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Research Article

Evaluation of efficacy of Flexiqule (Boswellia Phyto Extract) in osteoarthritis of Knee

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Abstract: Osteoarthritis is major cause of morbidity and impaired quality of life among the elderly persons. The prolong use of NSAIDs in elderly, is required for constant relief of pain, but they are associated with adverse drug effects. Thus long term use of NSAIDs compromise with its safety profile. The present study was undertaken to evaluate the long term clinical efficacy and safety of Flexiqule (Boswellia phyto extract), and comparison with Etoricoxib (ETX) as a remedial measure. Boswellia phyto extract, a herbal extract contains Boswellic acid as active ingredient, which has exhibited anti-inflammatory and analgesic effect. Etoricoxib is Cox 2 inhibitor, frequently used NSAIDs, but not without side effects. One hundred patients of either sex, in age group of 50 to 65 years, with clinical and radiological evidence of Osteoarthritis of knee were selected for trial. Patients were randomly divided into two groups. Group A received capsule Flexiqule 300 per day and group B received Etoricoxib 90 mg per day. All symptoms along with severity and duration were recorded prior to start of drug treatment. Routine hematological and radiological assessment was done before and the end of treatment. The patients were followed up every 04 weekly for six months. Symptomatic assessment score was carried out to determine the clinical efficacy of Flexiqule as compared to Etoricaxib. The minimal level of significance was fixed at 95% confidence limits and a 2-sided p value of <0.05 was considered significant. Clinical Efficacy was assessed by decrease in total sign and symptom scores. Results revealed that the average symptom score for joints involved, before and after the treatment was 7.140 to 1.060 in Flexiqule group while in Etoricoxib group was 6.800 to 1.840. There was reduction in symptom score 86% in Flexiqule group and 82% in ETX group. Thus objective improvement was comparatively better in Flexiqule groups. As for the side effects, No Adverse Reaction(ADRs), was noted in Flexiqule group, While Etoricoxib group experienced side effects -gastrointestinal, neurological or dermatological symptoms, which required due care. Though there was no significant alteration in hematological level, there was significant lowering in SGOT and SGPT levels, which indicated hepatoprotective effect of Flexiqule, and also significant decrease in Creatinine level indicated its renoprotective effect. No Adverse drug side effects were positive factor for prolong usage of Flexiqule as compared to Etoricoxid group. This study indicates that Flexiqule (Boswellia Phyto Extract) has proved better symptom relief in terms of relief of pain and free mobility of joints, equally effective but a safe alternative for long -term use in management of mild to moderate osteoarthritis, in patients unwilling for surgery.
Keywords: Osteoarthritis, Flexiqule (Boswellia Phyto extract), NSAIDs.

INTRODUCTION

Osteoarthritis (OA) is a slow progressive degenerative disease of joints involving both weight bearing and non-weight bearing joints. OA is most common clinical arthritis of aging person, thus a major cause of morbidity, disability, and impaired quality of life in elderly. Clinically OA manifests as pain, swelling, discomfort and stiffness of the joint. They may be associated with loss of flexibility of joint, increased intraosseus pressure, periosteal proliferation, subchondral fractures and evidence of sclerosis, ligament laxity, muscle spasm and synovitis [1]

Etiologically, Osteoarthritis is multifactorial, and is influenced by age, sex, genetic, biomechanical and biochemical factors. The association between repetitive joint trauma (sports, work -related or accidental) and osteoarthritis is well documented [2-3]

The cardinal features of osteoarthritis is the lesion in cartilage that disrupts the chondrocyte -matrix association and alters metabolic response in the chondrocytes to contribute to the functional breakdown of the joint's cartilage, leading to constant friction between bone ends [4].

The diagnosis of OA is arrived through detailed clinical history, physical and radiological examination of joint, and if required joint aspiration. About 60% of patients have suggestive radiological signs, while only about 1/3 may have actual symptoms of OA[5].

Treatment includes symptomatic therapy for pain, stiffness, and swelling. The therapy is directed to modify the joint structure leading to retardation and

reversal or prevention of disease process. The drug treatment options for OA, includes topical and systemic analgesics, Anti-inflammatory agents (NSAID), and intra -articular injection of corticosteroids and hyaluronic acid [6]. Cyclo-oxygenase enzyme inhibitors widely used for OA, but present evidence does not suggest their efficacy as prevention of progression. Furthermore, the usage of NSAIDs is associated with short or long -term side effects and associated morbidity in older age. An intra-articular injection of corticosteroids or hyaluronic acid offers analgesia for 4 to 6 months but there is high risk of infections.

