Comparative study of amrutbhallataka and glucosamine sulphate in osteoarthritis: Six months open label randomized controlled clinical trial

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ABSTRACT

Background: AmrutBhallatak (ABFN02), a *'rasayana'* drug from Ayurveda is indicated in degenerative diseases and arthritis. **Objective:** To evaluate safety and efficacy of ABFN02 in osteoarthritis (OA) and compare it with Glucosamine sulphate (GS) **Materials and Methods:** This was a randomized open comparative study. Ambulant OPD patients of OA knees (n = 112) were enrolled for 24 weeks. Tablets (750mg each) of GS and ABFN02 were matched. Three groups of patients: (A) GS, one tablet × twice/day × 24 weeks. (B) ABFN02, incremental pulse dosage (one tablet x twice/day × two weeks, two tablets × twice/day × two weeks, three tablets × twice/day × two weeks), two such cycles of drug and non-drug phases alternately for six weeks each (C) ABFN02 continuous dosage akin to GS. Pain visual analogue score (Pain-VAS) and Western Ontario and Mc-Master University Osteoarthritis Index (WOMAC) were the primary outcome measures. Secondary outcome measures were Health assessment questionnaire (HAQ), paracetamol consumption, 50 feet walking, physician and patient global assessment, knee stiffness, knee status, urinary CTX II, serum TNFa-SRI, SRII and MRI knee in randomly selected patients. **Results:** ABFNO2 and GS demonstrated, adherence to treatment 87.75% and 74.3%, reduction in Pain-VAS at rest 61.05% and 57.1%, reduction in pain-VAS on activity 57.4% and 59.8%, WOMAC score drop 62.8% and 59.1% respectively. Secondary outcome measures were comparable in all groups. Safety measures were also comparable. No serious adverse events reported. However, asymptomatic reversible rise in liver enzymes was noted in the ABFNO2 group. **Conclusions:** ABFN02 has significant activity in OA; the formulation needs further investigation.

Key words: Ayurveda, Bhallatak, Rasayana, reverse pharmacology, *Semecrpus anacardium, Tinospora cordifolia*

INTRODUCTION

Osteoarthritis is recognized as the most common form of rheumatic disorder worldwide. World Health Organization and International League of Associations of Rheumatology launched Community Oriented Program for Control of Rheumatic Diseases [WHO-ILAR COPCORD] study from the rural population of Western India has reported about 5.5% prevalence of osteoarthritis.[1] Prevalence of osteoarthritis increases as the age advances. With an increase in aging population, the burden of this disease is going to be substantial on society at large. Currently palliative management through analgesics and non-steroidal anti-inflammatory drugs is the mainstay of pharmacotherapy. The use of which is also apprehended due to serious side effects; particularly on long-term use. Dependable disease-modifying anti-osteoarthritic drug is still a distant dream. Only option left for patients is either conservative non-pharmacological measures or radical surgical interventions. Hence; the search continues for safe, effective and convenient drugs.

ABFN02 is developed on the foundation of a classical Ayurvedic formulation which is indicated for degenerative diseases and arthritis.[2] The formulation has two main ingredients *viz*. Bhallatak (*Semecarpus anacardium*) and Guduchi *(Tinospora cordipholia)*. Both these ingredients are reputed as '*rasayana*' (rejuvenative/reparative) drugs in

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Ayurvedic literature.[3,4] However; Bhallatak is known for its adverse effects.[5,6] The study is aimed at evaluating the long-term (six month) efficacy and safety of ABFN02 and compares it with glucosamine sulphate. Glucosamine sulphate is widely used natural product consumed world over for the treatment of osteoarthritis which has also demonstrated to have disease modifying benefits.[7,8] Therefore it was thought appropriate to compare it with ABFN02 the natural product from Ayurveda.

This CSIR-NMITLI Government of India funded project was founded on the principles of Reverse pharmacology[9] for the development of globally competitive herbal product inspired from Ayurveda.[10]

MATERIALS AND METHODS

Total 112 patients of osteoarthritis of knee were allocated at two clinical centers during the period July 2006 to March 2007. All patients were in the age group of 40 to 75 years, ambulant and seeking medication for their ailment.

