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Bone healing efficacy of Lakshagrishtiksheeradi churna over Calcium +Vit D3 in Avrana Kanda Bhagna (Closed fractures of long bones) - A Randomized controlled clinical trial

Research Article

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Abstract

Background: Delayed bone healing or non-union of fractures owns high rate of complications, morbidity and mortality. It possesses enormous burden to both patients and healthcare system. Till now there is no proven molecule which could enhance the process of bone healing. Hence, time tested *Lakshagrishtiksheeradi churna*, an *Ayurvedic* formulation is explored for its efficacy in the management of *Avrana Kanda Bhagna*. Objective: To Evaluate Bone healing efficacy of *Lakshagrishtiksheeradi churna* in *Avrana Kanda Bhagna.* Methods: Total 30 patients meeting the inclusion criteria of *Avrana Kanda Bhagna*, with age group 14-50 years participated in the study. They were randomly divided into two groups. Group A received *Lakshagrishtiksheeradi churna* 6 grams and group B Tab Calcium 500 mg +VitD3 respectively twice a day for 30days. Assessments were done through various variables like Pain, Tenderness, Swelling and Bone callus index. Follow up visit was on 30th day and 45th day. Results: Study showed that both *Lakshagrishtiksheeradi churna* and Calcium + Vit D3 produced improvement in most of the variables and were comparable. However, marked improvements were seen in various variables like Pain, Tenderness, Swelling and Bone callus Index. Conclusion: Clinical efficacy showed that *Lakshagrishtiksheeradi churna* is safe, effective oral medication in the management of *Avrana Kanda Bhagna* (Closed Fractures of long bones).

Key Words: *Ayurveda*, *Avrana Kanda Bhagna,* Closed Fractures of Long bones, Bone callus Index, *Lakshagrishtiksheeradi churna,* Calcium + Vit D3.

Introduction

World Health Organisation considers injury as a significant cause for morbidity and mortality in low and middle-income countries (LMICs) (1). The Centre for Disease Control and Prevention designates that fractures are one among the top-20 first-line diagnoses presenting to emergency departments (2). Since Immemorial times insalubrities have been drawing his attention, Trauma being the birth accomplice of man has constantly baffled him [3]. He experienced wounds, Fractures and attempted his level best to oversee, which is obvious by his long excursion for example at the point when he was very uncouth to the present day and when he is profoundly humanized and in a tangled state (3). Fracture is defined as 'any loss in the continuity of bone (4). Over the last several years due to widespread industrialization, use of vehicles and falls long bone fractures are becoming increasingly common (5). Skeletal injury influences all age gatherings and its frequency is continuously expanding. The burden of fractures impacts society through the loss of productivity, direct and indirect costs of treatment and the additional contribution to morbidity and mortality (6). Skeletal injuries are unavoidable and demands immediate management, present day orthopaedics is profoundly refreshing because of its most recent methods like internal fixation and bone grafting. Contemporary management of fracture progresses through 4 'R's i.e Resuscitation, Reduction, Retention and Rehabilitation followed by Calcium + Vit D3 administration, but lacks in combating the factors which can accelerate the process of bone healing (7). Ancient *ayurvedic* texts are enriched with treatment pertaining to fractures, we encounter one such reference given by Acharya Shushruta where Internal administration of *Grishtiksheer* (colostrum milk) with drugs of *Kakolyadi* group has been emphasised in fracture management (8), but in the present time it is difficult to find primipara cow hence readily available colostrum milk churna was

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procured from a GMP certified pharmacy and the former combination containing *Grishtiksheer* (2part) and drugs of *kakolyadi* group (Table 3) i.e *Ashwagandha* (*Withania somnifera* (L) Dunal), *Shatavari* (*Asparagus racemosus* Willd), *Laksha* (Laccifer lacca) , *Yashtimadhu* (*Glycerhiza glabra* L) (1part each) was formulated. Till now no research work has been carried out using this combination in *Avrana Kanda Bhagna*. The pharmaceutical industry is enriched with drugs and formulations pertaining to fractures, but none of the formulation possesses *Grishtiksheer* as a constituent, hence an attempt has been made to evaluate bone healing efficacy of *Laksha grishtiksheeradi churna*.

Materials and methods

The patients attending outpatient department of KLE Ayurveda hospital and KLE Centenary charitable hospital, Yellur, Belagavi were recruited for the study. The CONSORT statement guidelines have been followed in reporting the outcomes of the study (9).