Flexiqule is comprised of herbal formulation containing specially processed concentrate - Phyto Extract of Boswellia Serrata (also known as Shallaki) and Ginger(Zingiber Officinale) .The active ingredient is 3-O -acetyl -11-keto -beta - boswellic acid (AKBA) ,which has clinically proved to possess effective anti-inflammatory and analgesic activities and improves glycoaminoglycons production in human chondrocytes [7-8]

The present study was conducted to evaluate clinical efficacy and long -term safety of Flexiqule in patients with OA in Knee joints in comparision to Etoricoxib (ETX), a commonly used NSAIDs.

MATERIAL AND METHODS

The aim of study is to evaluate efficacy and long- term safety of Flexiqule, in comparison with Etoricoxib (ETX), in patients with osteoarthritis both knee joints. The study was conducted in one hundred patients of either sex, in age group of 50 to 65 years, with osteoarthritis of one or both knee joints who attended the Department of Orthopedics, and Department of Pathology, Hind Institute of Medical Sciences, Barabanki, between Feb, 2012 to August 2012,were included. The approval from institutional Ethics Committee and Alchem was taken. They were divided into two groups. The study medication group was given Boswellia phyto extract(capsule Flexiqule *150 mg marketed by Alchem) two capsules daily and other Placebo group received Etoricoxib 90 mg (ETX 90) for period of 6 months. The two groups were similar with regards to their demographic data, baseline parameters and pain score.

Inclusion criteria :

Ambulatory patients of both sexes between age group of 50 to 65 years, with primary osteoarthritis of knee ,were included in study. All patients had clinical symptoms of OA for at least 6 months prior to the study and were suffering from moderate to severe knee pain (with or without morning stiffness of <30 minutes duration) .These patients had radiological evidence of osteophytes with findings like marginal lipping, narrowing of joint space, and sharp articular margin or sclerosis, damaged, thickened, eburnated subchondral bone, or the bone cyst.

Patients with established hypertension, renal, hepatic or cardiac failure, patients on long -term steroid therapy, or with biochemical and clinical evidence of rheumatoid arthritis or gout were excluded from the study.

Methodology:

Before start of trial, patients underwent a complete physical examination with their written consent. All signs and symptoms with regards to severity and duration were recorded before commencement of treatment. A complete systemic and joints examination was also performed.

Biochemical investigation and Radiography of the joints were noted at 3 months and after 6 months. Blood chemistry investigations included complete Haemogram (ESR, WBC, Erythrocyte and Platelet count), complete Liver function test (Bilirubin, SGOT, SGPT, S-Alkaline Phosphatase, Total protein and Prothombin time), Renal function test (including Uric acid, urea and Creatinine),assessing RA factor and immunoglobulin (IgA and Ig M).

Radiological examination of affected knee was carried out for osteophytes, spiking of tibial spine, subchondral sclerosis and cyst, loose bodies, and presence of varus/valgus knee deformity.

Follow up and assessment:

Subjective and objective evaluation was carried out every 4 weekly intervals for 6 months. The Scoring System was designed to evaluate subjective and objective symptom and signs (Table 1), which were compared before and after treatment.

A complete clinical, biochemical and radio graphical evaluation was carried out at the end of the three and six months.

Assessment Criteria:

Efficacy was assessed by decrease in total sympotoms and signs scores at the end of 6 months. The criteria of total symptom score was based on the number of joints involved, degree of pain, joint swelling, stiffness and activity level. Total sign score was based on joint effusion and tenderness, crepitus, range of motion, synovial hypertrophy, muscle wasting and joint deformity (Table 1).

