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Efficacy and safety of tablet Ligashot in patients with ligament injury of knee and shoulder

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ABSTRACT

Background: Ligament injuries of knee and shoulder disrupts joint homeostasis and leads to an imbalance between joint mobility and stability. Many drugs are available in the market for treating ligament injury grade 1 and 2 along with standard of care but there is still need for drugs with least adverse effects. So, in this study, an attempt has been done with tablet Ligashot, a nutraceutical for treating grade 1 and 2 ligament injury of knee and shoulder.
Methods: This is an outcome, quasi-experimental study where patients with ligament injury of knee and shoulder were given tablet Ligashot daily for 3 months. A total of 30 male and female patients were included in the study. Changes from baseline to 12 weeks in pain intensity measured by pain visual analogue scale (VAS) and inflammatory markers (ESR, Hs CRP), MRI changes, time to return to pre-injury level of activity, patient reported physical function and quality of life (QoL) were assessed.
Results: There was a statistically significant improvement after 12 weeks of treatment compared to baseline in VAS pain scale, time to return to pre-injury level of activity, patient reported physical function and in QoL questionnaire. There was also a statistically significant reduction in inflammatory markers-ESR and Hs-CRP ($p<0.001$).
Conclusions: Ligashot tablet has proved to be safe and effective in the management of ligament injury of knee, shoulder joint by reducing inflammation, pain. It also improves visco-elasticity and participant's functional capacity without causing any major side effects.

Keywords: Ligament injury, Ligashot tablet, ESR, VAS, CRP

INTRODUCTION

Ligament of joints are responsible for connecting one bone to another and for controlling the range of motion within a joint. Traffic and sports-related accidents, involving high-energy and low-energy trauma respectively, are the primary causes cruciate ligament injuries.[1] Ligament injury of knee and shoulder accounts for 31% among adult population in India.[2] Grade 1 and 2 ligament injury treatment involves acute symptomatic treatment followed by 12 weeks of supervised physiotherapy, beginning with restoring a full range of motion.[3] Ligashot Tablet is a nutraceutical, acting on the musculo-skeletal system of the body.

The active ingredients of Ligashot tab are chondroitin sulfate 200 mg, collagen peptide 150 mg, curcumin 100 mg, cyanocobalamin 1 µg, aflapin 100 mg, vitamin B6-1.4 mg, vitamin B12 0.001 mg, silica (*Bambusa vulgaris*)-7.5 mg, elemental iron 10 mg, glucosamine 250 mg, L-glutamic acid 50 mg, L-lysine 100 mg, manganese sulphate 1 mg, niacinamide 5 mg, proline 100 mg, quercetin 25 mg, vitamin C 35 mg and zinc sulphate 10 mg.

Low doses of glucosamine and chondroitin sulphate effectively stimulate collagen and non-collagenous protein (NCP) synthesis of ligament cells *in vitro*.[4] Vitamin C functions as a potent antioxidant by neutralizing harmful reactive oxygen species (ROS), which cause cell apoptosis during the inflammatory phase.[5] Bamboo silica extract is derived from the leaves and stem of the *Bambusa vulgaris* found in India.[6] Curcumin extract's analgesic and anti-inflammatory properties can aid in the post-operative healing of ligament injuries.[7]Aflapin obtained from Boswellia serrata gum resin. It reduces pain and improves physical function in inflammatory conditions of knee.[8]

Ligashot tablet efficacy in grade 1 and 2 ligament injury of knee and shoulder assessed by decrease in pain intensity at 12 weeks of treatment, changes in inflammatory parameters, improvement in MRI changes and improvement in QoL. Its safety assessed by adverse drug reactions and events during the study period. Many drugs are available in the market for treating symptoms of grade 1 and 2 ligament injury of knee and shoulder, but there is still need for drugs with least adverse effects. So, in this study, an attempt has been done with tablet Ligashot for treating symptoms of grade 1 and 2 ligament injury of knee and shoulder.

