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SAFETY AND EFFICACY WITH GASTRIC TOLERABILITY OF THE FIXED DOSE COMBINATION OF ACECLOFENAC, PARACETAMOL AND RABEPRAZOLE IN THE TREATMENT OF ACUTE PAIN

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ABSTRACT

Pain is defined as "An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage". This definition recognizes that pain is a perception and not a sensation. The purpose of this study is to compare the safety and efficacy of our fixed dose combination with the reference for 6 month in 36 patient with rheumatoid arthritis. The combination of drugs Aceclofenac 100mg + Paracetamol 325mg + Rabeprazol 10 mg is a novel concept of anti-inflammatory properties with increase gastric tolerability. Pain was evaluated using Western Ontario and McMaster Universities Arthritis Index (WOMAC) & Visual Analog Scale **(**VAS). These scales are used to measure the pain index. The safety of the fixed dose combination in terms of pain after the treatment in test group was found to be 72% where as in reference it was about 55%. Hence it can be concluded that our fixed dose combination showed better therapeutic benefit than the reference drug.

KEYWORDS: Pain, rheumatoid arthritis, Aceclofenac, Paracetamol, Rabeprazol, anti-inflammatory.

PAIN

The most widely accepted definition of pain is the one used by The International Association for the Study of Pain.[1] It defines pain as "An unpleasant sensory and emotional experience

arising from actual or potential tissue damage or described in terms of such damage". This definition recognizes that pain is a perception and not a sensation.

One influential model described pain in terms of three hierarchical levels: a sensory-discriminative component (e.g.., location, intensity, quality), a motivational-affective component (e.g., depression, anxiety), and a cognitive- evaluative component (e.g., thoughts concerning the cause and significance of the pain.

TYPES OF PAIN

Pain is divided into two types:

1. Acute pain
2. Chronic pain

ACUTE PAIN

"Acute pain" is pain of sudden onset, lasting for hours to days and disappears once the underlying cause is treated. Acute pain has a clear cause. It could result from any illness, trauma, surgery or any painful medical procedures. Hence it is beneficial to the patient because but for the pain, the individual will ignore his illness resulting in complications and even death.

CHRONIC PAIN

Chronic pain is the pain that starts as an acute pain and continues beyond the normal time expected for resolution of the problem or persists or recurs for various other reasons It is not therapeutically beneficial to the patient.

Chronic pain is further divided into

1. Nociceptive pain
2. Neuropathic pain

3. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs),[2] are among the most widely used of all therapeutic agents worldwide. They are frequently prescribed for 'rheumatic' musculoskeletal complaints and are often taken without prescription for minor aches and pains

4. PHARMACOLOGICAL ACTIONS

NSAIDs include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect:

- Anti-inflammatory effects: modification of the inflammatory reaction
- Analgesic effect: reduction of certain sorts of pain
- Antipyretic effect: lowering of a raised temperature.
- There are two types of cyclooxygenase enzyme,namely COX-1 and COX-2.[3]
- COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets. It has a house-keeping role in the body being involved in tissue homeostasis.
- COX-2 is induced in inflammatory cells when they are activated, and the primary inflammatory cytokines-interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation. Most traditional NSAIDs in current use are inhibitors of both isoenzymes, though they vary in the degree of inhibition of each.[4]

ANALGESIC EFFECT

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because they decrease production of the prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin. Therefore, they are effective in arthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhoea, the pain of postpartum states and the pain of cancer metastases in bone-all conditions that are associated with increased prostaglandin synthesis. In combination with opioids, they decrease postoperative pain and in some cases can reduce the requirement for opioids by as much as one third. Their ability to relieve headache may be related to the abrogation of the vasodilator effect of prostaglandins on the cerebral vasculature.

MECHANISM OF ACTION

The main action of NSAIDs is, as stated above, inhibition of arachidonic acid-metabolising activity of COX.[5]

The cyclooxygenase enzymes are bifunctional, having two distinct activities: the main action, which gives PGG_2, and a peroxidase action, which converts PGG_2 to PGH_2. Both COX-1 and COX-2 inhibitors inhibit only the main cyclooxygenation reaction. Both COX-1 and COX-2 are associated with the membrane and each consists of a long channel with a bend at the end, the channel being wider in COX-2.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have three major pharmacologically desirable actions, all of which result mainly from the inhibition of arachidonic acid cyclooxygenase in inflammatory cells (the COX-2 isoenzyme), and the resultant decrease in prostanoid synthesis. They are:

- An anti-inflammatory action: the decrease in vasodilator prostaglandins (PGE_2, prostacyclin) means less vasodilatation and, indirectly, less oedema. Accumulation of inflammatory cells is not reduced.