This was a randomized comparative open clinical study of 24 weeks with the assessor blind. Patients were evaluated before treatment (baseline), at periodic intervals (2, 4, 6, 12, 14, 16, 18 weeks) during treatment and after completion of treatment (24 weeks). The clinical study was conducted as per the Good Clinical Practices by International Conference of Harmonization guidelines, declaration of Helsinki and national regulatory norms.

Ethics Committee approval from respective institutions and patient's informed written consent was obtained before initiation of the study.

Criteria for Selection

Diagnosis of osteoarthritis of the knee was made using clinical classification of American College of Rheumatology Criteria.[11] All patients having knee pain, with visual analogue scale for pain (Pain-VAS) more than '4' on scale of 10; either at rest or on activity in last 24 h and having radiological evidence of osteoarthritis were included for the study.

Pregnant or lactating women of child bearing potential and not following adequate contraceptive measures, patients with known hypersensitivity to Bhallatak and history of allergic diatheses with vesication and chronic alcoholics were excluded. Patients having severe disabling arthritis, active peptic ulcer, bleeding ulcer, severe renal, hepatic, hematopoietic disease or cardiac insufficiency were not included. Patients on treatment of anticoagulants, hydantoin, lithium, corticosteroids, analgesics, anti-inflammatory drugs, methotrexate, colchicine and having received intra-articular steroid injection and any investigational drug within a month preceding the study were excluded. Subjects with positive Rheumatoid factor (RA test) were excluded since Rheumatoid arthritis on rare occasions may initially present as a single/pauciarticular disease.

Drug material

Investigational drug Amrut Bhallatak (ABFN02) was specially prepared at Shree Dhootpapeshwar Ltd. by a classical method described in Brihat Nighantu Ratnakar[2] and were made available in the form of tablets of 750 mg each. Glucosamine sulphate (GS) was also made available by Meyer Organics in the form of 750 mg tablet each. The size, shape, color and texture of both these tablets of ABFN02 and GS were comparable and were supplied in a similar container with a coded label.

Purity of the product was ensured for heavy metal content, pesticide residue, microbial load and aflatoxins contamination as per WHO guidelines.[12] Acute animal toxicity Study carried under OECD Guidelines No. 423. LD_{50} of ABFN02 was > 2000 mg/kg body weight confirmed in two species mice and rats.

Dosage schedule

The dosage schedules were either same dose continuous or incremental pulse dosage schedule. The incremental pulse dosage schedule was inspired from classical *'Vardhamana-Prayoga'* and earlier exploratory study[13] whereas; same dose continuous dosage schedule was akin to standard schedule of Glucosamine.

Randomized in three groups' *viz.* Group (A): Glucosamine Sulphate (GS), 750 mg × twice/day for 24 weeks (n = 35), Group (B): ABFN02, 750mg × twice/day for two weeks, 1500 mg × twice/day for next two weeks, 2250 mg × twice/day for further two weeks, subsequently no drug for six weeks, subsequently no drug for six weeks, such a drug and non-drug phases of six weeks each were repeated. (n = 39), Group (C): ABFN02 750 mg × twice/day for 24 weeks (n = 38) akin to GS drug schedule. Special instructions were given to avoid pitta aggravating factors. (To consume tablets with milk in the morning, after breakfast and at night after dinner; to drink plenty of water, avoid fasting, spicy, hot and salty food items, prolonged working outdoor under the sun, prolonged working near the fire and keeping awake late at night).

Randomization

Patients were screened and randomized on first cum first served basis. The simple randomization table was generated through computer based standard software program. Same randomization table was used for both the centers.