METHODS

The present study is an outcome, quasi-experimental study where patients with ligament injury of knee and shoulder, according to inclusion criteria were included and assessed after treatment. Patients were given tablet Ligashot daily for 3 months. Tablet Ligashot sponsored by Innovcare lifesciences Pvt Ltd, Mumbai. The study was done in Thirumalai Medical Centre and in Sri Ortho Care Clinic in Pondicherry during October 2023 to April 2024. The study was registered in clinical trial registry of India: CTRI/2023/09/057919. Independent ethics committee approval obtained for this study from ethique De La nature association in 19th August 2023.

Inclusion criteria

Male or female patients aged more than 18 years with grade 1and 2 ligament injury of knee, shoulder-with or without dislocation, pain defined by a level of greater than or equal to 30 mm on a 100 mm VAS, patient who has not participated in any other clinical trial during the past 3 months. Participants who are willing to give written, signed and dated informed and consent to participate in the study were included in study.

Exclusion criteria

Patient who had prior ligament tear surgery of knee and shoulder joint in the past 6 months, torn or avulsed patellar or quadriceps tendon, periarticular or long bone fracture that is anticipated to preclude weight-bearing after surgery, patients who are unable to bear weight on the contralateral uninjured leg, traumatic brain injury (TBI) that limits their ability to participate in their post-operative care, surgical procedures that precludes early weight-bearing or range of motion, any condition that would preclude the ability to comply with post-operative guidelines. Moderate to severe renal impairment, pregnant or lactating women, history of hypersensitivity to any of the test products and any systemic condition of patient decided as unfit for study by clinical investigator were excluded.

Investigational drug

Ligashot-one tablet twice daily orally after food for 12 weeks. Ligashot tablet composition is shown in Table 1.

Table 1: Ligashot tablet composition.

Ingredient	Strength
Aflapin	100 mg
Collagen peptide	150 mg
Glucosamine sulphate	250 mg
Chondroitin	200 mg
Quercitin	25 mg
Vitamin C	35 mg
Manganese	25 mg
Iron	10 mg
Zinc	10 mg
L-glutamine	50 mg
Niacinamide	5 mg
L-proline	100 mg
L-lysine HCl	100 mg
Vitamin B6 (Pyridoxine)	1.4 mg
Vitamin B 12 (Cyanocobalamin)	0.001 mg
Curcumin	100 mg
Silica (from *Bambusa vulgaris*)	7.5 mg

Duration of study drug given was 12 weeks.

Primary outcome

Changes from baseline to 12 weeks in pain intensity measured by pain VAS (0-100 mm). Time to return to pre-injury level of activity. Patient-reported physical function-activity limitation scale of the multiple ligament QoL (MLQoL) questionnaire.

The activity limitation scale score ranges from 0 to 100 with a score of 0 representing no activity limitations due to knee, shoulder ligament injury.

Changes from base line to 3 months in following laboratory parameter(s): Hs-C reactive protein, ESR and improvement in MRI was also noted.

Global rating of change (GRC) [Time frame: 3 months]- The GRC asks the individual to compare his/her current functional status to his/her functional status at the time of enrolment/post-injury. The responses for the GRC range from +7 (greatly better) to-7 (greatly worse). Higher scores

representing greater improvement in function since the time of enrolment.

Changes from base line to 3 months in QoL-questionnaires (Short form health-12).

Secondary outcome of the stud

Adverse drug reactions observed during the study period (for safety assessment).

Statistical analysis

Changes in score of pain intensity, improvement scores between baseline and at 4th, 8th and at 12th week of treatment in Ligashot tablet is measured by repeated measures of ANOVA. Statistical significance is measured by $p<0.05$.

RESULTS

Age and gender wise distribution of patients with ligament injury of knee, shoulder in the study is depicted in Table 2.

Table 2: Age and gender wise inclusion of patients in Ligashot tablet group.

