ORIGINAL RESEARCH

Safety and tolerability of aceclofenac compared to diclofenac and paracetamol in osteoarthritis

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Abstract
The disease process of OA is often a complex interplay of constitutional and multiple risk factors such as ageing, female gender, genetic factors, obesity, repetitive use of the joint, previous trauma, and prior inflammation. Of these, obesity is the most common predisposing factor among knee and hip joint OA. The subjects who met the eligibility criteria were randomized in 1:1:1 into 3 groups of 80 each, to receive standard dose of either Aceclofenac, Diclofenac, or Paracetamol as per the age and weight respectively for 6 weeks after obtaining their informed consent. After randomization, each subject received the allotted drug with instructions as per the scheduled dosage and all the subjects were also instructed to continue the physical activity and physical therapy. There was higher incidence of GI adverse effects of Gastritis (42.5%), pain abdomen (10%), and epigastric pain (5%) in Diclofenac than the Aceclofenac and Paracetamol treated groups. Although not statistically significant, fewer patients experienced side effects in Paracetamol and Aceclofenac treated groups compared to Diclofenac. Non- compliance to the medication was not noted among all the studied groups.

Keywords: Aceclofenac, paracetamol, osteoar Diclofenac

Introduction

Osteoarthritis (OA), the most common form of arthritis, is a progressive chronic degenerative disease characterised by gradual loss of articular cartilage, resulting in pain and functional disability.[1]

The global statistics, estimates over 100 million individuals affected by OA worldwide,[2] which is one of the common causes of pain, functional impairment,[3] activity limitation, excess health care utilization and reduced quality of life in elderly patients aged above 40 years.[4] It is also estimated to rise to the fourth leading cause of disability by 2020.[5]

In India, a total of 60 million people are estimated to have OA and it is ranked third in the world. Of these, approximately 20% are above 60 years of age and 15% of them have symptomatic OA.[6]

World Health Organisation (WHO) estimates that 9.6% of men and 18% of women aged above 60 years have symptomatic OA of hip or knee joint.[5, 7] There is increase in prevalence of OA among elderly population over 60 years and above. It is more common in women and in obese.[8] It also estimated that prevalence will increase by 66- 100% by 2020.[9]

The disease process of OA is often a complex interplay of constitutional and multiple risk factors such as ageing, female gender, genetic factors, obesity, repetitive use of the joint, previous trauma, and prior inflammation.[10] Of these, obesity is the most common predisposing factor among knee and hip joint OA.

OA commonly affects weight bearing joints which include knee, hip and small joints of hand and vertebral joints.[11] Knee joint is the most common joint attributed to OA with estimates of about 48.3% of the limb arthritis.[12]

OA has variable presentation and course. The symptoms are often unilateral, sometimes present bilaterally.

However, the symptoms on one side are more severe than the other. Pain is the most common complaint, and also swelling of joint, limitation of movements are present to an extent.[13]

The diagnosis is primarily made clinically and by conventional radiograph (CR). The characteristic radiological manifestations of OA are joint space narrowing, reduction of joint cartilage, increased

subchondral sclerosis, peri-articular osteophyte formation and joint effusion.[14]

Paracetamol is an effective and commonly used analgesic worldwide which is available as over the counter (OTC) drug both in mono and multi component preparations. It is the drug of choice (the first step of analgesic ladder) for pain as per the WHO analgesic ladder. It is recommended as a first line treatment for pain associated with OA because of its excellent safety profile in contrast to NSAIDs.

NSAIDs are the widely used analgesics for persistent pain seen in chronic diseases like osteoarthritis, rheumatoid arthritis (RA), and other musculoskeletal disorders and also for diverse forms of the pain. Currently, NSAIDs are available over the counter, higher proportion of elderly people are exposed to NSAIDs with an estimate of 40% of people aged 65 years and above for at least one or more NSAIDs each year.