Table-1: Symptom and sign score

Scoring for symptoms				Scoring for sign.				
1-No. of joints involved				1-Joint effusion				
	One	:	0		a.	Absent	:	0
	More than 1	:	1		b.	Present	:	1
2-Pain on				2- Joint line tenderness				
a.	More than routine work	:	0	a.		Absent	:	0
b.	Routine work	:	1	b.		Present	:	1
c.	Less than routine work	:	2	3.Crepitus				
d.	at Rest	:	3	a.		Absent	:	0
3-Joint swelling				b.		Present	:	1
a.	Absent	:	0	4.Range of movements				
b.	Present	:	1	a.		>130	:	1
4-joint Stiffness				b.		100-130	:	2
a.	Absent	:	0	c.		<100	:	3
	Present	:	1	5.Synovial hypertrophy				
5-Activity level				a.		Absent	:	0
a.	Straight walking	:	Yes/No 0/1	b.		Present	:	1
b.	Sitting Cross- Legged	:	Yes/No 0/1	6. Muscle wasting				
	Squatting	:	Yes/No 0/1		a.	Absent	:	0
	Stair climbing	:	Yes/No 0/1		b.	Present	:	1
For each of the above activity level *if the symptom is present (yes) : 0 *if the symptom is absent (no) : 1 **Maximum symptom score per patient : 10**				7-Deformity (varus/valgus)				
					a.	Absent	:	0
					b.	Present	:	1
				Maximum signs score per patient : 09				

Safety was assessed by incidence of adverse effects and laboratory evaluation of complete haemogram with clinical biochemistry including liver and renal function tests.

Statistical analysis:

Statistical analysis was done with Comparison of the two groups for baseline comparability of different parameters by unpaired t test. Changes in various parameters from baseline values after three and six months were evaluated by paired t test. The reduction in pain and swelling scores were evaluated to differentiate between the two treatment groups by unpaired t test. The minimal level of significance was fixed at 95% confidence limit and a two sided p value of <0.05 was considered significant.

RESULT:

Table-2: Age wise Distribution

Age (Years)	**Flexiqule Group**		**ETX Group**		**Total**	
	Number	**%**	**Number**	**%**	**Number**	**%**
50-55	38	76	26	52	64	64
56-60	7	14	17	34	24	24
61-65	5	10	7	14	12	12
Total	50	100	50	100	100	100
Mean ± SD	53.90±4.28		55.83±4.19			

In Flexiqule group 76% patients were in age group of 50 to 55 years. male to female ratio was almost equal. While in ETX group, there was male preponderance (1.7:1); this difference was due to randomization.(Table 2).

Majority of patients in both groups had bilateral involvement but only a few (8% in Flexiqule group and 14 % in ETX group) had unilateral signs and symptoms. A majority of patients in both groups had a pre therapy total score of 7 points (72% in Flexiqule group and 84% in ETX group).

Before initiation of the therapy, a majority of patients in both groups had pain during less than routine work, swelling of joints or stiff joints, were comfortable only with straight walking and found difficulty or inability to cross -leg sitting, squatting, and stair climbing activities.

In more than 80% of cases in both groups (86% in Flexiqule group and 82% in ETX group), the post therapy total symptom score reduced (Table 3).

Table No. 3 Symptom Score of Pre and Post-Therapy

Score	Pre therapy						Post therapy					
	Flexiqule group		**ETX group**		**Total**		**Flexiqule group**		**ETX group**		**Total**	
	No. of patient	%	No. of patient	%	No. of patient	%	No. of patient	%	No. of patient	%	No. of patient	%
4	-	-	1	2	1	1	4	8	8	16	12	12
	-	-	-				43	86	42	84	85	85
6	5	10	7	14	12	12	1	2	-		1	1
7	36	72	42	84	78	78			-			
8	7	14	-		7	14	2	4	-		2	2
9	1	2	-		1	1	-		-			
10	1	2	-		1	1	-		-			
Total	**50**	**100**	**50**	**100**	**100**	**100**	**50**	**100**	**50**	**100**	**100**	**100**

All these patients, at the end of therapy, experienced pain only during more than routine work, there was reduction in swelling and joint stiffness and they were comfortable with straight walking, cross -leg sitting, squatting, and stair climbing activities.

The relief of symptom was comparable in both groups and onset of appreciable improvement was marginally faster with ETX (within 5 days as compared to Flexiqule (10 to 12 days). The objective improvement was comparable in both groups and there was statistically significant reduction in the symptom scores after treatment in both groups. By the end of six months, all the patients had significant pain relief, improvement in joint tenderness, decrease in joint stiffness, increase in joint mobility, and improved activity level (Table 4).