ASPIRIN

Aspirin (acetylsalicylic acid) was amongst the earliest drugs synthesised and is now one of the most commonly consumed drugs, worldwide. It is relatively insoluble but its sodium and calcium salts are readily soluble. A newer member of this group is diflunisal.

Aspirin in non-inflammatory conditions

It is becoming increasingly clear that aspirin-previously thought of as an old anti-inflammatory workhorse-is now approaching the status of wonder drug in that it is of benefit not only in inflammation but in an increasing number of other conditions:

- Cardiovascular disorders: through the antiplatelet action of low-dose aspirin.[6]
- Colonic and rectal cancer: regular and sustained use of aspirin is reported to reduce (virtually halve) the risk of cancer of the colon and possibly also rectal cancer, which between them cause 25000 deaths a year in the UK (but note that the selective COX-2 inhibitors may be more effective).

Pharmacokinetic aspects

Aspirin, being a weak acid, is largely un-ionised in the acid environment of the stomach and its absorption is thus facilitated. Most absorption, however, occurs in the ileum because of the extensive surface area of the microvilli.[7] Aspirin is hydrolysed by esterases in the plasma and the tissues-particularly the liver-yielding salicylate.

Unwanted effects

Salicylates may produce local and systemic toxic effects.

Aspirin has many of the general unwanted effects of NSAIDs outlined above. In addition there are certain specific unwanted effects that occur with aspirin and other salicylates.

MATERIAL AND METHODS

FACTORS TO BE IDENTIFIED

- Efficacy and safety within finished population.
- Pharmacoeconomics.

1.1 DATA FOCUS

- Efficacy
- Adverse events

1.2 DESIGN FEATURES

- Randomized
- Controlled
- 2 treatment arms
- Observational

STUDY DURATION

- 6 months

1.3 POPULATION

Individuals with target disease.

1.4 SAMPLE SIZE

- 36 Patients

STUDY ARMS

Test: Aceclofenac, Paracetamol, and Rabeprazole.

Reference: Aceclofenac, Paracetamol

1.5 METHOD

The study was conducted in the department of rheumatology, OMNI HOSPITAL, Hyderabad.

- Patients, who satisfied the eligibility criteria, were accrued during the study period.
- These patients were randomized into 2-Arms, and were then evaluated according to the treatment protocol.

  Patients were evaluated on the basis of their
- Registration no

- Name
- Age (yrs)
- Sex
- Weight
- Height
- Heart rate, BP
- Adverse events-response rates

1.6 OBSERVATION

The following observations were made:

- Median age distribution
- Sex ratio distribution
- The Two treatment groups
- Commonly observed laboratory adverse effects
- Response rates

Subject Profile

Number of subjects: 18 subjects of both gender

- Duration of the study: 6 Months
- Site: Omni Hospital-Kothapet, Hyderabad

STUDY INCLUSIVE AND EXCLUSIVE CRITERIA

Inclusion Criteria

- Healthy adult male and female subjects between the ages of 21-55 years inclusive.
- RA male and female subjects between the ages of 21-70 years inclusive
- Evidence of active RA disease
- Inadequate response to biologic or non-biologic DMARDs
- Subjects will be required to be on background therapy with methotrexate.
- Subjects must have at least > 4 score on the VAS scale for the inclusion in the study at the time of screening
- Female subjects of child-bearing potential: subject is not pregnant.

Exclusion Criteria:

- BMI <18 or >32 kg/m2

- Clinically significant findings in physical exams and laboratory tests at screening and/or baseline
- Unwilling to abstain from alcohol for 48 hours prior to study start, during CRU confinement, as applicable, and for 48 hours prior to study visits.
- Unwilling to abstain from exercise more strenuous than walking during CRU confinement, as applicable, and for 48 hours prior to study visits.
- Use of any prescription, non-prescription, or herbal medications as well as supplements or vitamins within 4 weeks prior to dosing, unless approved by the Investigator.
- Smoking more than 10 cigarettes, or the equivalent, per day.
- Current or previous history of inflammatory joint disease other than RA
- Evidence of extra-articular RA disease or systemic involvement
- Currently taking any medications other than those allowed per protocol guidelines
- Any surgical procedure including bone or joint surgery within 12 weeks prior to dosing
- Use of intra-articular (IA), intramuscular (IM), or IV corticosteroids for RA
- Neuropathies and neurovasculopathies
- Concomitant use of statins while on study.

ASSESSMENT OF SAFETY AND EFFICACY EVALUATIONS

Analgesic pain can be evaluated by two scales.