Subjects

Total 30 patients who were diagnosed with *Avrana Kanda Bhagna* (closed fractures of long bones) as per inclusion criteria were recruited from patients visiting outpatient department of KLE Ayurveda hospital and KLE Centenary charitable hospital, Yellur, Belagavi, Karnataka, India.

Inclusion Criteria

The Patients of either sex, irrespective of socio-economic status between 14-50 years of age were included in the study will be taken.

Exclusion Criteria

The Patients with History of Pathological Fracture, Non-union, Ischemic heart disease Solitary bone cyst, Metastatic tumour, Osteomyelitis, Rheumatoid arthritis, injury to the blood vessels, nerves, Systemic illness and allergic history to milk and dairy products were excluded from the study.

Screening Methods

All patients included in this study were examined thoroughly and data was recorded systematically. Digital X rays were carried out at Dept of Radiology, KLE Centenary charitable hospital, Yellur, Belgaum in all patients at baseline and on 30th and 45th day of intervention.

Research Design

The study was a randomized controlled clinical study. Computer generated random numbers were utilized for the study. The patients were allocated in control and intervention groups in 1:1 ratio. The sample size was 15 in each group.

Intervention

All the patients were randomly divided into two groups: group A and group B. Group A (n = 15) (Figure 1) received *Lakshagrishtiksheeradi churna* 6 gram twice daily, while Group B (n=15) received Calcium 500mg+ Vit D3 twice daily. Both groups received their respective interventions with *GoGhrita* and water after food intake. The intervention administered to group A has been taken from a reference mentioned in *Sushruta Samhita* (8) and dosage of interventions were as per respective classical literature, intervention administered to group B is standard drug. The ingredients of *Lakshagrishtiksheeradi churna* were procured from authentic distributors, GMP certified pharmacy and prepared in GMP approved KLE *Ayurveda* Pharmacy, Belagavi as per standard procedures. Calcium + Vit D3 tablets were procured from Genius Remedies LLP, Mumbai, Maharashtra. Duration of intervention was 30 days with follow-up on 30th and 45th day. The nature and design of the study were explained to patients, and informed consent was obtained. The study was approved by the Institutional Ethics Committee (Protocol Id e BMK/17/PG/SL/03, KAHER's Shri BMK Ayurveda Mahavidyalaya Belagavi, Date of Approval e 20.03.2018. CTRI Registration Number e CTRI/2018/10/015). Data collection was from November 2018 to November 2019. During the study, patients were asked to adhere to the treatment protocol and report any adverse events to the investigators at the earliest. Any manifestations either existing or new during the course of intervention which can cause considerable distress were screened for possible adverse events.

Criteria for assessment

Primary Outcomes

Pain, Tenderness, Swelling and Bone Callus Index (10) were primary outcomes. Pain was assessed by VAS scale, Tenderness was assessed by present or absent with numbers i.e. absent (0) and present (1), Swelling was assessed by present or absent with numbers i.e. absent (0) and present (1) and Bone Callus Index (Assessed by digital radiographs using Orthoread software). They were recorded by following standard operating procedures.

Statistical methods

Statistical analysis was carried out using SPSS Version 20.0. Comparison of primary outcomes like Pain, Tenderness and swelling within groups at two time points was carried out by Wilcoxon Matched Paired Test and between groups at two time points was carried out by Mann- Whitney U test. Comparison of Bone callus Index within groups at two time points was carried out by Unpaired t-test and between groups at two time points was carried out by Paired t-test. Values are reported as mean ± standard deviation. All tests were considered statistically significant at $p < 0.05$.

Results

A total of 30 patients participated in the study. No patients in either groups reported any adverse effects. No patient dropped out of our study (Fig.1).

Subject characteristics

The mean age (p= 0.7150), gender (p= 0.2560), socio-economic status (p= 1.0000), BMI (p= 0.3380), Line of fracture (p=1.000) were comparable between groups (Table 1). Clinical variables like Pain, Tenderness, Swelling and Bone callus Index of the patients were comparable in both the groups.

3.2. Primary outcome

The study showed that improvement in both groups (Table 2) was comparable in Pain (Graph 1), Tenderness (Graph 2), Swelling (Graph 3) and Bone callus Index (Graph 4). However, within group comparison showed significant improvement in both the groups on all these four variables at all the two time points (Table 2). Both interventions produced significant reduction in pain at 45th day ($p < 0.05$) and 0 to 45th day ($p < 0.05$) of treatment. Tenderness showed significant reduction ($p < 0.05$) at both 0 to 30th day and 0 to 45th day; however, at 0 to 45th day, improvement in group A (p= 0.0117) and group B (p = 0.0431) was different. Swelling improvement in both groups was significant ($p < 0.001$) at 0 to 45th day of treatment. Interventions produced significant improvement in Bone Callus Index scores (Figure 2) at all two time points in both groups ($p < 0.001$).