Table no-4: Effect of Flexiqule and ETX on symptom score in Osteoarthritic patients

Symptom score	Flexiqule Group			ETX Group		
Parameter	Pretreatment	Post treatment	P value	Pretreatment	Post treatment	P value
Pain*	2.040 ±0.283	0.080 ±0.274	<.0001;S	1.980 ±0.141	.000 ±.000	<.0001;S
Swelling	0.160 ±0.370	.000 ±.000	<.0003;S	0.000 ±0.000	.000 ±.000	
Joint stiffness	0.960 ±0.198	.000 ±.000	<.0001;S	0.960 ±0.198	.000 ±.000	<.0001;S
Activity level*	3.020 ±0.141	.040 ±0.283	<.0001;S	2.980 ±0.141	.000 ±.000	<.0001;S
Total score *	7.140 ±0.700	1.060 ±0.682	<.0001;S	6.800 ±0.535	0.840 ±0.370	<.0001;S
*patient test , chi square test, n= 50 in each group , S + significant , ns = Not significant						

No significant alterations were seen in most hematological parameters in both groups, except a significant decrease in eosinophils and ESR and significant increase in neutrophil in Flexiqule group. (Table 5).

Table no.-5 Hematology investigations

Symptom Score	Flexiqule Group			ETX Group		
Parameter	Pretreatment	Post treatment	P value	Pretreatment	Post treatment	P value
Hemoglobin (gm%)	12.95 ±0.23	12.89 ±0.20	NS	12.73 ±0.22	12.86 ±0.20	NS
Total WBC Count (/mm^3)	8914.15 ±304.21	8872.00 ±202.31	NS	8979.59 ±315.58	8600.00 ±266.32	NS
Polymorphs (%)	65.90 ±105	68.96 ±1.00	<0.12	65.24 ±0.97	66.14 ±0.74	NS
Lymphocytes (%)	30.48 ±1.02	29.44 ±0.97	NS	32.02 ±0.92	32.67 ±0.67	NS
Eosinophils(%)	2.16 ±0.23	1.22 ±0.19	<.0004	2.16 ±0.23	0.78 ±0.16	<.0001;S
Monocytes (%)	0.28 ±0.11	0.38 ±0.10	NS	0.59 ±0.10	0.53 ±0.15	NS
ESR(mm/hr)	32.00 ±3.47	21.04 ±2.34	<.001	23.61 ±3.37	2.73 ±0.23	<.038;S
Platelets (10^5/mm^3)	2.49 ±0.21	2.35 ±0.06	NS	2.67 ±0.35	2.73 ±0.23	NS
Prothrombin Time (sec.)	14.37 ±0.06	14.42 ±0.09	NS	15.59 ±0.12	15.14 ±0.11	NS

In Biochemical parameters, total proteins, ALP and BUN showed significant increase in ETX group, while Flexiqule group showed significant decrease in SGOT and SGPT. Creatinine levels was found decreased in Flexiqule group and increased in ETX group.(Table 6) .

Table no.-6 Biochemical investigations

Parameter	Flexiqule Group			ETX Group		
	Pretreatment	Post treatment	P value	Pretreatment	Post treatment	P value
Total Bilirubin (mg%)	0.78 ±0.04	0.70 ±0.03	<.003	0.75 ±0.03	0.79 ±0.03	<.029;S
Total protein(g%)	6.83 ±.07	6.73 ±0.06	NS	6.62 ±0.06	6.78 ±0.05	<.0015;S
SGOT(IU/L)	30.21 ±2.11	26.31 ±1.69	<.0009	30.48 ±2.50	28.78 ±1.85	NS
SGPT(IU/L)	29.63 ±2.61	25.53 ±1.78	<.004	30.78 ±3.56	28.50 ±1.25	
ALP(IU/L)	152.29 ±6.25	145.36 ±3.83	<.NS	142.81 ±3.68	149.25 ±2.93	<.038;S
BUN(mg%)	20.71 ±0.62	21.71 ±0.60	NS	19.49 ±0.66	22.35 ±0.61	<.001;S
Creatinine (mg%)	0.88 ±0.04	0.78 ±0.03	<.003	0.85 ±0.04	0.91 ±0.04	<.004;S
IgA(IU/L)	1.40 ±0.11	1.51 ±0.12	NS	1.56 ±0.18	1.60 ±0.16	NS
IgM (IU/L)	1.61 ±0.23	1.46 ±0.09	NS	1.81 ±0.31	1.54 ±0.19	NS

Note: - Statistical analysis were carried out using paired t test; n = 50 patients in each group; S=Significant ; NS = Not significant ±

Radiological examination done at 3 and 6 months did not show any deterioration as compared to pretherapy images.