Assessment Criteria

Clinical

All patients were evaluated primarily on the scale of pain VAS and Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC)[14,15] before treatment (baseline), at periodic intervals (2, 4, 6, 12, 14, 16, 18 weeks) during treatment and after completion of treatment (24 weeks).Other secondary criteria for clinical evaluation were change in status of knee arthritis, walking time, patients and physician global assessment, paracetamol consumption and Health Assessment Questionnaire (HAQ).[16] Both WOMAC and HAQ CRD Pune versions are validated modified versions for Indian use and details of their use and scoring are available at the website (www.rheumatologyindia.org). A special case record form was also made to document patient's *Prakruti* and Ayurvedic evaluation.

Laboratory

All patients were screened and evaluated for organ function safety before treatment (baseline), at periodic intervals (4, 6, 16, 18 weeks) during treatment and after completion of treatment (24 weeks). Other secondary criteria were, Urinary C-Terminal Tellopeptides of Collagen Type II (Urinary CTX-II), Tumor Necrosis Factor Alpha Soluble Receptor I and Soluble Receptor II (TNF α-SRI and SRII). Twelve patients were randomly selected for pre and post treatment Magnetic Resonance Imaging (MRI) assessment. The semi quantitative MRI assessment was done by blinded assessor for 15 parameters (Articular Cartilage Integrity, Subcondral Bone marrow abnormality, Subarticular Cyst, Subarticular bone Attrision, Marginal Osteophytes, Medial Meniscal integrity, Lateral Meniscal integrity, Anterior cruciate ligament integrity, Posterior cruciate ligament integrity, Medial collateral ligament integrity, Lateral collateral ligament integrity, Synovitis/Effusion, Intra-articular loose bodies, Periarticular cyst, Bursitis).

Adverse events

All patients who were allocated were assessed at every visit for potential drug related events and were also asked for any adverse event experienced during the treatment period. All these symptoms were checked against baseline symptoms and recorded in a separate form of adverse events.

STATISTICAL ANALYSIS

The available data was analyzed for demographic information, efficacy and safety. Total allocation of 120 patients was planned and was randomized in three groups using standard software program. Demographic data and baseline information was analyzed by descriptive method and is presented with summary statistics (*n*, mean, standard deviation, range) for continuous variables, whereas counts and percentages for categorical variables. These summaries are presented as per treatment groups. Efficacy variables are analyzed using the per protocol set.

For assessment of primary efficacy variables *viz*. pain-VAS and WOMAC score, the change in value to endpoint are calculated as difference and are compared between the groups. Summary statistics per treatment group is tabulated. The changes within groups and comparison with other groups are estimated by analysis of variance with Kruskal Wallis test. When change between groups was significant post hoc Friedman test was applied.

For all secondary variables like Health assessment questionnaire score, mean changes from baseline to each time points and comparison with other groups were analyzed by ANOVA with Krusakal wallis test. When change between groups was significant *post hoc* Friedman test were applied. For categorical variables like Physicians global assessment,% reduction in pain by VAS score and changes in Knee status were analyzed and compared by Chi square test.

All other continuous data like Lab data were analyzed by ANOVA with *post hoc* test when the differences between groups were significant. The safety analysis consists of all patients who were allocated into the study, who have received at least one intervention of the study medication and have evaluable safety data. All values are reported based on two-sided and all the statistical tests are interpreted at 5% level of significance.

RESULTS

Total 123 patients were screened for enrollment [Figure 1] of which 11 patients could not be enrolled for various reasons such as, blood investigations showed Positive RA factor (3), revealed cardiovascular disorders (2), lack of radiological features expected for inclusion (1) and patients did not turn up for enrolment (4), whereas one patient decided not to initiate the study. Out of 112 patients' allocated; 93 patients completed six months study. All the three treatment groups matched for age, sex ratio, height, weight, mean BMI and *Prakruti* types [Tables 1 and 2]. Age of the patients ranged between 41 to 73 years, female patients were more in all the three groups ranging between 60 and 77%. The major type of *Prakruti* found amongst all was *Pitta-Kapha* (57/112); it was also the major type in each of the three interventional groups.

