STUDY ON THE EFFICACY AND SAFETY LOXOPROFEN SODIUM ON OSTEOARTHRITIS OF THE KNEE

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INTRODUCTION

In order to study the efficacy and safety of Loxoprofen Sodium in osteoarthritis of the knee a clinical trial was carried out at the department of orthopaedic surgery King Edward Medical and Mayo Hospital, Lahore.

OBJECTIVE

To study the efficacy and safety of Loxoprofen Sodium on Osteoarthritis of the knee in both sexes of Pakistani population.

INCLUSION AND EXCLUSION CRITERIA

Subjects were patients with osteoarthrosis of the knee. The following patients were excluded.

a Patients with peptic ulcer.
b.. Patients with serious hematological, hepatic or renal disorders.
c. Patients with hypersensitivity to the test drug.
d. Patients with aspirin asthma or its previous history,
e. Patients who were considered not suitable for study by physicians.
f.. Patients who had received an intraarticular injection.

METHOD OF STUDY

a. Dosage and administration One tablet (60 mg) of Loxoprofen Sodium orally three timesa day. The dose was not adjusted according to age and symptoms.
b. Duration of treatment was 4 weeks.

PARAMETERS FOR CLINICAL FUNCTION

According to the Evaluation Criteria of knee joint functions provided by Sankyo Co Ltd Japan. for following parameters.
(Table I)

a. Pain`
b. Range of motion (to be entered on the basis of total range of motion)
c. Walking ability (to be assessed under the conditions without prosthetic appliance, stick or self help device).

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d. Daily activity.
e. Hydrarthrosis.

OVERALL EVALUATION

a Global improvement ratingEvaluation was made according to the following 6 grade scale, at the end or discontinuation of treatment or at the end of investigation (week 4) while continuing the treatment, as compared to the pre treatment conditions.

1. Markedly improved
2 Improved
3. Slightly improved.
4. Unchanged
5 Aggravated
6. Judgment impossible

b Overall safety rating: Evaluation was made according to the following 4 grade scale, on the basis of side effects and laboratory test values.

1 Safe (No side effect observed)
2 Essentially safe (Side effect was mild allowing it to continue the treatment without any measures taken for the side effect).
3. Problem with safety (Side effect occurred, but measures such as dose reduction allowed it to continue the treatment).
4. Not safe (Side effect was severe, resulting in discontinuation of the treatment).

c Utility Evaluation was according to the following 6 grade scale, on the basis of the global improvement rating and the overall safety rating.

1. Very useful
2. Useful
3 Hard to say which
4. Not useful
5. Judgment impossible

SIDE EFFECTS

Any side effect was recorded specifically with respect to time elasped from the treatment started to the onset of symptom, measures taken , outcome and causal relation to the test drug.

MATERIAL AND METHODS

Thirty (30) patients of both sexes were included in present clinical trial. The treatment was provided on out door basis. As a rule a proforma provided by Sankyo CO, Ltd. Japan was used to collect data from all patients. The patients profile part of the proforma provided informations regarding age, sex, weight, occupation, affected knee, evaluated knee, pre-treatment severity, abnormal x-ray findings, duration of problem, previous treatment, pre-existing diseases, history of allergy, concomitant drug used, drop out reason and side effects with details.

As a rule treatment was provided for 4 weeks. During the treatment one tablet (60 mg) of Loxoprofen Sodium was prescribed orally three times a day.

* Clinical findings regarding knee joint functions i.e., Pain, Range of motion, Walking ability , Daily activi y and Hydrarthrosis were recorded accordingly.

Table I : Evaluation criteria based on the rating scores from 0 to 3, as given in following table.

	Occasional tiredness or heaviness is felt, but no pain during daily activity.	None	0
Pain	Slight pain is present when starting any motion or walking a long distance	Mild	1
	Constant pain is present during walking but disappears by resting for short time.	Moderate	2
	Sharp pain develops by weight bearing or on motion but is relieved by rest Spontaneous pain occure occasionally, Altenatively, constant pain is present at rest or on motion.	Severe	3
	120 degree or more (Able to do activity) of daily life (ADL) of Pakistani style)	None	0
	90 - 119 degree (Able to go up and down stairs and rise from a sitting posn)	Mild	1
Range	60-89 degree (Able to walk on a flat place).	Moderate	2
of motion	30-59 degree (able to pick up some-thing on the floor) 0-29 degree (able to go up and down a step of 5 cm	Severe	3
	Able to walk with no limitation in daily activity, also able to walk fast.	Normal	0
Walking-ability	Able to walk to the neighborhoods (about 500 m to 1 km) if necessary	Mild	1
	Unable to walk more than 500 meters even if necessary. Daily activity is limited around the . patients house	. Moderate disability	2
	Hardly able to walk indoors or unable to walk. even indoor.	Severe disability	3
	To be assessed comprehensively on the basis of abilities to rise from a sitting position and to	Normal	0
Daily activity	go up and down satires.	Mild. disturbance	1
		Moderate. disturbance	2
		Severe disturbance	3
	Neither edema nor swelling	None	0
Hydrartrosis	Edema is present but does not require Puncture	Mild	1
	Puncture is occasionally required	Moderate	2
	Puncture is frequently required	Severe	3