Adverse Drug Reactions: (ADRs)

No untowards side effects were noted with Flexiqule during the trial in all the 50 patients. In ETX group 16 patients reported abdominal discomfort, retrosternal burning, gastritis, flatulence and dyspepsia at some stage of therapy. The patients were additionally prescribed either H2 receptor antagonist or antacid or both as required. Three patients developed headache and dizziness which eventually subsided on its own.

One patient presented with itching and rashes, which subsided with anti allergics.(Figure -1)

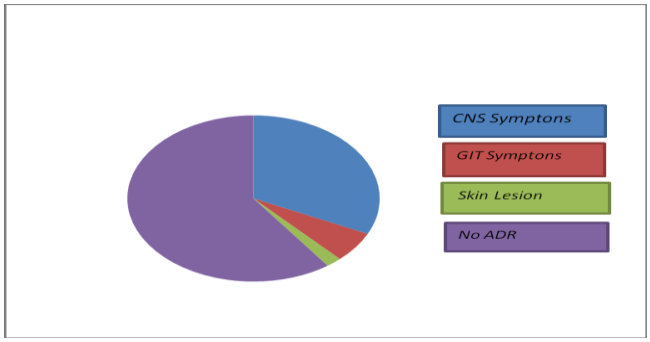

Figure-1 Adverse drug reactions in Refocoxib

DISCUSSION

Osteoarthritis is a chronic progressive disability affecting the elderly. Most of patients are in frequent use of NSAIDs. The long term use of NSAIDs in its management has been shown to be associated with serious adverse effects[9].

Herbal formulation has been proven to be effective and safe alternative to NSAIDs. The primary constituent of Flexiqule is *Boswellia Serrata*, which has been long used in the management of osteoarthritis conditions. Clinical studies using Boswellia have yielded good results in both osteoarthritis and rheumatoid arthritis [8,10].

In B. Serrata, the active compound is boswellic acid, which has exhibited anti-arthritic effects in experimental studies and several suggested mechanism of action includes inhibition of proinhibitory mediators (5- lipoxygenase including 5-hydroxyeicosa tetranoic acid and leukotrienes),prevention of decreased glucosaminoglycan synthesis (which is known to accelerate articular damage), and improved blood supply to joint tissues [11-12].

In study, those taking Flexiqule, there was excellent relief from pain at the end of therapy. Overall improvement in quality of life was seen in both groups .No significant change were recorded in hematological investigation in both groups In ETX group there was significant increase in total protein, alkaline phosphatase and blood urea nitrogen which may not be of any clinical significance. A significant decreased SGOT and SGPT in Flexiqule was indicative of hepatoprotective effect [13] of Flexiqule. Effect was proved to be renal protective also, as there was decrease in serum Creatinine in Flexiqule group as compared to ETX, where there was increase in Creatinine.

Radiological follow-up also confirmed inflammatory control by absence of any signs of deterioration as compared to pre therapy images in both groups.

The major clinically significant difference between two groups was noted in ADRs, which was a limiting factor in long term use of Etoricoxib. In contrast, Flexiqule appeared to be safer for long - term usage.

CONCLUSION

Arthritis and inflammatory disorders are the common causes of morbidity in aging population worldwide. Apart from pain, loss of joint function, restricted mobility, there is also considerable compromise in quality of life. Current non-surgical drug therapies, especially NSAIDs have their own limitations regarding their host of ADRs and are therefore of questionable advocacy for long-term use as for safety is concerned. Furthermore, the chronic nature of osteoarthritis process itself demands a long -term drug therapy for years, especially in cases where patients are not willing to undergo any surgical intervention.

This study indicated that Flexiqule is an equally effective and safer alternative for long -term use in management of mild to moderate osteoarthritis than NSAIDs.

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