NSAIDs are the first line approach for the management in OA as per the guidelines recommended by the Osteoarthritis Research Society International (OARSI), ACR, and by EULAR. Aim of the study to compare safety and tolerability of acecloenac, diclofenac and paracetamol in osteoarthritis patients

Methodology

Source of data: Confirmed Osteoarthritis patients in the Department of Orthopaedics.

Study design: Prospective, randomized, open-labelled active controlled study.

Study duration: 1 year.

Sample size: 240 patients.

Method of collection of data

A total of 240 patients with confirmed OA were recruited for the study. Informed, written consent was obtained from all subjects.

Procedure: A detailed history, complete physical examination and routine investigations were done for all the subjects. The subjects who met the eligibility criteria were randomized in 1:1:1 into 3 groups of 80 each, to receive standard dose of either Aceclofenac, Diclofenac, or Paracetamol as per the age and weight respectively for 6 weeks after obtaining their informed consent.

After randomization, each subject received the allotted drug with instructions as per the scheduled dosage and all the subjects were also instructed to continue the physical activity and physical therapy.

If the treatment response was found to be inadequate at any time point, subjects would be withdrawn from the study and will be switched to another suitable treatment. Patients were assessed at 3 visits i.e., at base line, 6 weeks and 10 weeks.

Inclusion Criteria: Patients aged > 40 years of either sex with confirmed osteoarthritis involving any joint.

Exclusion criteria

1. Patients with co-morbidities like renal / hepatic/ coagulation disorder.
2. Patients with hypersensitivity to NSAIDs.
3. Patients who require concomitant therapy with drugs (such as Warfarin, Aspirin, Corticosteroids, and Antiepileptics).
4. Pregnant and lactating women.
5. Patients with Rheumatic arthritis (RA), Gout.
6. All unstable patients suffering from any serious ailments.
7. Patients scheduled for Knee replacement therapy.
8. safety was assessed by following haematological investigation at base and at 6 th week

CBC

Liver Function Test

Serum Creatinine tolerability assessment was done based on adverse events reported by patients and treatment compliance. The reported adverse events were documented in standard adverse drug reaction form.

Results

Table 1: Complete blood count comparison between the groups

Laboratory data (CBC)	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
Hb - mg/dl				
Base line	12.16±2.09	12.87±1.00	12.84±1.08	-
10th week	11.99±2.01	12.72±1.00	12.83±1.08	-
p value	0.444	0.298	0.124	-
RBC- cells /cumm				
Base line	4.02±0.73	4.18±0.56	3.83±0.71	-
10th week	4.01±0.58	4.1±0.48	3.87±0.67	0.351
WBC - cells/cumm				
Baseline	6845.51±1687.79	6738.74±1313.33	6483.66±1731.51	0.336
10th week	6442.08±1324.64	6398.99±1413.36	6478.93±2111.08	0.954
p value	0.101	0.133	0.986	
Neutrophils				
Base line	64.78±5.77	64.78±5.77	62.00±4.66	-

10th week	63.00±4.69	63.02±4.69	61.83±4.70	0.964
Lymphocytes				
Base line	27.31±3.79	27.31±3.79	28.80±3.46	
10th week	27.81±3.50	27.67±3.5	28.91±3.39	0.978
Monocytes				
Base line	5.78±2.09	5.78±2.09	7.84±2.16	-
10th week	5.88±2.17	5.68±2.17	7.91±2.27	0.992
Eosinophils				
Base line	1.81±1.77	1.81±1.77	1.10±1.12	-
10th week	1.60±1.11	1.56±1.11	1.09±1.13	0.997
Platelets				
Base line	3.18±1.05	3.04±1.03	2.67±0.69	-
10th week	3.06±0.61	3.18±1.05	2.87±1.00	-

The baseline complete blood count parameters such as haemoglobin (Hb), red blood cells (RBC), white blood cells (WBC), differential count (DC) and platelet were comparable between the groups and showed no significant differences between the studied groups.