The adherence was measured depending on the continuation of the treatment for six months. Adherence over six

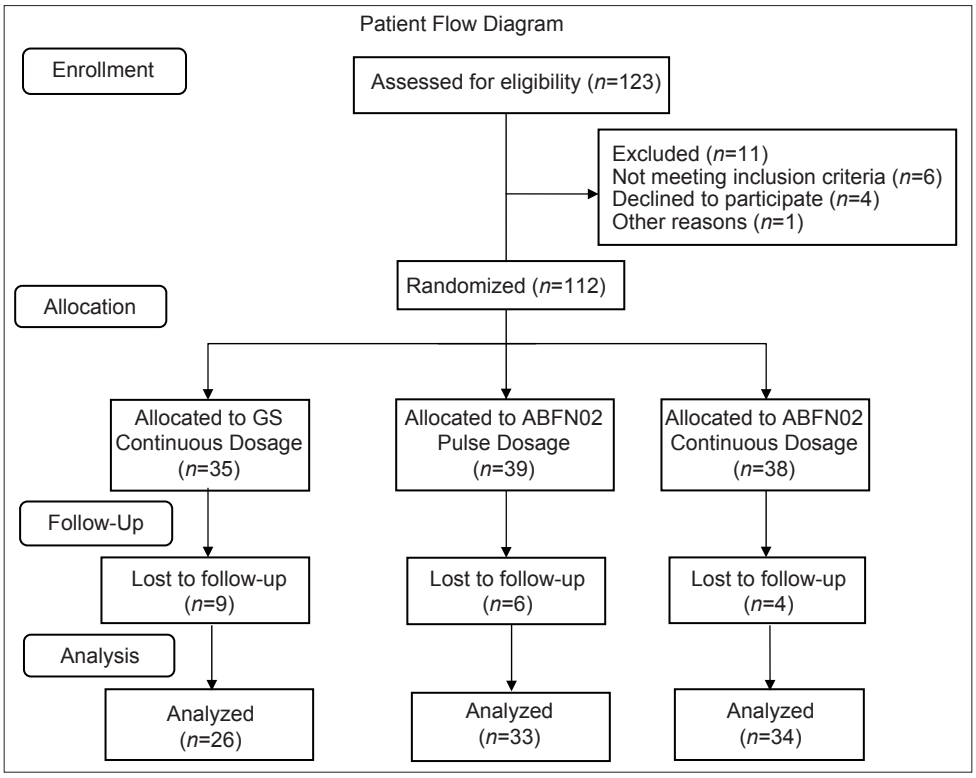

Figure 1: Flow of patients participation in three arm study of ABFN0$_2$ (Pulse dosage regimen and Continuous dosage regimen) and Glucosamine Sulphate (GS; Standard dosage regimen)

Table 1: Demographic data

Parameters	Group A	Group B	Group C
@Age (yrs)			
Mean	58.80	58.03	54.60
SD	7.38	8.57	8.37
Range	45-73 yrs.	45-73 yrs.	41-74 yrs.
@Weight (kg)			
Mean	63.47	65.73	66.71
SD	11.22	11.08	10.78
Range	42-86 kg	41-93 kg	39-100 kg
@Height (cm)			
Mean	155.16	154.65	156.39
SD	10.23	9.14	8.43
Range	142-183 cm	135-175 cm	140-185 cm
#Sex (%)			
Male	14 (40.0)	09 (23.1)	11 (28.9)
Female	21 (60.0)	30 (76.9)	27 (71.7)
Mean BMI	26.37	27.51	27.30

@By student '*t*' test# by Chi-square test. *P*>0.05 not significant for all the parameters between the three groups except for age between group A *v/s* C was *P*>0.02. Group A: Glucosamine sulphate standard dosage regimen, Group B: ABFN02-Pulse dosage regimen, Group C: ABFN02-contineous dosage regimen. BMI=Body mass index, SD=Standard deviation

Table 2: Profile of *Prakruti*

Prakruti type	Group A (*n*=35) No.%	Group B (*n*=39) No.%	Group C (*n*=38) No.%
VP	02 (05.7)	01 (02.6)	02 (05.3)
VK	04 (11.4)	03 (07.7)	01 (02.6)
PV	04 (11.4)	07 (17.9)	05 (13.2)
PK	14 (40.0)	18 (46.2)	25 (65.8)
KV	03 (08.6)	-	01 (02.6)
KP	08 (22.9)	10 (25.6)	04 (10.5)

