

## **Incremental cost-effectiveness and tolerability of Diclofenac + Proton pump inhibitor compared to tramadol in the treatment of knee osteoarthritis**

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### **ABSTRACT**

**Background:** In a climate of economic uncertainty, cost effectiveness analysis is a potentially important tool for making choices about health care interventions. Patients with knee osteoarthritis are treated mostly with Diclofenac (NSAID) + Proton Pump Inhibitors (PPI) and Tramadol (Opioids) in everyday practice.

**Aim:** Present study was aimed to assess clinical effectiveness, adverse events and cost-effectiveness between Diclofenac + PPI and Tramadol.

**Methods:** Authors conducted prospective randomised control open label study on 40 patients at Orthopedic OPD of tertiary care hospital. Patients were given either Tramadol controlled releases tablets (200mg CR OD) or Diclofenac sustained release tablets (100mg SR OD) + PPI (Omeprazole 20mg OD) for two weeks. Clinical effectiveness was assessed by KOOS osteoarthritis index score consisting of five parameters and visual analogue scale. Suspected ADRs were recorded and incremental cost effective ratio for both drugs was calculated.

**Results:** After application of KOOS questionnaire Authors found net quality gain in symptoms was 24.45 in diclofenac +PPI group which was much higher against 14.15 found in tramadol group. Again ADR profile of tramadol was 29 with nausea and somnolence topping the list which was far more than only 10 in DIC +PPI group. Lastly cost-effective analysis was done where again DIC+PPI showed average cost effective ratio 5.73 verses tramadol 11.8 with an incremental cost-effectiveness ratio (ICER) of -2.72.

**Conclusions:** Diclofenac +PPI is as effective as tramadol in the treatment of pain due to knee osteoarthritis with the potential for fewer side effects. Diclofenac + PPI was also found to be cost-effective when compared with tramadol.

**Keywords:** Cost-effectiveness, Diclofenac, KOOS, Osteoarthritis, Protein pump inhibitor, Tramadol, VAS

### **INTRODUCTION**

Osteoarthritis (OA) is a chronic inflammatory disease, with significant impact on health-related quality of life. It 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.<sup>1</sup> Prevalence of knee OA in India is reported to be in the range of 5.78-12%.<sup>2,3</sup> This is most

common cause of locomotor disability in elderly. 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. Economic evaluation of RA is very much important in influencing the physician on decision making as the treatment of RA lies at two extremes as far as cost of medicines is concerned. In some settings like in India, where there are financial constraints on health care

provisions, economic evaluation for management of diseases is meaningful.

The main oral pharmacological options currently used to treat pain caused by OA include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates.<sup>4</sup> 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.<sup>5</sup> 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). They also recommend the use of a gastro protective agent, such as a proton pump inhibitor (PPI), with oral NSAIDs to reduce gastrointestinal adverse events (AEs).<sup>5</sup> Also, NSAIDs, selective or not, should be used with caution in patients with cardiovascular risk factors.<sup>6</sup> Although the role of opioid analgesics for the treatment of chronic non-cancer pain has undergone re-evaluation, there are continued concerns on the part of patients and clinicians about long-term use, due to fears about physical dependence, tolerance, addiction, diversion, and adverse regulatory sanctions.

Pharmaco-economic analysis is important to select among alternative and help to optimize the treatment of pain in patients with OA.<sup>7</sup> In developing countries it is very important to assess what drugs may decrease the subsequent use of medical care resources considering their adverse events that are known to have a significant increase in medical care costs of patients with osteoarthritis.

Keeping the above aspects in mind authors have designed a study to evaluate cost-effectiveness and safety between two most commonly used drugs for OA which will help prescriber and patient to make better choice suitable for them.

## METHODS

Trial was registered in Clinical Drug Trial Registry-India, (www.ctri.nic.in). It was a Prospective randomized control open label study carried out at Orthopaedic OPD on 50 patients at tertiary care hospital from October 2012 to March 2014.

Inclusion Criteria were 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, indication for pain medication., having a score of 3 or more on the pain severity scale (0-10 scale) and willing to provide informed and written consent.

