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EVALUATING ADJUNCTIVE ROLE OF PPI AS ANTI INFLAMMATORY AGENT IN KNEE OSTEOARTHARITIS: A PROSPECTIVE STUDY IN TERTIARY CARE HOSPITAL

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ABSTRACT: Osteoarthritis (OA) is one of the main causes of disability worldwide. Patients are mostly treated with NSAIDS with PPI and H_2 blockers, analgesics, opoids etc in everyday practice. In addition to anti-secretory effects, PPIs have anti-oxidant and anti-inflammatory actions in vitro. But the role of PPIs as anti-inflammatory agents remains to be explored. **Aim:** Present study was aimed to compare efficacy and safety of Diclofenac (DIC) + Proton pump inhibitor(PPI) and Diclofenac+H2 blocker in patients with knee osteoarthritis **methodology:** We conducted prospective randomised control open label study on 40 patients at Orthopedic OPD of tertiary care hospital. Patients were given either DIC(100mg SR OD) + PPI (Omeprazole 20mg OD) or DIC (100mg SR OD)+ H_2 blocker (Famotidine 20mgOD) for two weeks. Clinical effectiveness was assessed by using Knee injury and Osteoarthritis Outcome Score (KOOS) and Visual analogue score(VAS) as efficacy parameters. Suspected ADRs were recorded at each visit. **Observation:** In the present study, the prevalence of osteoarthritis was more common in the age group 50-59 years (48%) with female predominance (95%). After application of KOOS questionnaire and VAS net quality gain in symptoms were better with SR diclofenac +PPI group than SR diclofenac+H_2 blockers. Less ADR profile were seen in diclofenac +PPI group with epigastric pain topping the list. C**onclusion:** Addition of PPI act not merely as potent acid suppressing agents but also add to the anti-inflammatory and analgesic action of diclofenac and increases patients adherence / compliance to the treatment.

INTRODUCTION: Osteoarthritis (OA) is a disease that causes pain and stiffness in the joints leading to a reduction in mobility and a large impact on quality of life of patients as well as consumption of medical resources. Knee joint is most commonly affected by osteoarthritis [1]. Prevalence of knee OA in India is reported to be in the range of 5.78-12% [2, 3].

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Symptoms are known to develop slowly over a number of years. Pain is usually the main symptom affecting these patients and treatment is essential to improve their quality of life. The main oral pharmacological options currently used to treat pain caused by OA include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates [4]. Recently, the International Osteoarthritis Research Society (OARSI) has published a series of recommendations based on review of available guidelines for the management of patients with OA of the hip and knees [5].

They recommend taking the lowest effective dose of NSAIDs, avoiding long-term use, as they are associated with dose- and duration-related risks of

gastrointestinal, cardiovascular, and renal-function adverse events (AEs). Guidelines from the 'Osteoarthritis Research Society International' recommend the use of a gastro protective agent, such as a proton pump inhibitor (PPI), with oral NSAIDs to reduce gastrointestinal adverse events (AEs). [5] Also, NSAIDs, selective or not, should be used with caution in patients with cardiovascular risk factors [6].

Routinely NSAIDS are given along with PPI. In addition to anti-secretory effects, however, PPIs have been found to have anti-oxidant properties and direct effects on neutrophils, monocytes, endothelial, and epithelial cells that might prevent inflammation[7]. Those anti-inflammatory effects of the PPIs might influence a variety of inflammatory disorders, both within and outside of the gastrointestinal tract. But the role of PPIs as anti-inflammatory agents in addition to their acid lowering property in osteoarthritis and cost-effectiveness remains to be explored.

Hence present study was udertaken with objective to assess clinical effectiveness and adverse events between Diclofenac + PPI and Diclofenac + H_2 blocker in patients with osteoarthritis

MATERIAL & METHODS:

This was prospective randomised control open label study on 40 patients at Orthopedic OPD of tertiary care hospital. The study was started after getting approval from institutional Ethics committee (No. BVDU/MC/47, 06/09/2012). Trial was registered in Clinical Drug Trial Registry-India, (www.ctri.nic.in), and the approval number allotted was CTRI/2013/05/003618.Study was conducted from June 2013 to Feb 2014.

Patients were screened and randomized by schedule of permuted block randomization with block size 4 was used drug allotment. Following criteria were used for screening.