VP=Vata-Pitta, VK=Vata-Kapha, PV=Pitta-Vata, PK=Pitta-Kapha, KV=Kapha-Vata, KP=Kapha-Pitta. Group A=Glucosamine sulphate standard dosage regimen, Group B=ABFN02-Pulse dosage regimen, Group C=ABFN02-Contineous dosage regimen

months to the drug intervention was overall 83% however Group A (receiving Glucosamine sulphate) had 74.3% adherence where as for Groups B and C (receiving ABFN02) had 87.75% adherence which was statistically significant.

Total pain-VAS after four weeks of treatment showed statistically significant drop in all the three groups; with Group A having 16.9% drop, group B 21.1% drop and group C 22.4% drop. Subsequently in all the three groups, percent drop in total pain VAS score went on increasing and at the end of 24 weeks; it was 57.3% in Group A, 58.4% in Group B and 58.5% in Group C [Figure 2]. Percentage grade-wise pain VAS response in individual patients showed good to excellent (>50%) in 53.8% of patients in Group A, while 63.7% in Group B, and 66.7% in Group C. However the difference between the groups was not statistically significant.

Total score for WOMAC index includes a semi-quantitative estimation of pain, stiffness and difficulty in activity. There was no statistical difference at baseline. After six weeks, a significant drop in WOMAC index score was observed that is 31.6% in group A, 32.5% in group B

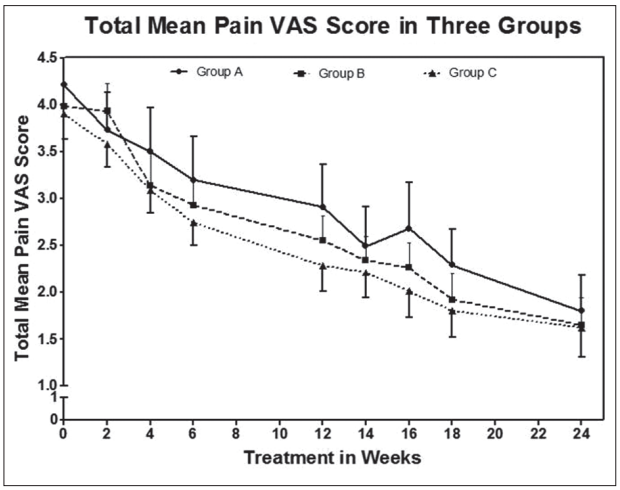

Figure 2: Reduction in total mean pain VAS comparison of change in total mean pain VAS score between the groups; Group A: Glucosamine sulphate standard dosage regimen, Group B: ABFN02-Pulse dosage regimen, Group C: ABFN02-Continuous dosage regimen. Statistical assessment By ANOVA Kruskal Wallis test, $P < 0.05$ significant, from 4th week till 24th week, in each group from baseline. Between groups, $P > 0.05$ not significant

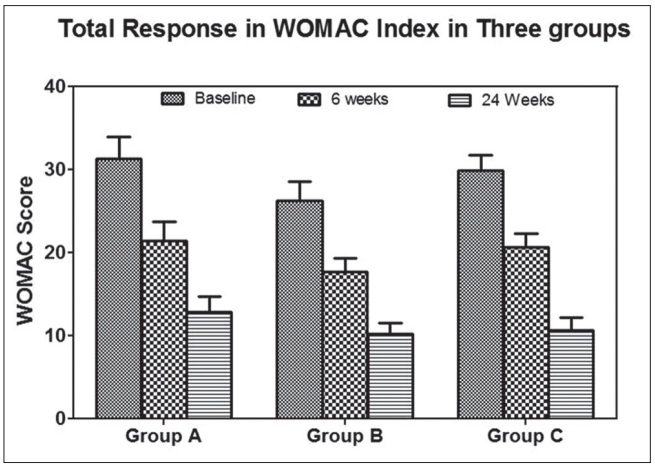

Figure 3: The response in WOMAC index gradual drop in total score of WOMAC index at different time intervals for all the three groups; Group A: Glucosamine sulphate standard dosage regimen, Group B: ABFN02-Pulse dosage regimen, Group C: ABFN02-Continuous dosage regimen. Statistical assessment by ANOVA Kruskal Wallis test, $P < 0.05$ Significant, from 6th week till 24th week, in each group from baseline. Between groups, $P > 0.05$ not significant