Table 1: Patient profile: Expressed in Mean, standard deviations (S.D.) and percentage

S.No.	Clinical Profile		Group A		Group B		Total	P value
			No.	%	No.	%		
1	Age		34.00+/-13.14		31.67+/- 15.82			0.6637
2	Gender	Male	11	73.33	8	53.33	19	0.2560
		Female	4	26.67	7	46.67	11	
3	Occupation	Housewife	4	26.67	5	33.33	9	0.1190
		Labourer	2	13.33	0	0.00	2	
		Retired	1	6.67	2	13.33	3	
		Shopkeeper	1	6.67	1	6.67	2	
		Student	3	20.00	7	46.67	10	
		Farmer	4	26.67	0	0.00	4	
4	Socio-economic status	Middle SES	13	86.67	13	86.67	26	1.0000
		Poor SES	2	13.33	2	13.33	4	
5	BMI	Under weight	2	13.33	4	26.67	6	0.3380
		Normal	7	46.67	7	46.67	14	
		Over weight	6	40.00	4	26.67	10	
6	Line of Fracture	Transverse	12	80.00	13	86.67	25	1.000
		Oblique	3	20.00	2	13.33	5	
7	Drop outs		0	0%	0	0%	0	
8	Study Completed		15	100%	15	100%	30	
9	Total		15		15		30	

Table 2: Effect of interventions on Pain, Tenderness, Swelling and Bone Callus Index Expressed in Mean and standard deviations (S.D.)

S. No.	Parameter	Intervention period	Group A	Group B	p-value
1	Effect on pain	0 day	9.13 ± 0.74	9.13±0.74	1.0000
		30 day	4.80 ± 0.77	5.27±0.96	0.1466
		45 day	0.27 ± 0.46	1.07±0.80	0.0095
		p-value	0.0007	0.0007	
2	Effect on swelling	0 day	1.0±0.0	1.0±0.0	1.0000
		30 day	0.7±0.5	0.7±0.5	0.7557
		45 day	0.0±0.0	0.2±0.4	0.3507
		p- value	0.0007	0.0022	
3	Effect on tenderness	0 day	1.0±0.0	1.0±0.0	1.0000
		30 day	0.5±0.5	0.4±0.5	0.5338
		45 day	0.0±0.0	0.1±0.3	0.7557
		p-value	0.0007	0.0010	
4	Bone Callus Index	0 day	0.00±0.00	0.00±0.00	---
		30 day	1.22±0.22	1.31±0.21	0.2823
		45 day	1.15±0.12	1.24±0.16	0.1150
		p-value	0.0001	0.0001	

Table 3: Ingredients of *Laksha grishtiksheeradi* Powder

S.no	Sanskrit name	Latin name	Form	Proportion
1	*Ashwagandha*	*Withania somnifera* (L.) Dunal	Powder	1
2	*Shatavari*	*Asparagus racemosus* Willd	Powder	1
3	*Yashtimadhu*	*Glycerhiza glabra* L.	Powder	1
4	*Laksha*	Laccifer lacca	Powder	1
5	*Grishtiksheer*	Colostrum milk	Powder	2
6	*Ghee*	Clarified Butter		