1. **Inclusion Criteria:** Patients' aged 45 years or older of either sex, consulting for non-traumatic knee pain/primary symptomatic knee OA (in one or both knees), in the general practice, complying to the clinical American College of Rheumatology (ACR) criteria for osteoarthritis of the knee, having an indication for pain medication, score of 3 or more on the pain severity scale (0-10 scale) and patients willing to provide informed and written consent

2. **Exclusion Criteria**: Contra-indication for NSAID use (these are: Gastrointestinal bleedings in history or active peptic ulcer, serious liver or kidney disease (glomerular filtration < 30 ml/min), an arthroplasty or osteotomy of the knee in contralateral or unilateral side, surgery or major trauma of the affected joint within the previous 6 months, pregnancy and lactating women, patients who were treated with corticosteroid and hyaluronic injection to the target joint within two months prior to the study medication administration, patient having disease more than 5 years, patients with Rheumatoid arthritis, Ankylosing spondylitis, Active gout or Active pseudo-gout.

Patients were selected as per criteria mentioned above. After taking written informed consent patients were allotted randomly into following two groups:

1. Diclofenac (100mg SR OD) + PPI (Omeprazole 20mg OD)

2. Diclofenac (100mg SR OD)+ H_2 blocker (Famotidine 20 mg OD)

Medications of the same brand were used for the entire duration of study. Patient were told to report study center after 2 wks.

Visit 1: Detailed history, symptoms of the patient of knee osteoarthritis was recorded. Patients were asked to fulfill the VAS and KOOS questionnaire. Respective drug was prescribed.

Visit 2: Follow up of the patient was done after 2 weeks and the questionnaire were filled again.

Efficacy variables:

VAS [8, 9]: The overall daily pain intensity was assessed with a 100 mm VAS (anchors: no pain,

extreme pain) by asking the patient, "What was your average pain over the past 2 wks.?"

KOOS questionnaire [10]: The Knee injury and Osteoarthritis Outcome Score (KOOS) is an extension of the Western Ontario and Mc-Master Universities Osteoarthritis Index (WOMAC). KOOS is a 42-item self-administered self-explanatory questionnaire that covers five patient-relevant dimensions: Pain (9 items), Other Disease-Specific Symptoms (7 items), ADL Function (17 items), Sport and Recreation Function (5 items), and knee-related Quality of Life (4 items). Each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0–100 scale, with 0 representing extreme knee problems and 100 representing no knee problems as common in orthopedic scales.

4. Adverse events:

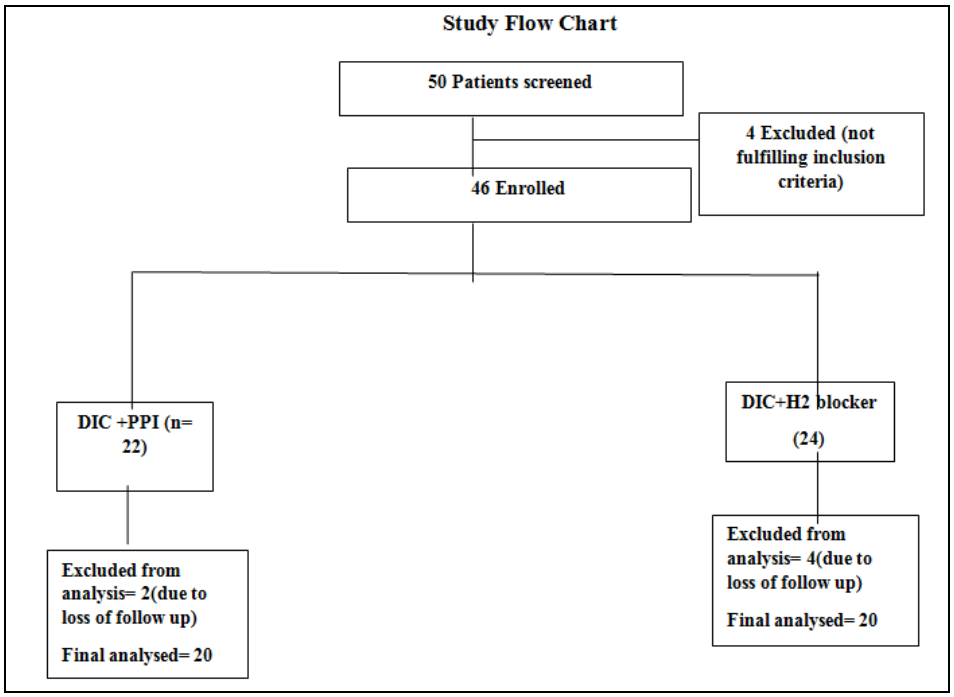
Spontaneously reported by patients and adverse events observed by the investigator were recorded at each visit.