1. Western Ontario and McMaster Universities Arthritis Index (WOMAC)
2. Visual analogue scale (VAS)

ASSESSMENT OF WOMAC

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints.

CONTENT

The WOMAC consists of 24 items divided into 3 subscales

Pain (5 items)

During Walking Using Stairs In Bed Sitting Or Lying Standing.

Stiffness (2 items)

After first waking and later in the day

Physical Function (17 items)

Stair Use Rising From Sitting Standing, Bending Walking Getting In / Out Of A Car Shopping Putting On / Taking Off Socks Rising From Bed Lying In Bed Getting In / Out Of Bath Sitting Getting On / Off Toilet Heavy Household Duties Light Household Duties.

Method of Delivery

Patient self-report questionnaire, accompanied by instruction sheet.

Description

The WOMAC Index was developed to assess and quantify pain, joint stiffness and disability related to osteoarthritis of the knee and hip. It has also been used with arthroplasty (joint replacement surgery) populations. The Index contains 24 questions, 5 related to pain, 2 to stiffness and 17 to physical function. It can be used to monitor the course of the disease or to determine the effectiveness of a variety of interventions (pharmacologic, surgical, physiotherapy etc.). It provides an excellent look at a patient's functional capacity and complements the more objective data provided by magnetic resonance imaging, arthroscopy, cartilage biopsy, and radiographs.

VISUAL ANALOG SCALE

The VAS is another validated approach to pain measurement and is conceptually similar to an NRS. The most common VAS consists of a 10-cm line with one end labeled "no pain" and the other end labeled "worst pain imaginable." The patient marks the line at the point that best describes the pain intensity. The length of the line to the patient's mark is measured and recorded in millimeters. The main theoretical advantage of the VAS is that it does not limit pain to 10 discrete levels of intensity, permitting a more detailed rating of pain.

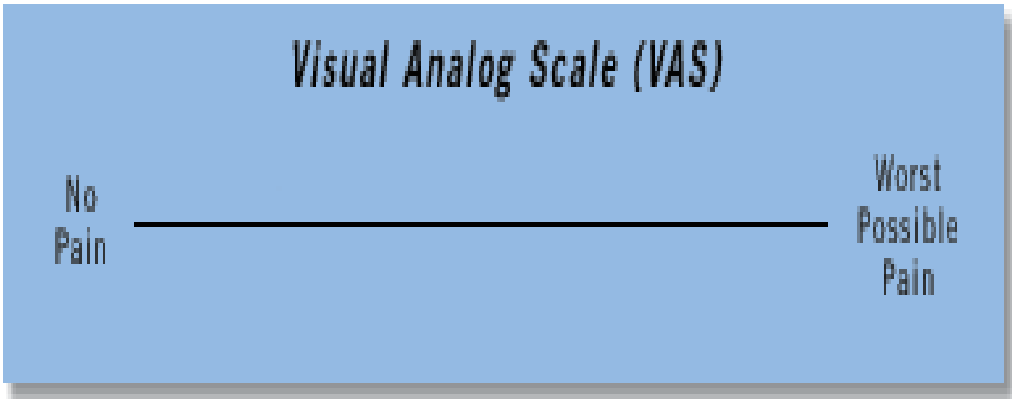


Figure No.6: Visual Analogue Scale (VAS)