Discussion

The study showed that *Laksha grishtiksheeradi churna* was comparable to Calcium + Vit D3 in the management of *Avrana Kanda Bhagna* in all the aspects, thus failed to reject the null hypothesis. Fracture has emerged as very common entity in all the age groups and possessing a global burden and threat. Many standard protocols and drugs like Calcium + Vit D3 exist for managing the condition but there is a dire need to search for safe and effective alternative. The Ancient texts beautifully portray the concept of fractures and strategies to combat it (11). *Acharya Sushruta* mentioned colostrum milk with indigenous herbal drugs to be administered in patient suffering from fracture thus reducing morbidity period (12). *Laksha grishtiksheeradi churna* administration to patients showed significant improvement in pain, tenderness, swelling along with great improvement in Bone callus index. Callus is a bridge made of bony and cartilaginous material which acts as bridge across a fracture during repair (10). Bone Callus index is defined as the ratio of the maximum callus diameter to bone diameter at the same level as the callus (10). Digital radiographs were taken at all three time points and using Radiant-Diacom viewer and Assessed using Orthoread software for Bone callous index (12). Callus index was calculated by dividing the total diameter of callus by the diameter of the bone (Figure 2). *Laksha grishtiksheeradi churna* is a formulation (Table 3) with drugs like *Ashwagandha* (*Withania somnifera* (L) Dunal) having analgesic, anti-inflammatory, anti-arthritic, anti-depressant, anti-coagulant, rejuvenating, regenerating and growth promoting properties (13). The active molecule Withaferin-A blocks the Prostaglandins (endogenous pain mediators). Withaferin- A has inhibitory action on cyclooxygenase pathway which is directly involved in prostaglandin biosynthesis (14). Withaferin-A helps to increase the osteoblastogenesis expression and decrease osteoclastogenesis expression (15). It exerts positive effect on osteoblast by increasing osteoblast proliferation and differentiation (15). *Shatavari* (*Asparagus racemosus* Willd) reduces swelling and shows anti-inflammatory activity due to Steroidal saponins (shatavarin I–IV) which are the major constituents of the plant. “Saponin” active molecule of *Shatavari* helps in Bone remodelling through life via synthesis of bone materials by action on the two major bone cells osteoblasts & osteoclasts (16). *Yashtimadhu* (*Glycyrrhiza glabra* L) contains Glycyrrhizin as an active molecule that inhibits cyclooxygenase activity and prostaglandin formation thus indirectly inhibiting platelet aggregation, reducing inflammation and pain (17). *Yashtimadhu* (*Glycyrrhiza glabra* L) possesses Glycyrrhizin, which is a triterpenoid mixture of potassium–calcium–magnesium salts of glycyrrhizic acid which helps in bone healing (17). Colostrum milk (*Grishtiksheer*a) is rich in IgG content, IgG’s form chelating complexes with bacterial and viral antigens in turn subsiding pain and inflammation (18). The reduction in oxidative stress is mainly attributed high level of antioxidants present in the colostrum (18). Anti-inflammatory, Pain and swelling substantiating activity of colostrum milk is mainly due to the presence of Lactoferrin and lactoperoxidase (18, 19). Lactoferrin present in Colostrum milk shows highly influential anabolic, differentiating, and antiapoptotic effects on osteoblasts and inhibits osteoclastogenesis (20).

The present study has various merits like it was Randomized controlled clinical study. multiple Variables like Pain, Tenderness, Swelling and Bone Callus Index. Limitations of the study were the lack of use of Serum Markers for assessment of bone healing.

Conclusion

The present study showed that both the drugs were comparable in management of *Avrana Kanda Bhagna*. *Ayurveda* drugs could demonstrate action on variables of multiple domains and showed to be a comprehensive management strategy for *Avrana Kanda Bhagna*. Laksha *grishtiksheeradi churna* appeared to be safe as there was absence of any adverse drug reactions. *Lakshagrishtiksheeradi churna* possesses analgesic, anti-inflammatory, anti-arthritic and osteoblastogenesis effect. Hence it can be incorporated in the treatment of *Avrana Kanda Bhagna.*

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Conflict of interest - None.

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Figures

Figure 1: CONSORT flow chart

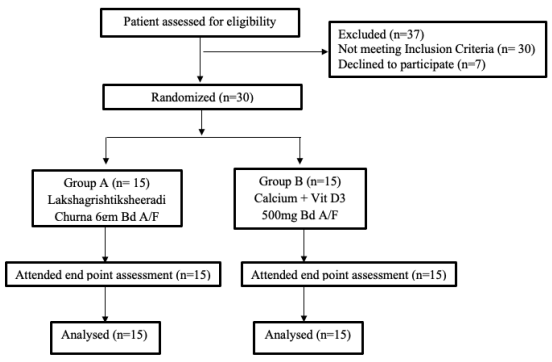
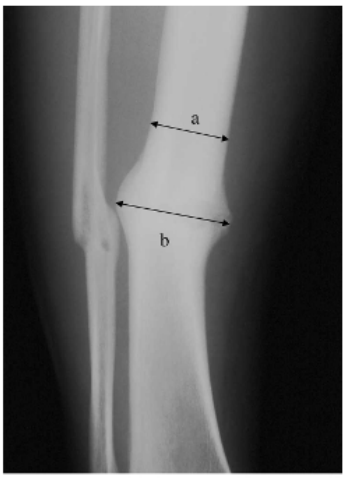