Patients who had contra-indication for NSAID or Paracetamol use (these are: Gastrointestinal bleedings in

history or active peptic ulcer, serious liver or kidney disease (glomerular filtration <30ml/min), patients with 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 were excluded from study.

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

- Tramadol (200mg CR OD)
- Diclofenac (100mg SR OD) + PPI (Omeprazole 20mgOD)

Patients were told to report to study centre after 2 wks.

### Visit 1

Detailed history, symptoms of the patient of knee osteoarthritis was recorded. Patients were asked to fulfil the VAS and KOOS questionnaire. Respective drug was prescribed.<sup>8-10</sup>

### Visit 2

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

### Average Cost Effectiveness Ratio (acer)<sup>11</sup>

ACER for different groups were calculated by dividing the cost of treatment by its clinical outcome to yield the ratio in terms of rupees.

$$\text{The average cost effectiveness} = \frac{\text{Net Cost}}{\text{Net Health Benefit}}$$

### Incremental cost effective ratio<sup>12</sup>

The ICER is essentially the incremental costs of implementing one program over the other divided by the incremental health gain from doing the next intervention. Formula for incremental cost-effectiveness ratio.

$$\text{ICER} = \frac{(\text{Cost of drug A} - \text{Cost of drug B})}{(\text{Benefits of drug A} - \text{benefits of drug B})}$$

### Cost of the study medications

Medications of the same brand were used for the entire duration of study. The costs of all the study medications were calculated based on the retail selling price from the hospital pharmacy.

**Adverse events**

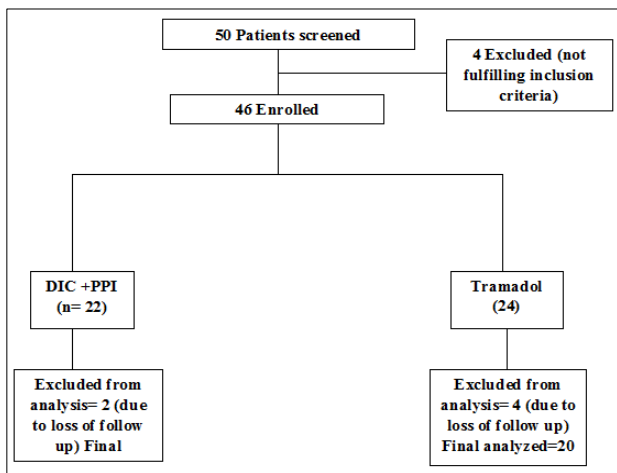
Spontaneously reported by patients and adverse events observed by the investigator were recorded at each visit.

**Statistical analysis**

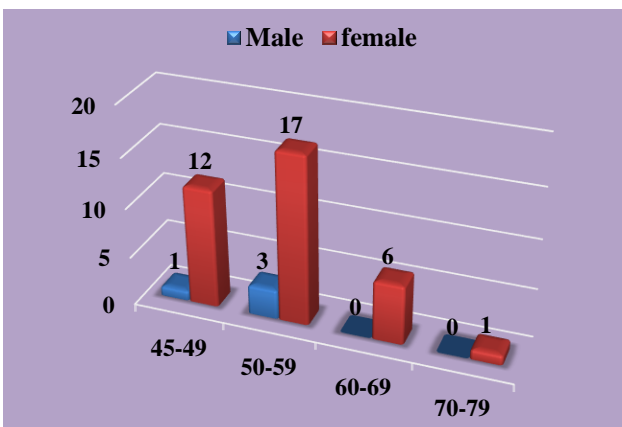
The characteristics of all treatment groups were compared for both demographic and efficacy variables. Data were expressed as mean ± standard error mean (SEM). Data analysis was performed using Graph Pad Prism 5.0 software (Graph Pad, San Diego, CA, USA). Analysis of variance (ANOVA) test was used with p<0.05 considered as significant.

