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Research Article

DIACEREIN VIS-À-VIS ETORICOXIB FOR OSTEOARTHRITIS OF KNEE: RESULTS OF A QUASI EXPERIMENTAL STUDY

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ABSTRACT
Osteoarthritis represents prime disability burdening the society. Therapy is largely symptomatic with NSAIDs which pose risk in the elderly. Supplement cartilage ingredients are sometimes employed with no consensus. Diacerein and its active metabolite rhein inhibit the synthesis of IL-1βin human OA synovium in vitro as well as the expression of IL-1 receptors on chondrocytes. Present observational study in 91 cases attempts to examine therapeutic outcome with Diacerein, a disease modifying drug in comparison with standard etoricoxib therapy in cases of knee osteoarthritis. 100 mg daily dose of Diacerein for 3 months was studied for clinical benefit on KOOS score measures in 50 cases with radiological grade I, II and III osteoarthritis. 41 cases treated with etoricoxib90 mg OD were the group for comparison. Diacerein therapy markedly benefited in overall improvement of KOOS score highly significantly as also the symptoms scores as well as in stiffness as compared to etoricoxib. Quality of life also significantly improved. Diacerein indeed has been reported to have specific anti-arthritic effects and promotive to general well-being. The study confirms Diacerein as superior therapeutic option to etoricoxib and supports its use as standard disease modifying agent disorder in osteoarthritis awaiting elaboration.

Keywords: *OA-osteoarthritis, KOOS-Knee Injury and Osteoarthritis Outcome Score, NSAID-Nonsteroidal Antiinflammatory Drug*

INTRODUCTION
Osteoarthritis is the most common form of arthritis (Felson, 1998). It is among the most prevalent and disabling chronic conditions affecting elderly population. It is difficult to estimate the prevalence of OA because there are no universally applicable criteria for its diagnosis. Osteoarthritis traditionally was considered as disease affecting articular cartilage. Now it is thought to involve the entire joint tissues, synovium, capsule, bone and ligaments leading to subchondral bone attrition and remodeling, meniscal degeneration, ligamentous laxity, fatpad extrution, amd impairments of neuromuscular control.
Symptomatic treatment with non-steroidal anti-inflammatory agents supplementing with intra-articular steroids is prevailing conventional approach of conservative management until surgical options become inevitable.
Progression of the disease through increasing years of age however poses obvious limitation of both safety and efficacy of conventional anti-inflammatory drugs. Use of selective COX-2 inhibitor NSAID (etoricoxib) bears risk of increasing cardio-vascular events in ageing population and topical preparations of NSAIDs remain too costly for prolong use in largely retired population. In any case the symptomatic therapy has little role in arresting or reversing the disease progression. Most patients would need non-surgical conservative treatment with drug for very long in course of lifetime. The realization lead to the call at 2010 Tokyo Workshop of the Osteoarthritis Research Society International for clinical research endeavors focused on optimizing all the available therapies toward individualized conservative management of osteoarthritic patients cellular and molecular mechanisms through which inflammatory

cytokines and growth factors influence the structure and function of synovial joints. There is enough evidence that interleukin IL-1 and tumor necrosis factor TNF-α disrupt the metabolism of synovial joint tissue. Their site of action is essentially proximal in understood pathology of disease and the downstream consequences must result only gradually to show benefits on pain and disability. These drugs are not meant to compete with NSAIDs in providing safer and quick relief in symptoms. These are also not the remedies to be considered after symptomatic therapy with NSAIDs becomes difficult. They may benefit most when anatomical derangements have not set to significant expect. These drugs may be essential as biological approach besides symptomatic therapy and surgery. Generation of clinical evidence base by pharmacologically appropriate use of disease modifying drugs is necessity to define right indications, proper therapeutic process and perhaps feasible makers to monitor their therapeutic effects.

Among such agents we prescribed Diacerein. It is oral interleukin inhibitor reported to have slow onset of action but persistant symptomatic relief in patients of osteoarthritis. Other observed effects of rhein have included inhibition of superoxide anion production, chemotaxis, and phagocytosis of neutrophils and macrophages. IL-1-dependent stromelysin 1 production was also diminished (Felisagn *et al.*, 1999). Diarrhoea is the most common adverse effect.