Variables	Ligashot tablet
Age (in years)-mean	41
Female	6
Male	24

Change from baseline to 12 weeks in joint pain intensity measured by pain VAS.

Table 3: Joint pain intensity measured by the pain VAS.

Group	Pain VAS (0-100 mm) (Mean±SD)			
	Day 0	Week 4	Week 8	Week 12
Ligashot, (n=30)	7.5± 2.5	4.9± 2.10*	3.1± 1.52*	2.50± 1.13*
P value*		<0.0001	<0.0001	<0.0001

*There was a statistically significant improvement in the VAS pain score at week 4, week 8, and week 12 compared to baseline post-treatment with Ligashot.

Table 4: Time to return to pre-injury level of the activity.

Time taken to return to pre-injury level of activity	N (%)
4 weeks	8 (27)
8 weeks	2 (40)
12 weeks	7 (23)

At 8 weeks of treatment with Ligashot tablet, 40% of patients showed pre injury level of activity as shown in Table 4.

There was a significant improvement in the activity limitation score from pre to post study in tablet Ligashot group as shown in Table 5.

There was a statistically significant reduction in the primary inflammatory markers like ESR and Hs-CRP from baseline to week 12 after treatment with Ligashot as shown in Table 6.

Also, there was a statistically significant improvement in the participant's GRC at week 4, week 8, and week 12 (Mean±SD=4.80±1.89), $p<0.0001$ compared to baseline post-treatment with Ligashot.

The improvements observed in the MRI of the patients after study period of 12 weeks has been highlighted in Figure 1 (A and B).

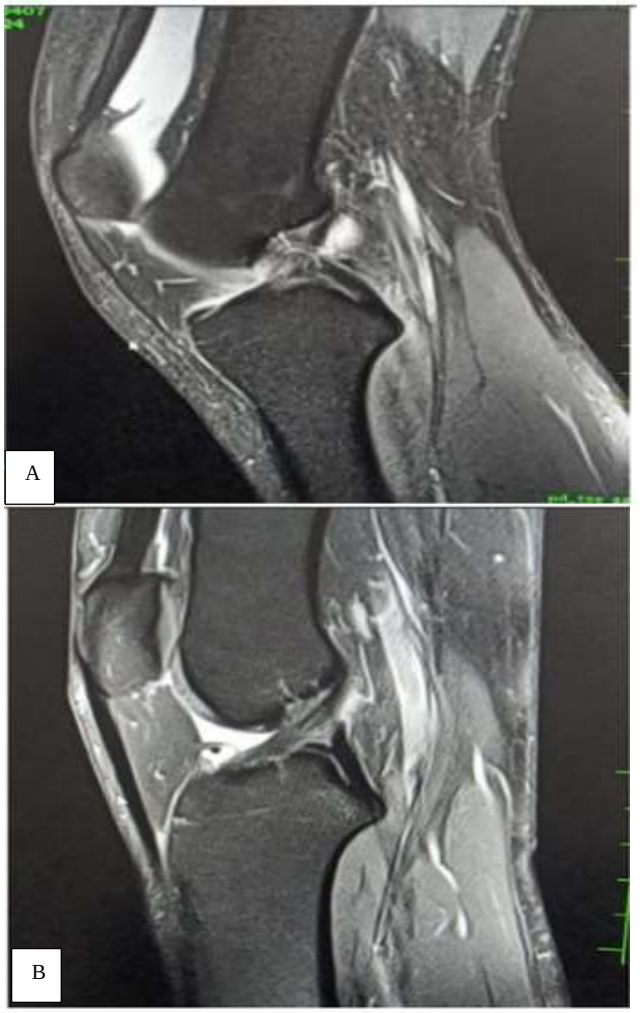

Figure 1 (A and B): MRI findings in knee joint (Pre and post study findings) in 38 years old female.

Near complete tear of anterior cruciate ligament (ACL) and moderate joint effusion were found in pre study findings in MRI. Partial tears in ACL and minimal joint effusion found in post study findings after 3 months of treatment with tablet Ligashot as shown in Figure 1 A.