and 30.7% in group C. Subsequently there was a gradual drop in mean WOMAC index. At 24 weeks, reductions were 59.1% in group A, 60.8% in group B and 64.1% in group C [Figure 3].

Secondary objectives were clinical, laboratory and imaging. Median paracetamol consumption over 24 weeks were 10.5 tablets (range 0 to 150 tablets) for Group A, 22 tablets (range 0 to 100 tablets) for Group B and 24 tablets (range 0 to 110 tablets) for Group C. HAQ score drop [Group A (47%), Group B (49%), Group C (52.7%)] and morning stiffness reduction [Group A (77.9%), Group B (60.2%), Group C (62.2%)], were observed from baseline after treatment in both ABFN-02 (group B and group C) and GS (group A) however there was no intergroup difference of statistical significance. Walking time for 50 feet measured in minutes, physician global assessment, patient global assessment, and knee status which were assessed according to gradations such as mild, moderate and severe were also improved from baseline after treatment in all the three groups however again there was no intergroup difference of statistical significance (Data not shared).

The laboratory parameters evaluated were urinary CTX-II, and serum TNF-α SR-I, SR-II. Urinary CTX-II values had post treatment reduction in all the groups; Group A (467.02 ± 338.38 to 321.38 ± 221.56), Group B (390.18 ± 184.93 to 329.00 ± 187.79), Group C (372.08 ± 239.35 to 371.30 ± 244.11) however since the standard deviation was wide, statistical difference is not applied. TNF-α SR-I and SR-II values remained in normal range for pre and post treatment evaluation; TNF- α SR-I, Group A (2.41 ± 0.85 to 2.77 ± 0.95), Group B (2.67 ± 0.80 to 2.74 ± 1.10), Group C (2.33 ± 0.73 to 2.46 ± 0.60) and TNF- α SR-II Group A (7.77 ± 2.58 to7.23 ± 2.32), Group B (7.11 ± 2.61to 7.16 ± 6.27), Group C (6.93 ± 2.22 to 5.87 ± 1.91).

MRI of the most affected knee joint was planned in 12 patients selected randomly. Eight patients were available for pre-treatment and post-treatment evaluation. One out of two patients in glucosamine sulphate group had MRI improvement in bone marrow swelling and bone attrition, while four out of six patients taking ABFN-02 had improvement seen on MRI on account of bone marrow swelling, synovitis and bursitis.

The average values of total and differential leucocytes count, platelet count, hemoglobin, blood urea nitrogen, serum creatinine, serum bilirubin, Serum Glutamic Oxaloacetic Transaminase [SGOT], Serum Glutamic Pyruvic Transaminase [SGPT], alkaline phosphatase, S. uric acid, all were within normal limits before and after treatment. However, the rise in liver aminotransfereses (SGPT and/or SGOT) was observed in 9/39 patients of group B and 5/38 of group C whereas 2/35 in group A. The rise in liver aminotransfereses to the tune of three to five fold of Upper Limit of Normal [ULN] was observed in 4/9 patients in group B and 1/5 in group C. All these patients were asymptomatic and were detected on scheduled laboratory investigations in the later visits. These patients were followed up carefully and all of them recovered within six weeks after discontinuation of medicine without any active

intervention. This rise in liver aminotransfereses could not be attributed to Pitta dominant dwandwajaprakruti.

Adverse events reported were comparable in all the three groups. None of the three groups reported any severe or life threatening adverse drug reaction. None of them required indoor management and events resolved without sequelae. The commonest adverse events reported were itching/skin rashes/eruption and epigastric pain followed by diarrhea, burning micturation and other as listed [Table 3].