Present observational study prospectively examine the clinical outcome following administration of etoricoxib (selective COX 2 inhibitor) and diacerein using KOOS scores, an instrument based on patient reported information. The cases of knee osteoarthritis considered were radiologically graded as having disease of I to III grades. Preliminary assessment of any bearing of the host and disease associated factors was also done toward defining specificity of therapeutic indications of studied agents.

The base of clinical evidence resulting from study in 91patients constitutes modest endeavor for A RATIONALE definition of particulars of disease and sufferer likely to benefit as well as the correct therapeutic practice of the available disease modifying drugs for osteoarthritis of knee.

MATERIALS AND METHODS

Subjects and Methods

The study was conducted over a period from Dec 2009 to June 2011 in the orthopedic outpatients of University S.S. hospital of BHU. Cases clinically diagnosed as suffering from OA supplemented with radiographs of knees. Fresh patients reporting to the OPD as well as those receiving only non-specific anti-inflammatory drugs as per needs were considered.

Inclusion Criteria

1. Patients with age group of either sex between 40 -70 years of age.
2. Patients with radiographic evidence of suffering grade I, II and grade III OA.
3. Patients having mild to moderate grade of hypertension controlled with therapies as well as those with diabetes well controlled with therapies and suffering from OA were also included.

Exclusion Criteria

1. Patients suffering from severe grades of hypertension and diabetes mellitus requiring more than oral hypoglycemic therapies were excluded.
2. Untreated or poorly controlled diabetics and hypertensives were excluded.
3. Patients suffering from any other major systemic disease or active infection were excluded.
4. Patients with H/O trauma to knee in past before or after the onset of osteoarthritic symptoms were excluded.
5. Patients with more advanced (radiological grade IV) OA were excluded.
6. Patients developing any illness causing restriction of routine for one day or more as also those needing more than 3 days course of therapy for emergent illness were excluded.
7. Occasional use of single or two doses of medications up-to two instances during the 12 weeks observational period were allowed.
8. No case of pregnancy or H/O any surgery in last 3 years was included.
9. Patients non-compliant to therapy at more than two recalled occasions during any 2 weeks in treatment course were excluded.

The patients diagnosed and described OA therapy by the orthopedic consultant co-supervisor and suited to above-mentioned inclusion and exclusion criteria were considered.
They were informed of nature of study in which there is need for regular follow-up visits and compliance to the therapy.
They were assured that the information of monitoring the progress of their disease was the objective of non-interventional and purely observational research study and that their personal identities shall never be revealed without seeking their concurrence. The scoring was done at initial visit and subsequent follow-up visits at 12 weeks.
Drug Regimens:

The patients were prescribed various regimens of therapies entirely at discretion of the orthopedic consultant. On the basis of prescribed regimens following treatment groups emerged:

1. NSAID group: The drug prescribed was etoricoxib90mg OD for 12 weeks

2. Diacerein group: diacerein 50mg OD for 12 weeks and etoricoxib 90mg OD for first 2 weeks.

On every visit patients were practically asked for any breeches in prescribed therapeutic regimens as well as any other medical complaints besides the disability as with OA. Any other drug therapy received during the course was also specifically asked for.

An informed written consent was obtained from all the patients for inclusion of their data in this observational study, and the protocol has ascent of institute ethical committee.

Detailed history and clinical examination was performed on the patients at first and subsequent follow-up visits till the final follow-up at 12weeks. Following investigations were sought viz.

1.Bilateral knee radiograph
2.Routine hematologic test including ESR, Random blood sugar, and blood uric acid (to rule out gouty arthropathy). In some cases c-RP profile was also done as per clinical discretion.
Knee OA was then subjected to follow specific scrutinies:
a) Radiologic grading: The method of Kellgren and Laurence was adapted to grade radiological staging of OA (Kellgren, 1957)
b) Clinicalosteoarthritic disability was scored following KOOS (Knee injury and Osteoarthritis Outcomes assessment Score) (Fries *et al.*, 1980).