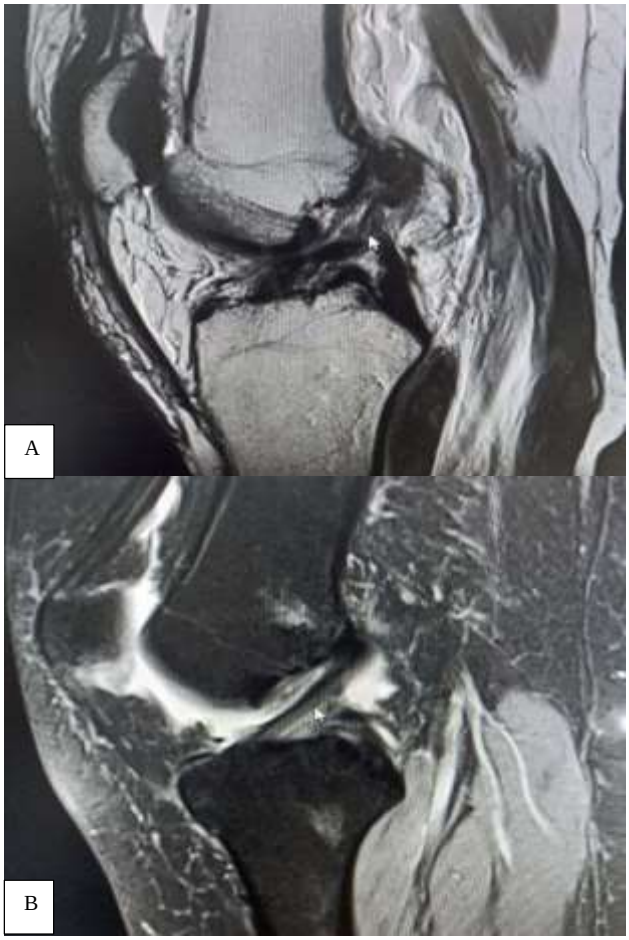

Figure 2 (A and B): MRI Findings in knee joint (Pre and post study findings) in 20 years old male.

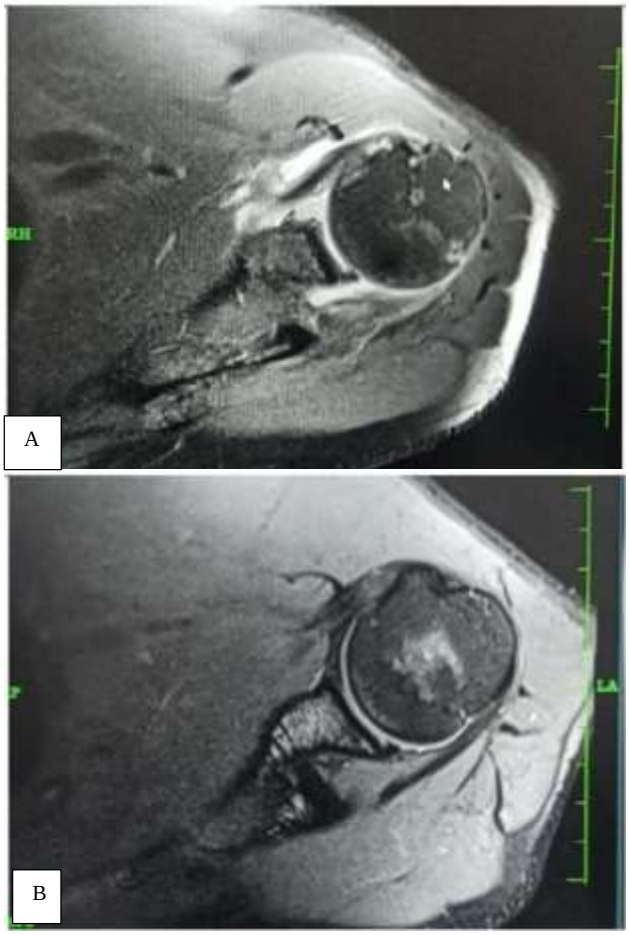

Figure 3 (A and B): MRI findings in shoulder joint (Pre and post study findings) in 50 years old male.