**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.



**Figure 1: Total number of patients finally analysed.**



study population (n=40)

**Figure 2: Distribution of patients according to age groups.**

As shown in Figure 2, 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 1: Pre treatment comparison of various parameters of KOOS arthritis index in DIC+PPI and tramadol group.**

Parameters	DIC+PPI		Tramadol		P-value
	Mean	SD	Mean	SD	
Pain	45.96	12.62	50.28	14.33	0.318
Symptom	76.07	11.30	75.89	13.21	0.963
ADL	47.28	10.89	55.44	15.67	0.063
Sport/Rec	31.25	8.87	39.25	13.01	0.059
QOL	37.50	9.07	39.06	8.57	0.579
Total score	57.02	6.84	51.98	10.01	0.068

By using one-way ANOVA p-value >0.05, therefore there is no significant difference between mean pain, symptom, ADL, Sport/Rec and QOL among pre treatment groups of DIC +PPI and tramadol.

**Table 2: Post treatment comparison of various parameters of KOOS arthritis index in DIC+PPI and tramadol group.**

Parameters	DIC+PPI		Tramadol		P-value
	Mean	SD	Mean	SD	
Pain	71.25	19.19	65.14	14.66	0.265
Symptom	89.29	8.27	87.32	9.73	0.494
ADL	75.29	17.15	69.26	14.45	0.237
Sport/Rec	64.25	22.02	54.00	15.27	0.095
QOL	57.19	11.52	55.31	9.35	0.574
Total score	71.50	14.01	63.30	10.02	0.575

By using one-way ANOVA p-value > 0.05, therefore there is no significant difference between mean pain, symptom, ADL, Sport/Rec and QOL among post treatment group of DIC +PPI and tramadol.

**Table 3: Pre and post treatment comparison of VAS score between study groups.**

Parameters	DIC+PPI		Tramadol		P-value
	Mean	SD	Mean	SD	
Pre treatment VAS	67.00	8.01	61.50	9.88	0.061
Post treatment VAS	31.00	10.71	40.50	18.20	0.051

By using one-way ANOVA p-value > 0.05, therefore there is no significant difference of VAS score in pre-treatment

groups of DIC+PPI and tramadol and post treatment groups of DIC+PPI and tramadol.

**Table 4: Incidence of most common adverse events.**

ADR	N=20	
	DIC+PPI	Tramadol
Dizziness	1	3
Nausea	4	10
Abdominal pain/ epigastric pain	4	2
Constipation	0	2
Somnolence	1	7
Vomiting	0	4
Headache	0	0
Sweating	0	1
Total	10(25.64%)	29(74.36%)

As shown in Table 4, the most frequently occurred ADRs were gastro-intestinal system disorders like nausea (highest in tramadol group), epigastric pain (highest in DIC+PPI group), and vomiting (highest in tramadol group). This was followed by somnolence which occurred in Tramadol group. Least common ADR was headache and sweating which were also seen in Tramadol group.

Cost effectiveness (CE) ratio for different groups was calculated by dividing the cost of treatment by its clinical

outcome (Total KOOS score) to yield the ratio in terms of rupees.

**Table 5: Cost effective analysis.**

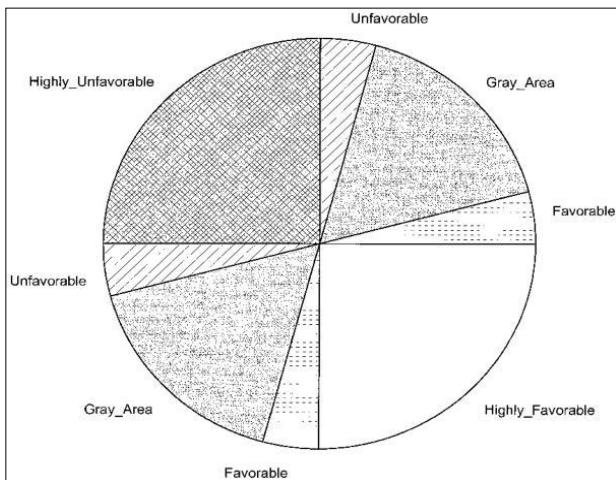
Intervention	QALY gained	Net cost	Average (cost/QALY)
Group 1 DIC + PPI	24.45	91+49=140	5.73
Group 2 TRMADOL	14.15	168	11.8

Diclofenac+PPI had maximum improvement in symptoms (24.45 QALY) when compared to Tramadol groups. The Average Cost effectiveness (CE) ratio of Diclofenac +PPI was more than the Tramadol. The mean cost is less with Diclofenac+PPI and more in Tramadol group. Diclofenac+PPI had maximum improvement in symptoms (24.45 QALY) when compared to Tramadol group.