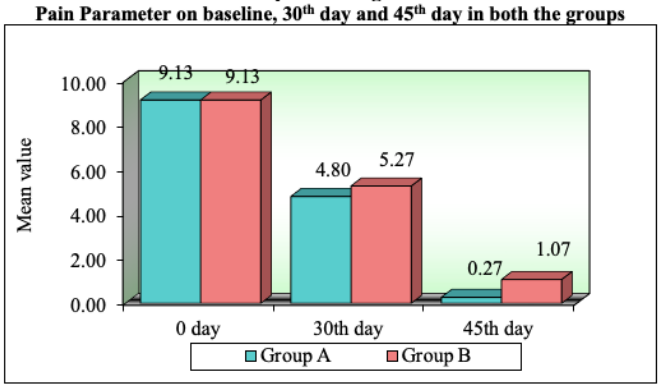
Figure 2: Bone Callus Index



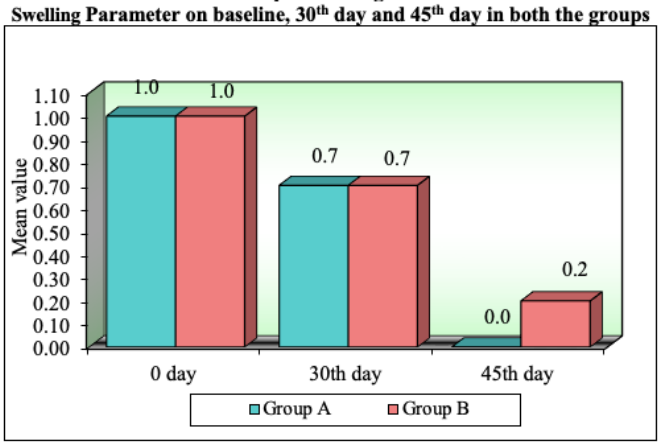
Callus Index = b/a

Graphs showing changes in Pain, Tenderness, Swelling and Bone Callus Index parameters in group A (n= 15) and group B (n= 15) as assessed on 0 (baseline), 30th and 45th day of intervention. Results are expressed in Mean ± standard deviation

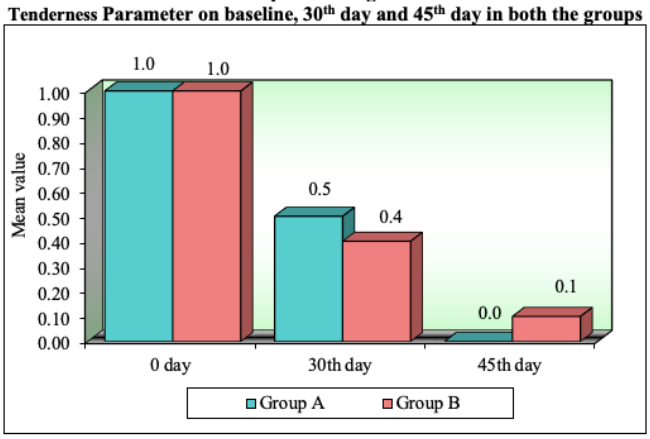
Graph 1: Changes in Pain Parameter on baseline, 30th day and 45th day in both the groups



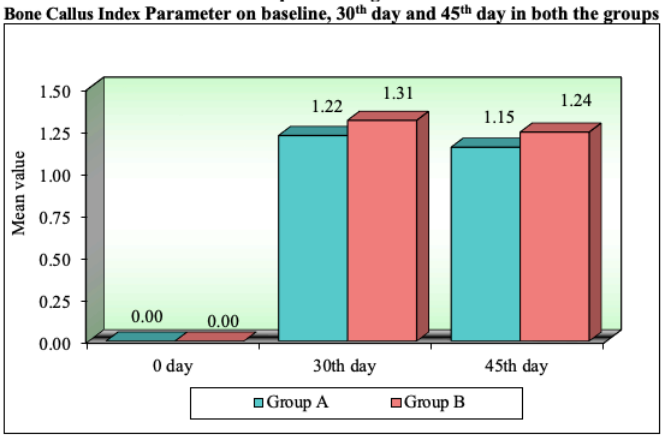
Graph 2: Changes in Swelling Parameter on baseline, 30th day and 45th day in both the groups



Graph 3: Changes in Tenderness Parameter on baseline, 30th day and 45th day in both the groups



Graph 4: Changes in Bone Callus Index Parameter on baseline, 30th day and 45th day in both the groups



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