Grade II partial tear of ACL in the mid third region, low grade partial tears in the upper 1/3rd of posterior cruciate ligament, degenerative changes in both medial and lateral menisci, an oblique tear in the posterior horn of medial meniscus seen in pre study MRI findings. While in post study MRI after treatment period, grade I partial tear of ACL in the mid third region, few old tiny tears noted in the upper 1/3rd of the posterior cruciate ligament.

Partial tear of subscapularis in shoulder joint and mild joint effusion seen in pre study findings while in post study MRI after treatment period, no joint effusion seen.

The side effects observed were mostly gastrointestinal (nausea in 3 patients and gastritis in 4 patients) in the study group and no serious adverse effects were recorded during the study period.

Table 5: Activity limitation score (pre and post study): score ranges from 0 to 100 with a score of 0 representing no activity limitations.

Questionnaire	Activity limitation score pre study (Mean)	Activity limitation score post study (Mean)
Straightening your knee/ankle/shoulder is difficult or impossible	100	20
Sitting is difficult due to your knee/ankle/shoulder	80	5
It is difficult to rise from bed due to your knee/ankle/shoulder	100	5
Walking on flat surfaces is difficult due to your knee/ankle/shoulder.	80	5
Lying in bed is difficult due to your knee/ankle/shoulder (including turning over and maintaining knee position).	90	10
Going shopping is difficult due to your knee/ankle/shoulder	90	5

Continued.

Questionnaire	Activity limitation score pre study (Mean)	Activity limitation score post study (Mean)
Putting/removing on socks and/or stockings is difficult due to your knee/ankle/shoulder	80	5
Getting on and/or off the toilet is difficult due to your knee/ankle/shoulder	70	5
You need support during walking due to your knee/ankle/shoulder problem (i.e., a cane, crutches, walker, or other person).	70	5
You require a wheelchair due to your knee/ankle/shoulder problem	10	0
Your knee/ankle/shoulder condition makes you limit light duties	60	0
Your knee/ankle/shoulder limits your daily activity level	60	0
Your knee/ankle/shoulder condition makes you limit moderate work	70	5
Bending your knee/ankle/shoulder is difficult	100	20
Your knee/ankle/shoulder makes it difficult to participate in your favourite sport or recreational activity.	100	20
P value		<0.0001

Table 6: Changes from baseline to 12 weeks in inflammatory markers.

Group	ESR (Mean±SD)		Hs-CRP (Mean±SD)	
	Day 0	Week 12	Day 0	Week 12
Ligashot, (n=30)	27.4±3.2	11.06±1.83*	5.7±3.1	3.1±0.4*
P value*	<0.0001		0.0001	

Table 7: QoL-questionnaires-short form health-12.

Questionnaire	Ligashot group, (n=30) (%)	
	Day 0	Week 12
In general, would you say your health is:*		
Excellent	0	0
Very good	2	50
Good	24	50
Fair	65	0
Poor	8	0
Moderate activities such as moving a table, pushing a vacuum cleaner, or playing*		
Yes, limited a lot	40	0
Yes, limited a little	46	17
No, not limited at all	13	83
Climbing several flights of stairs*		
Yes, limited a lot	54	4
Yes, limited a little	33	23
No, not limited at all	13	73
Accomplished less than you would like (due to problems in physical health)*		
Yes	90	13
No	10	87
Were limited in the kind of work or other activities (due to problems in physical health)*		
Yes	90	13
No	10	87
Accomplished less than you would like (due to any emotional problems)*		
Yes	90	13
No	10	87
Did work activities less carefully than usual. (due to any emotional problems)*		
Yes	90	13
No	10	87

Continued.

