of the joints. Tikta Rasa has Vayu and Akasha Mahabhuta in dominance. Hence it has affinity towards the body elements like Asthi having Vayu and Akasha Mahabhuta in dominance. Due to the Ushna property of Guggulu, it is one of the major Vatashamaka Dravya. Due to its Ruksha and Vishada Guna it acts as a Medohara. Due to its Katu Rasa it acts as a Rasayana which helps in preventing any degenerative change in the body. Pharmacologically Guggulu has the property of antiinflammatory, immunomodulatory and antilipidaemic action. Overall effect of the Shadanga Guggulu is that it helps in pacification of aggravated Vata.

CONCLUSION

This study was mainly under taken to have a better understanding of Samprapti and Samprapti Vighatana of Sandhigata Vata. Janusandhigata Vata comes under Vatavyadhi which is commonly associated with the Vardhakya and Dhatukshaya is a prominent feature in its manifestation. Overall patients of group B treated with Guggulutiktaka Ghrita with Shadanga Guggulu showed better response clinically and statistically than patients of group A Guggulutiktaka Ghrita in almost all the parameters (Tenderness, Shoola during movement, Ruja). Overall response is significantly better in patients of Group В (Moderate/Marked response (66.19%)when compared to patients of Group A (52.28%).

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Thus the study proves the fundamental principles involved in the Samprapti and Samprapti Vighatana of Sandhigata Vata as mentioned in the classics. The Samprapti of Sandhigata Vata involves predominantly Vata Dosha and the Dravya that is Guggulu Tiktaka Ghrita and Shadanga Guggulu both are more effective in releving the symptoms. But Guggulu Tiktaka Ghrita along with Shadanga Guggulu showed the better results in decline the signs and symptoms of Janusandhigata Vata rather than the single drug (Guggulu Tiktaka Ghrita).

REFERENCES

- Agnivesha, Charaka Samhita with Ayurveda Deepika commentary by Chakrapanidutta, edited by VaidyaJadavaji Trikamji Acharya. Varanasi: Chaukhamba Surabharathi Prakashan 2009, ChikitsaSthana 28/72,P.No:620
- Jadhavji Trikamji Acharya , editor Charaka Samhita of Agnivesa elaborated by Caraka and Dridabala with the Ayurveda deepika commentary by chakrapanidatta. Reprint edition, Varansi: Chaukhamba Surbharati Prakashan, 2000 : su.28/27; 180.
- Suryanarayana.K. Studies on Sandhigata Vata with special reference to its management, Jamnagar, Jamnagar University, 1986.
- Vaghbhata. Ashtanga Hridaya with Sarvangasundar commentary edited by Harishastriparadkar, 7th edition, Choukhamba Orientalia, Varanasi, 1982, p723.
- Kumar & Clark Clinical Medicine. 6th Edition. p. 551. Ch. 10.
- 6. Ibid. (1), Ch. 321. :1987.
- Jadhavji Trikamji Acharya , editor Charaka Samhita of Agnivesa elaborated by Caraka and Dridabala with the Ayurveda deepika commentary by chakrapanidatta. Reprint edition, Varansi: Chaukhamba Surbharati Prakashan, 2000 : Sutrasthan 26/5, p. 144.
- Jadhavji Trikamji Acharya , editor Charaka Samhita of Agnivesa elaborated by Caraka and Dridabala with the Ayurveda deepika commentary by chakrapanidatta. Reprint edition, Varansi: Chaukhamba Surbharati Prakashan, 2000 : Sutrasthan 26/5, p. 144.
- 9. Sushruta Samhita, Edited with Susrutavimarsini Hindi commentary by Dr. Anant Ram Sharma, Chaukhambha

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