At the end of the trial the data was analysed in Epi-Info Medical Statistical Software produced by Center for Disease Control, Atlanta USA.

RESULTS

Thirty (30) patients with osteoarthritis of the knee joint were included in this study. Eleven (11) were male and nineteen (19) were female.

Male to Female ration = 1: 1.7. Age of the patients ranged from 26 years to 86 years Mean age 54 years (±1 S. D=9.8).

The body weight of the patients ranged from 45 kg to 87 kg with mean weight 65 kg (±1 S.D.=12).At the time of first examination more pain in 16 patients (54%) was in both knee joints, in 10 patients (33%) was in right knee joint and in 4 patients (13%) was in left knee joint. For purpose of evaluation during treatment 26 right and 4 left knee joints were evaluated.

The study of affected knee in both sexes (Table II) showed that ratio of involvement of different knee joints in population studied was proportionate.

Table II: Affected Knee and Sex Relationship.

	Male	Female	Total
Left Knee	4	7	11
Right knee	2	2	4
Both knee	5	10	15
Total	11	19	30

The severity of pain before starting the treatment was mild in 10 (33%) patients, moderate in 12 (40%) patients and severe in 8 (27%) patients.

Knee joints of all patients were x-rayed before starting the treatment and in 28 patients abnormal findings were recorded (detail given in Table III).

Table III : Abnormal X-ray Findings (n - 30)

Abnormal Finding			Severity of Abnormality			
Present	Absent	Total	Mild	Moderate	Severe	Total
28	2	30	11	11	6	28

Duration of problem in the knee joints before getting treatment in present study varied from 1 month to more than 12 months (for detail table IV).

Table IV: Duration of Problem from Onset to Present Study.

S.No	Description of Duration	No of pts
1	upto 1 month	6
2.	upto 3 months	5
3.	upto 6 months	3
4.	upto 12 month	5
5.	More than 12 months	11
	Total :	30

PRE TREATMENT

History of previous treatment was absent in 10 patients whereas 20 patients had treatment for their knee problems before they were included in present study. All 20 patients who had received treatment before the present study were given more than one drug. 15 out of these 20 were also advised physiotherapy in terms of Isometric Quadriceps exercises. 5 patients out 15 who had physiotherapy also received short wave diathermy to their affected knee joints.

The drugs given in pre-treatment period to these 20 patients included Algaphan, Ketaflan, Piroxicam 20 mg, Profen , Ansaid, Panadal, Brufen, Baseral, Proxen, and Diclofenac Sodium. 3 patients out of these 20 also complained that during their pre-treatment period they experienced rise in the Blood Pressure.

According to the Evaluation Criteria of knee joint functions Pain, Range of Motion, Walking ability, Daily activity and Hydrarthrosis were recorded according to the rating scores from 0 to 3 at four different times at week 0, week 1, week 2 and week 4 and were recorded accordingly. The evaluations carried out are summarized in Tables V, VI, VII, VIII and IX.

Table V : Influnce on knee pain of use of Loxoprofen Sodium for different durations.

Evaluation Criteria for Pain			Scores at different Intervals			
Description	Severity	Score	Week 0	Week 1	Week 2	Week 4
Occasional tiredness but no pain	None	0	0	4	9	16
Slight pain at start of motion	Mild	1	6	13	14	11

Constant pain during walking disappear on rest	Moderate	2	16	10	7	3
Sharp pain on weight bearing otherwise constant pain	Severe	3	8	3	0	0
		Total:	30	30	30	30

Table VI : Influence on Range of Motion of knee of use of Loxoprofen Sodium for different duration.

Evaluation Criteria for ROM			Score at different Intervals			
Decription	Severity	Score	Week 0	Week 1	Week 2	Week 4
120 or more	None	0	6	11	14	18
90 - 119	Mild	1	14	11	13	12
60- 89	Moderate	2	8	7	3	0
0- 59	Severe	3	2	1	0	0
		Total	30	30	30	30

Table VII: Influence on Walking ability of use of Loxoprofen Sodium for different duration.