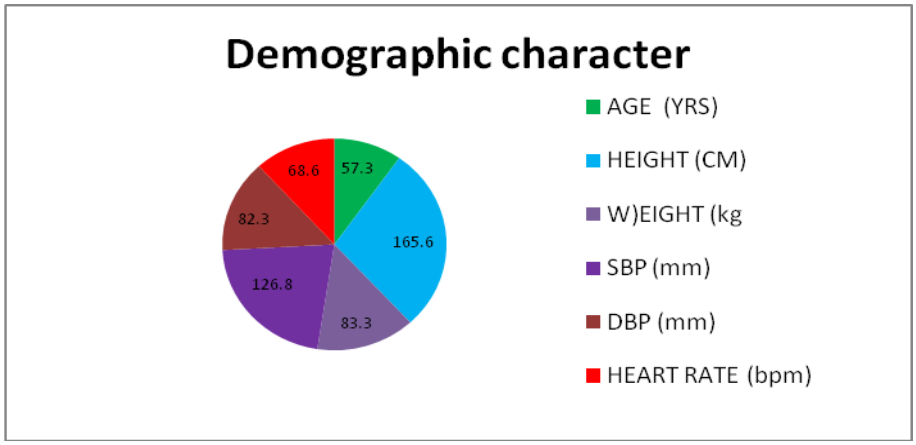
RESULTS

- Acute pain is the most common, and it is often associated with significant disability and an impaired quality of life. Clinical and radiographic surveys have found that the prevalence of osteoarthritis increases with age from 1% in people <30 years to 10% in those <40 years to more than 50% in individuals >60 years of age.
- Although there are no curative therapies currently available for pain, individualized treatment programs are available to help relieve pain and stiffness, and to maintain and/or improve functional status.
- Total 56 subjects were enrolled in the study, due to inclusive and exclusive criteria 20 patients were withdrawn from the study. Hence 36 subjects were randomized into 2 groups, test group (18) and reference group(18).
- The informed consent was received from subjects. The data was taken into case report forms.
- Subjects were randomized and baseline characteristics were collected from patients like Weight, BP, Age, Gender , Height, Heart Beat which are shown in the table 1, and are presented in the graph 1, 2 .The treatment was given to the Patient at the first visit . Subjects were asked to take the investigational product once daily for 4 weeks.
- The treatment was asked to be stop at the end of 4th week. The efficacy assessment was done by asking the patients to fill the questionnaires and is noted in the case report form.

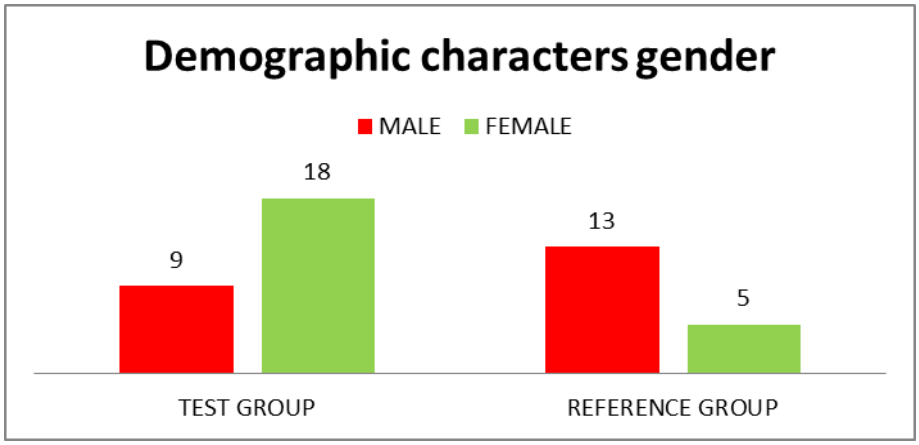
SUBJECTS ENROLLED, BASELINE CHARACTERICS:

Demographic characters of the subjects are described in the table below. Various parameters taken into account were Age, Sex, Height, Weight, SBP, DBP and Heart Rate.

Demographic Characters	**TEST Group-1 (n= 18)**	**REFERENCE Group -II (n=18)**
Age (Years)	57.3 ±9.64	57.6 ±9.98
Sex: male/ female (%)	(9/18) 50%	(13/18) 72.2%
Height (cm)	165.6± 9.80	165.5± 8.63
Weight (Kg)	83.3 ±15.3	86.4± 21.3
SBP (mm Hg)	126.8± 8.63	128.8 ±11.3
DBP (mm Hg)	82.3± 6.53	80.4± 9.62
Heart Rate (bpm)	68.6± 7.52	66.5± 8.63



Graph No.1- Demographic Character

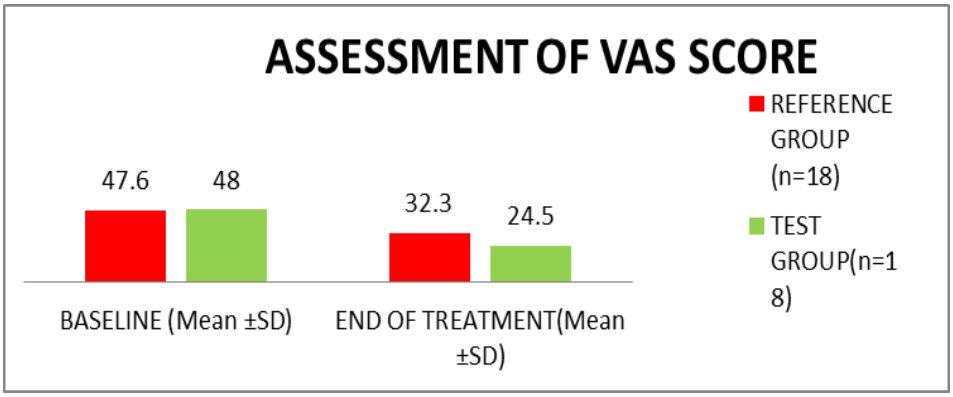


Graph 2: Sex Distribution

- Table no 3 presents the assessment of vas score in both the groups. The response was taken before and after the treatment, the vas score denotes that there is significant change for before and after treatment, which is presented in terms of mean and SD. Graph no 4 represents the reduction in the vas score before and after the treatment in both groups.