Table 2: Liver Function Test comparison between the groups

Liver function test (LFT)	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
SGOT				
Baseline	18.65±4.71	18.65±4.71	20.89±6.71	-
10th week	19.94±8.23	17.98±6.85	20.72±5.61	-
SGPT				
Baseline	26.84±5.18	28.20±6.32	43.48±15.22	-
10th week	25.73±16.38	27.66±10.93	52.25±19.53	<0.001**
Albumin				
Baseline	4.55±0.66	4.56±0.66	4.56±0.66	0.991
10th week	4.60±0.74	4.48±0.53	4.62±0.65	-
Globulin				
Baseline	2.46±0.52	2.53±0.54	2.52±0.47	-
10th week	2.52±0.47	2.58±0.52	2.60±0.59	-
Total protein				
Baseline	7.23±0.74	7.24±0.66	7.12±0.83	0.557
10th week	7.24±0.47	7.24±0.66	7.17±0.76	0.746
p value	0.897	0.320	0.572	-

The parameters of LFT were comparable between the groups and showed no significant difference between the groups at base line.

On 10th week, there was significant increase in SGPT with the mean score of 52.25±19.53 vs. 43.48±15.22 at base line which was noted in Paracetamol group and this rise was statistically significant compared to the Aceclofenac (25.73±16.38 vs. 26.84±5.18) and Diclofenac (27.66±10.93 vs. 28.20±6.32) treated groups (p<0.001).

However, the studied groups showed no significant differences in LFT parameters on base line and 10th weeks, as regards to SGPT, significant increases were noted in Paracetamol group.

Table 3: Comparison of serum Creatinine level between the groups

Serum Creatinine	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
0 week	0.69±0.15	0.77±0.14	0.80±0.16	-
6th week	0.70±0.13	0.72±0.12	0.79±0.13	-
p value	0.467	0.512	0.559	-

There were no significant differences between the groups on from base line to 10th week with respect to serum Creatinine.

Table 4: Overall incidence of adverse effects at 6 week

Adverse reactions	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III
6 weeks			
Nil	3 (3.8%)	0 (0%)	2 (2.5%)
Gastritis	19 (23.8%)	27 (33.8%)	0 (0%)
Nausea	6 (7.5%)	4 (5%)	35 (43.8%)

Pain abdomen	13 (16.3%)	15 (18.8%)	12 (15%)
Epigastric pain	11 (13.8%)	16 (20%)	0 (0%)
Headache	7 (8.8%)	15 (18.8%)	0 (0%)
Diarrhoea	0 (0%)	11 (13.8%)	0 (0%)
Weakness	0 (0%)	0 (0%)	10 (12.5%)
Vomiting	0 (0%)	0 (0%)	9 (11.3%)
Dizziness	0 (0%)	7 (8.8%)	0 (0%)
Chest pain	0 (0%)	6 (7.5%)	0 (0%)
Tiredness	0 (0%)	0 (0%)	6 (7.5%)
Constipation	0 (0%)	0 (0%)	5 (6.3%)
Rash	0 (0%)	0 (0%)	1 (1.3%)
At 10 weeks			
Nil	43 (53.8%)	33 (41.3%)	54 (67.5%)
Gastritis	14(15%)	34 (42.5%)	4 (5%)
Pain abdomen	2 (2.5%)	8 (10%)	17 (21.3%)
Epigastric pain	0 (0%)	4 (5%)	5 (6.3%)
Headache	2 (2.5%)	0 (0%)	0 (0%)
Diarrhoea	1 (1.3%)	0 (0%)	0 (0%)

On 6th week, the adverse effects like weakness / tiredness, dizziness, chest pain, constipation, rash and vomiting were minimal in the studied groups. Higher incidence of nausea, weakness/tiredness, vomiting, constipation and rash were noted in Paracetamol group. Pain abdomen, epigastric pain, headache, diarrhoea were found to be higher among Diclofenac group compared to Aceclofenac group.