Questionnaire	Ligashot group, (n=30) (%)	
	Day 0	Week 12
During the past 4 weeks, how much did pain interfere with your normal work (Including work outside the home and housework)?*		
Not at all	6	50
A little bit	30	50
Moderately	50	0
Quite a bit	4	0
Extremely	10	0
Have you felt calm and peaceful?*		
All of the time	0	24
Most of the time	24	36
A good bit of the time	24	17
Some of the time	36	23
A little of the time	16	0
None of the time	0	0
Did you have a lot of energy?*		
All of the time	0	10
Most of the time	3	40
A good bit of the time	24	50
Some of the time	16	0
A little of the time	40	0
None of the time	17	0
Have you felt downhearted and blue?		
All of the time	0	0
Most of the time	0	0
A good bit of the time	0	0
Some of the time	0	0
A little of the time	10	10
None of the time	90	90
During the last 4 weeks, how much of the time have your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?*		
All of the time	0	0
Most of the time	4	0
Some of the time	40	10
A little of the time	54	90
None of the time	2	0

*P<0.05. There was a significant improvement in the mean percentage scores of QoL-questionnaires on physical activity status after treatment for 12 weeks with Ligashot tablet.

DISCUSSION

Ligaments connect one bone to another and regulate the joint's range of motion. Ligament injury of knee and Shoulder results in abnormal knee kinematics and damage to surrounding tissues in and around the joint, leading to morbidity and pain.[9] The rupture of the ACL, the sprain of the medial or lateral collateral ligament of the knee most commonly occurs in ligament injury of the knee.[10] Ligashot Tablet is a nutraceutical, acting on the musculo-skeletal system of the body.

Vitamin C plays a crucial role in connective tissue healing, serving as a cofactor for the enzyme's prolyl hydroxylase and lysyl hydroxylase. These enzymes catalyse the hydroxylation of proline and lysine residues in procollagen, facilitating the correct folding of the stable collagen triple-helix structure and help in ligament strenghthening.[11]Aflapin obtained from Boswellia serrata gum resin exhibits superior anti-inflammatory, cartilage-protective property. An *in vitro* study indicated that aflapin has a protective effect against the chondrocyte-destructive properties of the proinflammatory cytokine IL-1β.[12]

In vivo study by Silva et al in rats, they found that combined glucosamine and chondroitin sulfate provides functional and structural benefit in the ACL transection model.[13] Coury et al in their *in vivo* study showed that administration of curcumin lowered tissue and serum levels of pro-inflammatory cytokines and matrix Metallo proteinases (MMP) in ACL transection injury-induced model in rabbits.[14] In a Ostojic et al randomized, double-blind study of glucosamine or a placebo for 28 days, the patients from the glucosamine group demonstrated significant improvement in pain intensity and functional capacity in knee injury.[15]

Each ingredient in Ligashot tablet help support bone health, reduce inflammation and pain, has antioxidant properties that can help in improving symptoms of ligament injury. In this study all ingredients together in a tablet form are evaluated for its efficacy in patients with grade 1 and 2 ligament injury of knee and shoulder. Our study showed a statistically significant reduction in inflammatory markers ESR and Hs-CRP ($p<0.001$) after 12 weeks of treatment with tablet Ligashot. There was also a statistically significant improvement after 12 weeks of treatment compared to baseline in VAS pain scale, MRI changes (Post study), time to return to pre-injury level of activity, patient reported physical function ($p<0.0001$) and in QoL questionnaire.

Limitations

This study was done without any comparator groups which may increase bias in outcome of study. Small sample size of study group in this study.

CONCLUSION

The test product tablet Ligashot has proved to be safe and effective in treating symptoms of Ligament injury of Knee, shoulder joint by reducing inflammation, pain and enhancing the visco-elasticity. It also improves the Participant's functional capacity without causing any major side effects.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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