DISCUSSION

This active comparator controlled study of 24 weeks duration demonstrates the effectiveness of Ayurvedic herbal product (ABFN02) in osteoarthritis. ABFN02 which has Bhallatak (*Semecarpus anacardium*) as a main ingredient, known to produce intolerance and toxic effects was better adhered to than Glucosamine sulphate (GS) which is considered as a natural product/dietary supplement sold over the counter.[17] Better adherence to ABFN02 may be attributed to abiding to the ancillary clinical instructions desired for the intake of Bhallatak-based formulations (*vide supra*), the improvisation of traditional dosage form (Avaleha-electuary) into the convenient tablet form and fidelity to the classical manufacturing process for the development of the product (ABFN02). The classical manufacturing process probably subdues the potential toxic phenols present in the pericarp of Bhallatak seed, mainly responsible for the toxic effects.

Table 3: Profile of adverse events

Events	Group A (*n*=35)		Group B (*n*=39)		Group C (*n*=38)	
	No.	%	No.	%	No.	%
Clinical						
Itching/skin rashes/eruptions	03	(08.6)	06	(15.4)	04	(10.5)
Diarrhoea	02	(05.7)	02	(05.1)	-	-
Epigastric pain	04	(11.4)	04	(10.3)	03	(07.9)
Ulcer	01	(02.9)	-	-	02	(05.3)
Abdominal pain	01	(02.9)	-	-	01	(02.6)
Stomatitis	01	(02.9)	-	-	-	-
Increased bowel movement	01	(02.9)	-	-	-	-
Dryness of mouth	01	(02.9)	01	(02.6)	-	-
Burning	01	(02.9)	-	-	-	-
Dysuria	-	-	01	(02.6)	-	-
Burning micturition	-	-	01	(02.6)	02	(05.3)
Anal burning	-	-	01	(02.6)	-	-
Fever	-	-	-	-	01	(02.6)
No. of events	15	(42.9)	16	(41.0)	13	(34.2)
No. of pts	10	(28.6)	09	(23.1)	09	(23.7)
Laboratory						
Rise in liver aminotransferase	02	(05.7)	09	(23.1)	05	(13.2)
Rise>3 fold of ULN	-	-	04	(10.2)	01	(02.6)

Group A=Glucosamine sulphate standard dosage regimen, Group B=ABFN02-pulse dosage regimen, Group C=ABFN02-continuous dosage regimen, UNL=Upper limit of normal

Total pain VAS (Visual Analogue Score) was calculated after taking an average of pain VAS of both the Knee (Right and Left) on activity and at rest has shown statistically significant improvement from baseline in all the three groups. Although ABFN02 had an edge over GS there was no significant superiority of one over other. Similarly proportion of patients with > 50% total pain VAS score reduction was found to be higher with ABFN02 (44/67) over GS (14/26). Total WOMAC index (semi-quantitative estimation of pain, stiffness and difficulty in activity measures) and HAQ score have also shown statistically significant reduction from baseline in all the three groups with higher reduction in ABFN02 over GS. In this study, we have observed consistently significant symptom modifying effects with ABFN02 as well as with Glucosamine sulphate. It has been reported that the symptomatic effect size of glucosamine varies greatly depending on the formulation used and the quality of clinical trials.[17]

All the three categories clinical, laboratory and imaging evaluated for secondary objective variables have shown improvement in all the three groups however notable are urinary CTX-II and MRI for disease modifying effects. The CTX-II values have demonstrated wide standard deviation in all the three groups' pre and post treatment. However not withstanding with the statistical application the quantum of average drop in CTX-II value is larger in Group A (GS) than in Group B and C (ABFN02). This observation is difficult to explain in view of the conflicting clinical evidence against GS for disease modifying activity[17,18] and traditional reputation of the ABFN02 ingredients having Rasayana (reparative and reconstructive) activity[3,4] as well as our exploratory study results of carryover effects.[13] Our previous exploratory study of six weeks duration in 45 patients of OA knee noted substantial pain relief in these patients. Also persistence of therapeutic effect was reported in majority of these patients after withdrawal of the drug. Patients who had reappearance of pain showed reproducibility of the effect on reintroduction of the drug.