The ICER for tramadol group is -2.72. The ICER for tramadol group is negative. The difference in the mean costs and effect in Tramadol in comparison with Diclofenac +PPI group when plotted on the cost-effectiveness plane fell in the fourth quadrant (Figure 3). This means that the new treatment is more costly and less effective, so it is highly unfavourable or should be rejected. Whereas Diclofenac + PPI group falls in 1<sup>st</sup> quadrant which indicates that the new treatment is costly but also more effective.

**Table 6: Incremental cost-effective analysis.**

Intervention group	Net cost	Difference	QALY Gained (~DALY eliminated)	Difference	ICER= diff in cost/ diff in quality
DIC + PPI	140		24.45		
TRAMADOL	168	168-140 =28	14.15	14.15-24.45= -10.3	-2.72



**Figure 3: The five regions in the cost effectiveness plane for decision making.**

**DISCUSSION**

The present randomized, open label parallel study was designed to compare controlled release (CR) tramadol formulation with sustained-release (SR) diclofenac plus proton pump inhibitor (PPI) in patients with osteoarthritic pain of moderate to greater intensity.

SR formulations offer the advantages of sustained blood levels, attenuation of adverse effects, improved patient compliance.<sup>13</sup> This is the reason we selected sustained release preparation of diclofenac and tramadol as study medication.<sup>14</sup> 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 our study and other studies.<sup>15</sup>

### ***Efficacy comparison of study intergroups in present study***

In the present study, scheduled, once-daily CR tramadol and SR diclofenac were used to a maximum dose of 200mg/day and 100mg/day, respectively. By using ANOVA test p-value >0.05 therefore there is no significant difference between mean pain, symptom, ADL, sports/rec, QOL and total scores with respect to treatment drugs among study groups at pre and post treatment. Beaulieu et al study showed similar result with 370.2mg of Diclofenac versus 164.8 mg for tramadol.<sup>16</sup> In an earlier study, IR tramadol was compared with IR diclofenac in OA patients.<sup>17</sup> Both medications were given as needed, to a maximum dose of 300mg/day for tramadol and 150mg/day for diclofenac. Correspondingly, patients experienced greater functional improvement in the overall WOMAC pain, stiffness and function scores in the present study, compared with the study, (26.8% versus 19.2% with tramadol, and 27.5% versus 24.8% with diclofenac).<sup>17</sup>

But as evident from the graphs mean scores for all the parameters has substantially increased in all the treatment groups with maximum increase in DIC+PPI group reflecting its maximum efficacy compared to tramadol group. This can be because diclofenac gets distributed in synovial fluid and has chondro protective and other action as mentioned like blockage of voltage-dependent sodium channels and acid-sensing ion channels (ASICs), positive allosteric modulation of KCNQ- and BK-potassium channels.<sup>18</sup> And addition of PPI may be responsible for increase efficacy due to its anti-inflammatory action as well as antisecretory action which decreases gastrointestinal adverse effect and increases compliance.<sup>19,20</sup>

The underlying mechanisms of PPI are not well established, and it is not clear that oral PPI dosing can achieve high drug concentrations in plasma and tissue that would be needed to produce some of the anti-inflammatory actions that have been observed in vitro.<sup>21</sup>

The inflammatory component of osteoarthritic pain is minimal. Perhaps osteoarthrosis would be more accurate term<sup>22</sup> That is the reason Tramadol and Diclofenac both drugs are found to be efficacious in management of osteoarthritic pain. This coincides with our results which are similar to previous studies where Tramadol and Diclofenac produced equal pain relief in OA.<sup>23</sup>

The American Pain Society suggests that tramadol can be used alone, or in combination with paracetamol or NSAIDs, for therapy at any stage during the treatment of a patient with osteoarthritis.<sup>24</sup>

### ***Adverse drug effects***

The present study showed a trend toward slightly higher incidences of adverse events with CR tramadol, compared with SR diclofenac.