On 10th week, greater percentage of patients were free of adverse effects in Paracetamol group (67.5%) than Aceclofenac (53.8%) and Diclofenac (41.3%) group.

There was higher incidence of GI adverse effects of Gastritis (42.5%), pain abdomen (10%), and epigastric pain (5%) in Diclofenac than the Aceclofenac and Paracetamol treated groups.

Although not statistically significant, fewer patients experienced side effects in Paracetamol and Aceclofenac treated groups compared to Diclofenac. Non- compliance to the medication was not noted among all the studied groups.

Discussion

Present study results are in contrast with pareek et al study not required instead Diaz et al study can considered for comparison, comparative, randomized, and double- blind study conducted among 247 osteoarthritis patients, to compare efficacy and safety of Diclofenac with Aceclofenac. The results showed Aceclofenac superior to Diclofenac in efficacy parameters of WOMAC score and investigator assessment of pain and movement by Likert scale. The overall superior response was found in Aceclofenac treated patients than Diclofenac treated patients.[15]

The present study results are similar to another Pareek *et al*. study performed among 591 knee OA patients. The results showed both Aceclofenac and Diclofenac were equally efficacious and no statistically significant differences were noted between the groups.[16]

Another randomized double blind comparative study by Awan MMY *et al*. also reported the same results as that of the present study. There was statistically significant decrease in WOMAC and VAS score in the both Aceclofenac group and Diclofenac group and concluded both were equally efficacious in OA.[17]

Arshiya *et al*. study results were compatible with results of our study as well as Awan MMY and Pareek *et al*. studies. The results reported that both the drugs Diclofenac and Aceclofenac showed statistically significant ($p< 0.001$) improvement in all the efficacy parameters of WOMAC and VAS.[18]

The findings of this study are similar to that of previous study performed by Patil *et al*. that there was statistically significant improvement in all the three domains of WOMAC with Aceclofenac and Diclofenac ($p<0.0001$), but there was increased improvement noted in Aceclofenac group when compared to Diclofenac group. [19]

The haematological parameters such as CBC, LFT and serum Creatinine were comparable between the groups and showed no significant difference between the groups except for the rise in SGPT (52.25±19.53 vs. 43.48±15.22) which was statistically significant in Paracetamol group when compared to Aceclofenac and Diclofenac groups ($p<0.001$). This shows that haematological parameters of CBC, LFT and serum Creatinine in Aceclofenac and Diclofenac groups were equal. Whereas Paracetamol shows significant rise in SGPT on 10th week ($p<0.001$).

In our study higher incidence of GI adverse effects such as gastritis (42.5%), pain abdomen (10%) and epigastric pain (5%) were noted in Diclofenac group than the Aceclofenac and Paracetamol groups. This shows that the Paracetamol and Aceclofenac drug are gastric friendly compared to Diclofenac. Present study results, in terms of tolerability was similar to that of Ward *et al*. study, high tolerability was observed with Aceclofenac group when compared to Diclofenac group in terms of GI AEs like diarrhoea was more in

Diclofenac group (6.6%) compared to Aceclofenac group (1%).

Our study results were compatible with another randomized, double-blind study performed by Pareek *et al*. among 591 OA patients to compare GI tolerability and efficacy in Aceclofenac and Diclofenac. The results conclude that the overall incidence of GI AEs was higher in Diclofenac group than Aceclofenac group (73.6% vs. 57.3%). Aceclofenac was better tolerated in terms of incidence and severity of GI AEs.[16]

With regard to tolerability, Verkleji SPJ *et al*. study reported higher incidence of GI AEs in Diclofenac group than in Paracetamol group (36.5% vs. 13.5%).[20] Similarly, Arshiya *et al*. study also reported the same results that lesser GI AEs were reported in Aceclofenac group than Diclofenac group. These results were similar with present study findings.[18]

Conclusion

Aceclofenac and Paracetamol was tolerated better with lesser incidence of GI side effects than Diclofenac group. No serious adverse events were experienced with either drug..

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