Statistical analysis:

The characteristics of all treatment groups were compared for both demographic and efficacy variables. Data were expressed as mean ± standard error mean (SEM). Data analysis was performed using Graph Pad Prism 5.0 software (Graph Pad, San Diego, CA, USA). The values of symptom score for each group were analyzed by 2 independent sample t-test. Comparison was made between baseline and post treatment after two weeks between treatment groups. $p<0.05$ considered as significant.

Observations and results:

The present study was carried out in a tertiary care hospital, Pune. Total 50 patients with primary osteoarthritis were screened. Amongst them, 46 patients were enrolled as per study criteria. 6 patients did not turn up for follow up and were dropped. So final analysis was done with 40 patients, twenty (20) in each group.



Characteristics of the study population (n=40) are as follows.

TABLE 1: AGE AND SEX OF STUDY POPULATION (n=40)

Age	Number of patients(n=40)
45-49	13(1 male+12 female)
50-59	20 (3 male + 17 female)
60-69	6 (6 female)
70-79	1(1 female)

As shown in **Table 1,** in our study maximum number of patients were in age group of 50 to 59 years followed by the age group 45 to 49 years and around 90% of patients in our study population were females clearly indicating much higher

incidence of osteoarthritis in females as against males.

TABLE 2: PRE-TREATMENT COMPARISON OF VARIOUS PARAMETERS OF KOOS ARTHRITIS INDEX IN DIC+PPI AND DIC+ H2 BLOCKER GROUP.

Parameters	DIC+PPI		DIC+H_2 blocker		P-value
	Mean	SD	Mean	SD	
Pain	45.96	12.62	46.81	14.76	0.845
Symptom	76.07	11.30	75.89	11.64	0.960
ADL	47.28	10.89	48.16	10.76	0.789
Sport/Rec	31.25	8.87	34.25	9.07	0.296
QOL	37.50	9.07	38.13	10.71	0.842

Conclusion: By using 2 independent sample t-test p-value>0.05, therefore there is no significant difference between mean pain, symptom, ADL, Sport/Rec and QOL among pretreatment groups of DIC +PPI and DIC +H_2 blocker.

TABLE 3: POST TREATMENT COMPARISON OF VARIOUS PARAMETERS OF KOOS ARTHRITIS INDEX IN DIC+PPI AND DIC +H_2 BLOCKER GROUP.

Parameters	DIC+PPI		DIC +H2 blocker		P-value
	Mean	SD	Mean	SD	
Pain	81.25	19.19	61.72	20.05	0.003
Symptom	89.29	8.27	81.75	8.05	0.005
ADL	82.29	17.15	70.04	20.50	0.044
Sport/Rec	79.25	22.02	64.25	21.06	0.003
QOL	67.19	11.52	59.06	10.63	0.025

Conclusion: By using 2 independent sample t-test p-value < 0.05, therefore there is significant difference between mean pain, symptom, ADL, Sport/Rec and QOL among post treatment groups of DIC +PPI and DIC +H_2 blocker.

TABLE 4: PRE AND POST TREATMENT COMPARISON OF VAS SCORE BETWEEN STUDY GROUPS.

Parameters	DIC+PPI		DIC +H2 blocker		P-value
	Mean	SD	Mean	SD	
Pre Treatment VAS	67.00	8.01	68.00	6.16	0.660
PostTreatment VAS	31.00	10.71	44.00	10.95	< 0.001

Conclusion: By using 2 independent sample t-test p-value>0.05 when pretreatment values of treatment groups are compared indicating no significant difference, but when post treatment values are compared, P<0.05, indicating significant difference of VAS score between treatment groups thus proving superiority of DIC +PPI over DIC +H_2 blocker.