Pharmacokinetics and drug metabolism play important role in the bioavailability and eventual efficacy of GS.[18] Interestingly in this study, patients were advised to take the medicines with milk and were also advised to abide with certain ancillary Ayurvedic instructions (*vide supra*) which are obligatory when a product has a *Semecarpus anacardium* as a major ingredient. To avoid bias in this randomized comparative study these instructions were recommended to all the three groups including Group A receiving Glucosamine sulphate.

In the imaging modality of MRI although only eight patients could be evaluated before and after treatment of six months; four out of six patients taking ABFN-02 had improvement seen on MRI on account of bone marrow swelling, synovitis and bursitis indicating directionality towards disease modifying potential of the product. The study formulation ABFN02 which has only two ingredients Bhallatak (*Semecarpus anacardium*) and Guduchi (*Tinospora cordifolia*) have independently demonstrated their activity in degenerative disorders[19,20] and arthritis.[21,22]

No serious and severe clinical adverse event was reported by any patient in this six month study of 112 patients. All the laboratory investigations undertaken for assessment of safety profile were within normal range before, during and after treatment. However the liver aminotransferases had been raised in 18% of patients receiving ABFN02. Evidently the rise of SGOT and SGPT was primarily in the later visits of drug interventions. Although five patients (6.5%) had rise in aminotranferases to the tune of three to five fold of ULN; all these patients were asymptomatic and liver enzymes came back to normal within six weeks off the drug without any sequelae. In the earlier exploratory study[13] of six weeks duration, we had observed similar asymptomatic and reversible rise in liver enzymes in 3/45 patients when the effective dose of Bhallatak had crossed the dose of 20 gms Bhallatak RM/day (Raw Material) beyond 5th week of the study. For the present study the precaution was taken by limiting the highest possible daily dose of 18 gms Bhallatak RM/day in a pulse dose regimen gradually stepped up over six weeks. It needs to ascertain whether this is cumulative dose liver toxicity? Do we need to give longer gap of more than six weeks of duration when drug is repeated in the pulse dose incremental regimen? Whether we should limit long-term continuous administration of Bhallatak formulations even for relatively lower dose? Other clinical study having *Semecarpus anacardium* and *Tinospora cordifolia* in combination with other traditional herbs have demonstrated efficacy in osteoarthritis however here also 2/19 patients receiving Bhallatak in combination have shown rise in liver enzyme SGPT.[23] It is imperative to remind *Tinospora cordifolia* another equal amount of ingredient in the ABFN02 has well demonstrated hepatoprotective activity.[24] Notably our independent long-term (120 days) animal toxicity study has not demonstrated any significant liver damage on histopathology.[25]

Interestingly, Methotrexate the drug of choice amongst disease modifying antirheumatic drugs used conventionally in clinical practice is monitored for its liver toxicity and the effective dose is titrated against liver transaminases. Captivatingly the incidence of methotrexate induced increases in serum alanine aminotransferase (ALT) is approximately 14%, while the incidence of increases into the abnormal range of aspartate aminotransferase (AST) is 8%in non-malignant diseases on oral use and the abnormality of liver enzymes usually resolves within one month of discontinuation.[26]

CONCLUSION

Current study, earlier exploratory study, other concurrent clinical study and congruent experimental evidence suggests promising role for Bhallatak based formulations in the management of osteoarthritis. However the potential hepato-toxicity demands thorough phytochemical analysis for identification and optimization of phyto-actives and minimization of phyto-toxic components. Experimental studies with identified *in-vitro* and *in-vivo* models for better insight in mechanisms of action would help further improvise this age old classical Ayurvedic product and evaluate its disease modifying role in the management of osteoarthritis.

Meanwhile those using Bhallatak based formulation should be vigilant about liver enzymes.

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