Evaluation Criteria for Walking Ability			Score at different Intervals			
Description	Severity	Score	Week 0	Week 1	Week 2	Week 4
No limitation	Normal	0	8	11	14	18
Able to walk upto 1/2 KM	Mild	1	14	10	12	11
Unable to walk more 1/2 KM	Moderate	2	6	7	4	1
Hardly able to walk	Severe	3	2	2	0	0
		Total:	30	30	30	3

Table VIII: Influence on Daily Activity of use of Loxoprofen Sodium for Different durations.

Evaluation Criteria for Daily Activity		Score at different Intervals			
Severity description	Score	Week 0	Week 1	Week 2	Week 4
Normal	0	7	12	16	21
Mild Disturbance	1	12	11	11	9
Moderate Disturbance	2	8	7	3	0
Severe Disturbance	3	3	0	0	0
	Total	30	30	30	30

Table IX: Influence on Hydrarthrosis of knee with use of Loxoprofen Sodium for different duration.

Evaluation Criteria for Hydrarthrosis			Score at different Intervals			
Description	Severity	Score	Week 0	Week 1	Week 2	Week 4
Neither edema nor swelling	None	0	18	20	21	24
Edema Present no Fluctuation	Mild	1	9	9	9	6
Mild Fluctuation	Moderate	2	2	1	0	0
Fluctuation puncture required	Severe	3	1	0	0	0
		Total:	30	30	30	30

In present study patients problem at the time of start of treatment had different magnitude as out lined above. Total scores in each patient at each evaluation interval were calculated by summing up of scores in each knee function category. Before starting the treatment minimum score of 1 was present in 2 patients and maximum score of 11 in 2 patients with arithmetic mean 5.7 Sample S.D = 3.04 and population standard deviation = 2.99. The detail is given in Table X below.

Table X : Total scores of 30 patients recorded during Loxoprofen Sodium trial at different intervals.

S.No	Total score in each pts	No of Patients at different intervals			
		Week 0	Week 1	Week 2	Week 4
1.	0	0	3	5	10
2.	1	2	2	4	5
3.	2	2	4	2	7
4.	3	4	5	8	2
5.	4	3	2	4	2
6.	5	5	3	2	3
7.	6	2	4	2	1
8.	7	2	2	1	0
9.	8	2	4	2	0
10.	9	3	1	2	0
11.	10	3	0	0	0
12.	11	2	0	0	0
Total:		30	30	30	30

In present study there was only one drop out because of no show at week 2. New patient to complete size (n-30) was therefore included in the study.

The overall efficacy of the drug was also worked out according to Global improvement rating as given in Table XI.

Table XI : Global Improvement rating.

S.No	Improvement with Drug	No of pts	Percentage
1.	Marked improved	06	20%
2.	Improved	15	50%
3.	Slightly improved	05	17%
4.	Unchanged	04	13%
5.	Aggravated	0	0
6.	Judgment Impossible	0	0
	Total	30	100%

Table XI, shows that by treatment with Loxoprofen Sodium 87% patients showed over all improvement where as in only 13% the condition remained unchanged.

It was also found out if there was any correlation between Global improvement and sex of the patients. (Table XII)

Table XII: Relationship between Global improvement and sex

S No	Global Improvement		Score
	Male	Female	Total
1.	2	4	6
2.	5	10	15
3.	2	3	5*
4.	2	2	4
5.	0	0	0
Total :	11	19	30

The over all safety of the drug was also worked out according to the drug safety rating as given in Table XIII.

Table XIII: Over all safety rating for Loxoprofen Sodium.

S.No.	Safety level	No of pts	Percentage
1.	Safe	26	87%
2.	Essentially safe	4	13%
3.	Problem with safety	0	0
4.	Not safe	0	0
	Total :	30	100%

During present trial no problem with safety for Loxoprofen Sodium was encountered. In 28 patients there was no side effect where as one patient had mild problem of headache and other had skin variability. In both cases drug was not discontinued and symptomatic management was successful.

Based upon improvement and safety, utility of Loxoprofen Sodium for treatment of Osteoarthritis of knee joint was derived (Table IVX).

Table IVX: Utility of Loxoprofen Sodium in treatment of Osteoarthritis of knee joint.

S.No	Utility level	No of pts	Percentage
1.	Very useful	5	18%
2.	Useful	18	60%
3.	Slightly useful	3	10
4.	Hard to say	2	6%
5.	Not useful	2	6%
6.	Judgment impossible	0	0
	Total :	30	100%

In 88 % patients the treatment of osteoarthritis of knee with Loxoprofen Sodium was useful.