TABLE 5: INCIDENCE OF MOST COMMON ADVERSE EVENTS

ADR	N=20	N=20
	DIC+PPI	DIC + H2 blocker
Dizziness	1	1
Nausea	4	3
Abdominal pain/ epigastric pain	4	7
Constipation	0	0
Somnolence	1	2
Vomiting	0	1
Headache	0	0
Sweating	0	0

As shown in above table, the most frequently occurred ADRs were gastro-intestinal system disorders like nausea (highest in DIC +PPI group), epigastric pain (highest in DIC+ H_2 blocker group). This was followed by somnolence which occurred in DIC + H_2 blocker group.

DISCUSSION: The present randomized, open label parallel study was designed to compare controlled release (CR) tramadol formulation with sustained-release (SR) Diclofenac with and without proton pump inhibitor (PPI) in patients with osteoarthritic pain of moderate to greater intensity.

The present study was carried out at Orthopedic OPD in a tertiary care hospital, Pune. Total 50 patients with primary knee osteoarthritis were screened. Amongst them, 46 patients were enrolled as per study criteria. 6patients did not turn up for follow up and were dropped. So final analysis was done with 40 patients, twenty in each group. Ethics approval (No. BVDU/MC/47, 06/09/2012) was taken and the trial was registered in Clinical Drug Trial Registry-India, (www.ctri.nic.in), and the approval number allotted was CTRI/2013/05/003618.

We conducted an open label study as all drugs are marketed with proven efficacy. Drugs were prescribed to patients as per protocol. Blinded trials are not always feasible and also have a potential to introduce a design-specific bias [11]. Also open-label trials are less complex and can be conducted at lower costs. Double blinding often requires also a double-dummy design which increases tablet burden on patient and decreases patient compliance. If open-label trials have a lower patient selection and allow for a management of therapy closer to the daily clinical practice, it is reasonable to speculate that results of such trials are also nearer to the real world.

SR formulations offer the advantages of sustained blood levels, attenuation of adverse effects, improved patient compliance [12] .With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to the transiently high concentration. A reduction in the number of daily doses offered by extended-release products has the potential to improve compliance. This is the reason we selected sustained release preparation of diclofenac as study medication. In previous studies conducted by Beaulieu et al and Pavelka, they had also used sustained release preparation of diclofenac which were effective in management of painful osteoarthariti [13].

Knee osteoarthritis and subject characteristics:
In the present study, the prevalence of osteoarthritis in our sample was more common in the age group 50-59 years (48%) and then decreased. **Table 1**. In previous studies survey of 540 orthopaedic surgeons at all India institute of medical sciences also reported that osteoarthritis of major joints of hip and knee was reported to be more in the age group of 50 and above by 92% of them, but 8% surgeons said that the patients in 40 + years age group may also present with osteoarthritis [14]. This could be because osteoarthritis mostly hits women in their post-menopausal period that is age >50 [15]. In our study majority of patients were females 95%. **Table 1** Osteoarthritis affects women more than men. This difference may be explained by the lack of physical activity, mobility, social issues especially in our region and higher prevalence of obesity among women in general, which is consistent with the data from other studies [14, 16].

The study by Abdurhuman S et al in Saudi Arabia found strong association between excess weight and knee Osteoarthritis in females than males[17]. Women's hips are wider than their knees, their knee joints are not aligned as straight as men's, the alignment of a woman's body leads to a higher rate of knee injuries, and injuries can lead to osteoarthritis later in life. Also Osteoarthritis seems to run in families, and there appears in particular to be a genetic link among women. Female hormone estrogen protects cartilage from inflammation. But after menopause, when women's estrogen levels go down, they lose that protection and may have a higher risk of developing osteoarthritis. Giving birth is another risk factor for osteoarthritis.

Efficacy variables:
KOOS: KOOS is an extension of the Western Ontario and Mc-Master Universities Osteoarthritis Index (WOMAC).To increase sensitivity for patients with knee injury, items were added to the

WOMAC pain and stiffness section. Two new subscales were added resulting in 42 item questionnaire with five subscales. This increase in sensitivity and large score in turn allow smaller patient study groups when comparing treatment. The KOOS is self-administered and takes approximately 10 minutes to fill out with different subscales. That is the reason we used KOOS questionnaire to determine the effectiveness of study medications given for management of knee osteoarthritis.