Statistical Analysis

The pre-treatment and post-treatment KOOS scores in different patient groups were examined for difference by applying Mann Whitney-U test .Subsequently general median values for each score and parameters form the pooled data of 91 cases were found.
This served as a reference point for cut-off of values of each parameter as on the higher side or on lower side of the median.
Patients' characteristics, disease characteristics and response to various therapies were examined with respect to relative frequencies of occurrences above the median or at below the median values. Thus the Moods Median test was applied to compute statistical significance of differences.

RESULTS AND DISCUSSION

Observations and Results

Pre and post treatment KOOS scores of all cases were separately pooled to define the MEDIAN for whole as well as components of KOOS parameters. Relative frequencies of cases with values around respective MEDIANS were compared by MOODS median test. Patient characteristics, disease characteristics were also examined for bearing on outcomes besides the treatment.

Table 1: Distribution of patients as per treatment independent variables in the studied two groups around respective median values of the variables (numbers indicate the number of patients in the group)

Variables		Etoricoxib	Diacerein	p-value
Age	>median	19	17	0.473
	Median and below	22	27	
Sex	Male	18	23	0.440
	Female	23	27	
Radiological grade	I+II	21	26	0.466
	III	20	24	
Duration of disease	>median	19	17	0.473
	Median and below	22	27	
BMI	>median	16	26	0.221
	Median and below	25	24	
Family h/o	Positive	24	28	0.873
OA	Negative	17	22	
Alcohol consumption	Yes	4	10	0.398
	No	37	40	
Smoking habit	Yes	9	8	0.664
	No	32	42	

Table-2: KOOS score profiles studied in the two compared therapy groups distributed around respective median values (numbers indicate the number of patients in the group)

Group	Pre-treatment KOOS profiles around median 57			Post-treatment KOOS profiles around median 68			Net improvement KOOS profiles around median 11		
	>median	Median and below	p	>median	Median and below	p	>median	Median and below	p
Etoricoxib	17	24	**0.041**	4	37	0.0000***	5	36	0.0000***
Diacerein	22	28		27	23		34	16	

Note: median values (numbers indicate the number of patients in the group)

Table 3: Profile of percent improvement in component scores under KOOS studied in the two compared therapy groups distributed around respective median values (numbers indicate the number of patients in the group)

Percentage Improvement In	Etoricoxib >median	Median and below	Diacerin >median	Median and below	p
PAIN score around median 25%	18	23	30	20	0.126
STIFFNESS score around median 0.00%	16	25	33	17	0.010*
SYMPTOM score around median 16.67%	11	30	31	19	0.000***
ACTIVITIES Of Daily Life score around median 10%	12	29	22	28	0.148
RECREATIONAL ACTIVITY score around median 16.67%	14	27	12	38	0.148
QUALITY OF LIFE score around median 40%	11	30	33	17	0.000***

Table 4: Outcomes measured as improvement in KOOS scores (median=11) in patients stratified according to radiological grade

Groups	Radiological grade		Patients (N) with improvement above median	Below median	Total	P value (within same group)
NSAID	R grade	I+II	2	19	21	0.592
		III	3	17	20	
DIACEREIN	R grade	I+II	17	9	26	0.680
		III	17	7	24	

Table 5: Outcomes measured as improvement in KOOS scores (median=11) in patients stratified as having BMI above or below median=26

Groups			Patients(n) with improvement above median	median and below	P value(within same group)
NSAID	BMI	above median	2	14	0.962
		median and below	3	22	
DIACEREIN	BMI	Above median	16	10	0.308
		median and below	18	6	
	median and below		55	71	

Table 1 examines the baseline variables among two treatment groups i.e. toricoxib and diacerein, which may be confounding elements of the outcome.

However, no significant difference in subjects composing the two studied groups were found with regard to sex, age, radiologic grade, duration of complaints, body mass index, family history, alcohol consumption, smoking or tobacco chewing habits.

The patients included under diacerein treatment group significantly exceeded the NSAID treatment group in regard to disease severity based on KOOS score. However net improvement (increase) in KOOS score was significantly greater in diacerein treatment group compared to NSAID treatment group after 3 months of therapy (table 2).

Selective effects on components of KOOS are summarized in table 3. Diacerein treatment was associated with significantly greater improvement in stiffness, symptoms and the quality of life. The NSAID therapy did not differ with diacerein therapy in regard to improvements in pain, spontaneous recreational activities and activities of daily life.