Consistent with this atypical profile, and as recently summarized by WHO, no significant respiratory or cardiac side effects have been associated with tramadol when the drug is given at the recommended oral doses.<sup>25</sup> Tolerance, dependence, diversion and abuse also appear to be lower with tramadol than other opioids.<sup>25</sup> Similar to our study in an American post marketing surveillance study the rate of abuse was low, with only two cases per 100,000 patients in the first 18 months of availability, and a decline to one case per 100,000 patients in the succeeding 18 month period.<sup>25</sup> Most of the cases occurred in individuals with a history of substance abuse. In a second study of health care professionals the incidence of tramadol abuse or dependence was only 6.9 per 1000 patients per year.

The incidence of adverse events was also lower in a 12 week study (20% and 3% of patients during tramadol and diclofenac treatment respectively, compared with 55% and 29.7% in the study) which is consistent with the lower doses used when analgesics were prescribed on an as-needed basis.<sup>17</sup>

Adverse events usually occur at the beginning of tramadol therapy and diminish with continued treatment.<sup>25</sup> This may be another reason of less incidence of ADR in study where study duration was 12 wks.

However, patients receiving long-term NSAID therapy have risk of severe gastrointestinal symptoms, including ulceration and bleeding. NSAID-related ulceration and bleeding is estimated to result in up to 20,000 deaths each year in the United States. In most patients, and especially high-risk groups such as elderly patients, concurrent cytoprotective agents are recommended, increasing the cost of treatment. Diclofenac had a relative risk of serious cardio-vascular events of 1.40 (95% CI 1.16 to 1.70).<sup>26</sup>

For OA patients exhibiting gastrointestinal intolerance of NSAIDs, a trial course of tramadol would represent an alternative therapy without similar risks for gastrointestinal toxicities. The three-step ladder, proposed for cancer pain relief by the World Health Organization (WHO), is now widely used for all types of pain. Step 1 includes no opioid analgesics, step 2 weak opioids, and step 3 strong opioids.<sup>27</sup>

### ***Pharmacoeconomic evaluation***

Due to the impact of OA in our society and assuming that the analgesic efficacy of tramadol is equivalent to that of NSAIDs in the treatment of moderate pain, a pharmacoeconomic analysis is important to help optimize the treatment of pain in patients with OA.

### ***Cost effective analysis***

Through this cost-effectiveness analysis, in our study it has been shown that the drug with the lower cost is DIC+PPI (Rs140/patient), than tramadol (Rs168/patient) for two weeks. To avoid the appearance of GI AE, NSAIDs are

often prescribed with a PPI. The results of our study shows that despite the reduction in GI AE provided by the PPI, the cost of treatment with NSAIDs + PPI (140/two weeks) is superior to that of tramadol (168/two weeks). These results are in contrast to those shown previously in the Netherlands.<sup>28</sup> These authors found that tramadol is cost saving compared with NSAIDs + PPI when not considering kidney AE. We conducted cost effective analysis considering both health results and the cost for medical care. Cost effective ratio was more with Diclofenac + PPI. This superiority of diclofenac group is due to better efficacy and less cost compared to tramadol (Table 5). That is, one has to pay less for same quality of symptom relief.

To the best of our knowledge no studies regarding cost effective analysis of NSAID and Tramadol were conducted in India. We are not able to compare with other studies.

### **Incremental cost effectiveness ratio<sup>29</sup>**

The cost effective plane can be constructed for both the mean-based and median-based ICERs. The South East quadrant represents the situation when the new treatment is less costly and more effective, hence it is highly favourable. On the opposite side, in the North West quadrant, the new treatment is more costly and less effective, so it is highly unfavourable. In the North East quadrant, the new treatment is more costly but effective. Whereas Diclofenac + PPI group falls in 1<sup>st</sup> quadrant which indicates the new treatment is more costly and effective.

### **CONCLUSION**

The present study demonstrated no significant differences between CR tramadol and SR diclofenac + PPI at the end of the treatment period, not only with respect to pain intensity, but also for functional improvement and quality of life. For OA patients exhibiting gastrointestinal intolerance of NSAIDs, a trial course of tramadol would represent an alternative therapy without similar risks for gastrointestinal toxicities. Cost effective ratio was more with Diclofenac + PPI. This superiority of diclofenac group is due to better efficacy and less cost compared to tramadol. That is one has to pay less for same quality of symptom relief.

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