VAS: The VAS is widely used due to its simplicity and adaptability to a broad range of populations and settings. We used this scale to strengthen the evidence.

Efficacy of Diclofenac in management of symptoms:

The result of present study demonstrate that Diclofenac at dose of 100 mg SR preparation with H_2 blocker as well as with PPI showed significant improvement in all symptoms of knee osteoarthritis within two weeks. **Table 3, 4** Our results are similar with previous studies which also demonstrated SR Diclofenac is effective in management of osteoatharitis [18].

Besides the well-known and often-cited COX-inhibition, a number of other molecular targets of diclofenac possibly contributing to its pain-relieving actions have recently been identified. These include blockage of voltage-dependent sodium channels, Blockage of acid-sensing ion channels (ASICs), Positive allosteric modulation of KCNQ- and BK-potassium channels (diclofenac opens these channels, leading to hyperpolarization of the cell membrane. Some evidence indicates it inhibits the lipoxygenase pathways thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). It also may inhibit phospholipase A2 as part of its mechanism of action[19]. Diclofenac gets distributed in synovial fluid and has chondroprotectiveaction [20]. These additional actions may explain its high efficacy. In previous systematic review of randomised controlled trials it was shown that the efficacy of diclofenac is largely unchallenged in that it remains as effective as newer pain relief medications employed in OA [21].

Role of PPI:

To explore the anti inflamatory action of PPIs in osteoarthritis we compared efficacy of Diclofenac +PPI Vs Diclofenac +H_2. The results of the present study demonstrate that diclofenac +PPI at doses of 100mg/ day was more effective and statistically significant (P value < 0.05) than Diclofenac +H_2 blocker in the treatment of OA pain of the knee. **Table 3** and **4.**

The reason for this difference in efficacy can be because of anti-inflammatory properties of PPI in combating inflammation. In addition to anti-secretary effects, however, PPIs have been found to have anti-oxidant properties and direct effects on neutrophils, monocytes, endothelial, and epithelial cells that might prevent inflammation. [7]

In another study it was shown that proton pump inhibitors can attenuate neutrophil adherence to endothelial cells via inhibiting the expression of adhesion molecules, suggesting that proton pump inhibitors may have anti-inflammatory activity [22]. Those anti-inflammatory effects of the PPIs might influence a variety of inflammatory disorders, both within and outside of the gastrointestinal tract. Routinely NSAIDS are given along with PPI. This anti-inflammatory action of PPI may be beneficial for osteoartharitis patients. Another reason for having more efficacy of NSAIDS given along with PPI is that PPI relieve the gastrointestinal symptoms caused by NSAID, thus increasing the drug compliance.

The adverse event profile of patient groups taking PPI is also lower than those not taking PPIs, **Table 5** which was also seen in our study where ADR are less in Diclofenac +PPI group than Diclofenac + H2 blocker group. Increase adherence to the therapy also contributes to more efficacy of Diclofenac +PPI.

Adverse drug effects:

Patients in both groups reported epigastric pain **Table 5**. This is because diclofenac causes gastrointestinal ailments (upper abdominal and gastric pain, nausea, vomiting, diarrhoea or constipation). DIC +PPI group has less AEs because of protective effect of PPIs against gastrointestinal ailments. This can be because PPIs

have pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available. They have largely superseded H_2-receptor antagonists [23]. Also single dose of famotidine may not be sufficient to protect from GI Irritation.

The present study showed a trend toward slightly higher incidences of adverse events with DIC +H_2 blocker than in DIC +PPI. However patients receiving long-term NSAID therapy risk severe gastrointestinal symptoms, including ulceration and bleeding, nephrotoxicity. We were not able to detect any serious adverse effect in present study as duration of study was short .In clinical scenario practitioners generally advised to take analgesic drug for one or two week for mild to moderate pain in osteoarthritis. Then patients have to continue drug on an as-needed basis which is in line with our protocol.

CONCLUSION: As per our results addition of PPI act not merely as potent acid suppressing agents but also add to the anti-inflammatory and analgesic action of diclofenac and increases patients adherence / compliance to the treatment.

CONFLICT OF INTEREST: There was no conflict of interest among authors.

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