Age and BMI strata were also examined for any selective benefits either in early or in more advanced radiological stages of osteoarthritis on various components of KOOS score.

In table 4 results of therapies in milder (I and II) radiological grades of osteoarthritis are presented. It is seen that clinical improvement with standard NSAID is mostly below median in either case and differences in milder and severe radiological grade are not affecting the benefits. Diacerein gives superior (above median) benefit in 2/3rd of cases irrespective of radiological grade.

Table 5 examines therapeutic effects in patients with BMI above or the median 26. No significant difference was seen with NSAID therapy in two categories of patients. Diacerein benefited somewhat more in patients with BMI lower than median BMI.

Discussion

Osteoarthritis affecting 50% of people above middle age is most prevalent disability and basis of degraded quality of life. Palliative non-steroidal anti-inflammatory therapy is marred by health hazards for aging people who require long-term therapy amid presence of co- morbidities. Joint replacement surgery is not a feasible option for all. Disease modifying drugs have therefore evolved over past some decades but their role is not adequately explored and hence no certain guidelines exist for their use in osteoarthritis.

Present study prospectively examined the outcomes of use of disease modifying agent (diacerein) in comparison to NSAID (etoricoxib) in the orthopedic outpatients of SS Hospital at BHU, a tertiary care centre. This is observational prospective open uncontrolled study reviewing the outcomes and reflecting upon current medico-scientific information to draw rationales for using disease modifying remedy in routine management from available options, as are also amenable to judge from observed clinical evidence. Relative diversities of personal traits and disease stages in each studied group were identified. However, impact of such variations was duly examined by analyzing rates of good and poor responders to treatment. The prospective observational studies on therapeutic practices are vital means to achieve goal of evidence based individualized rational therapy in patients with optimization of knowledge generated to its utilization in practice.

It may be seen that several such independent factors likely to confound the observed outcomes did not significantly differ in compared groups of the study (table 1). Hence the observations may be taken as valid consequences of the treatment. Etoricoxib is relatively safe in causing little gastrointestinal adverse effects and constitutes primarily palliative treatment of pain and inflammation. Diacerein is reported to inhibit production of key cytokine interleukin- IL1 during inflammation and consequent nitric oxide, collagenases and metallogenases activity. Direct effect may also be involved (Falgarone and Dougados, 2011) thus osteoarthritic degeneration of cartilage is checked. The drug stimulates production of transforming growth factors TGF-β and their action on chondrocytes which is trophic or anabolic in effects improving vitality of cartilage and production of proteoglycans (Felisaz *et al.,* 1999). The drug also inhibits remodeling of subchondral bone and overgrowth of synoviocites by increasing their maturation (Pettelier *et al.,* 2001; Medhi *et al.,* 2007). Further, these effects persisted for several months even after discontinuation of therapy (Loutherence *et al.,* 2007). Our findings are in agreement with this report. The above discussed disease modifying effects are found to be clinically relevant in retarding radiological progression of disease by diacerein treatment (Laquasne *et al.,* 1998). Thus the overall benefits besides reduction of symptoms seen in our patients may have resulted from disease modifying effects of diacerein during the 3 months treatment period.

Diacerein is very relevant novel treatment and can render improved benefits in osteoarthritis. The combination with initial NSAIDs seems rational and studies on using diacerein instead of NSAIDs may be needed to judge merit of sole use of the agent. Diarrhoea was major problem in most cases and may be worse when used in full dose. Tetracycline like adverse effects needs also to be examined in prolonged use to ascertain safety. Tobacco was seen to particularly blunt beneficial effects of diacerein and interference also manifested with smoking and alcohol use to smaller extent.

Conclusion

Diacerein treatment exhibited multifaceted superiority over etoricoxib treatment alone. Overall improvement in KOOS score with particular boost of symptomatic relief was seen. Modest benefits were also seen on activity profiles. Diarrhea was a problem in majority of cases even at half the recommended dose. The safety profile may be elaborated; specially keeping in mind the drug is akin to tetracyclines. Betterment of tolerability and safety may make Diacerin the economical and effective disease modifying alternative to NSAIDs. As such its combination with NSAIDs is very rational, since that may limit diarrhea.

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