Table no: 3 Assessments Of Vas Score

Parameter and Treatment (VAS)	Baseline (Mean± SD) (n=18)	End of treatment 4 weeks (Mean± SD) (n=18)
Reference group	47.6 ± 9.7	32.3 ± 9.5
Test group	48.0 ± 6.0	24.5 ± 11.9



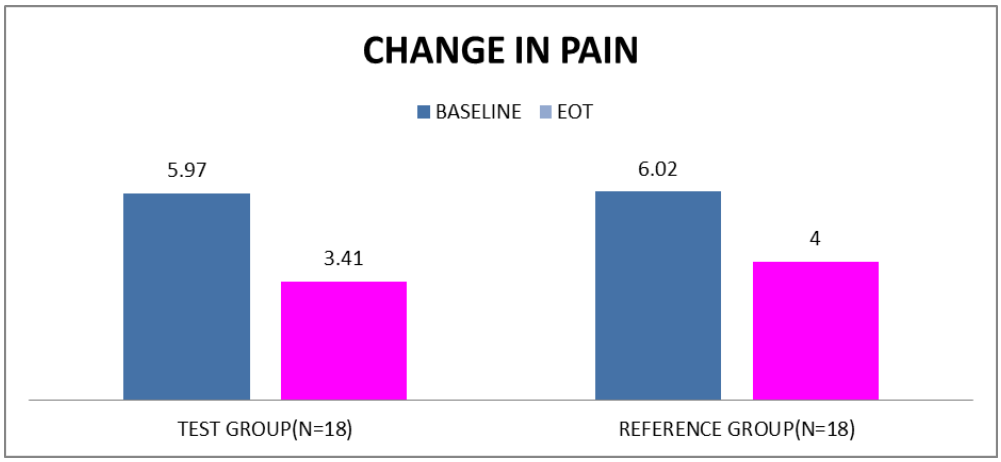
Assessment of Vas Score

Table no 4: Assessment of WOMAC

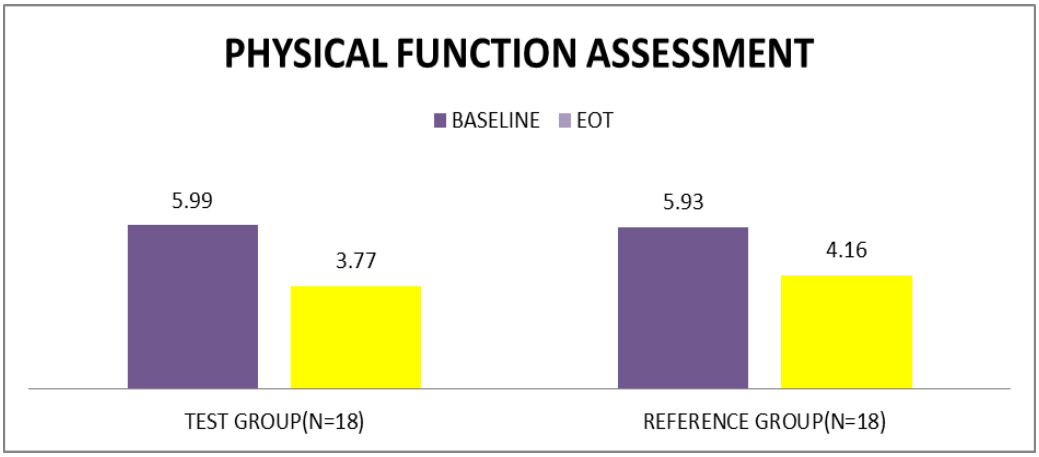
Category/Treatment	No of Patients	Mean (±SD) WOMAC Score	
		Baseline	Final
Pain	18	5.97± 1.46	3.41 ±1.82
TEST REFERENCE	18	6.02± 1.36	4.00 ±1.91
Joint stiffness	18	6.63± 1.71	4.25 ±2.08
TEST REFERENCE	18	6.58± 1.88	4.59 ±1.99
Physical function	18	5.99± 1.45	3.77 ±1.76
TEST REFERENCE	18	5.93 ±1.46	4.16 ±1.82
Overall	18	6.09 ±1.35	3.72 ±1.70
TEST REFERENCE	18	6.08 ±1.36	4.19 ±1.79

Assessment of womac

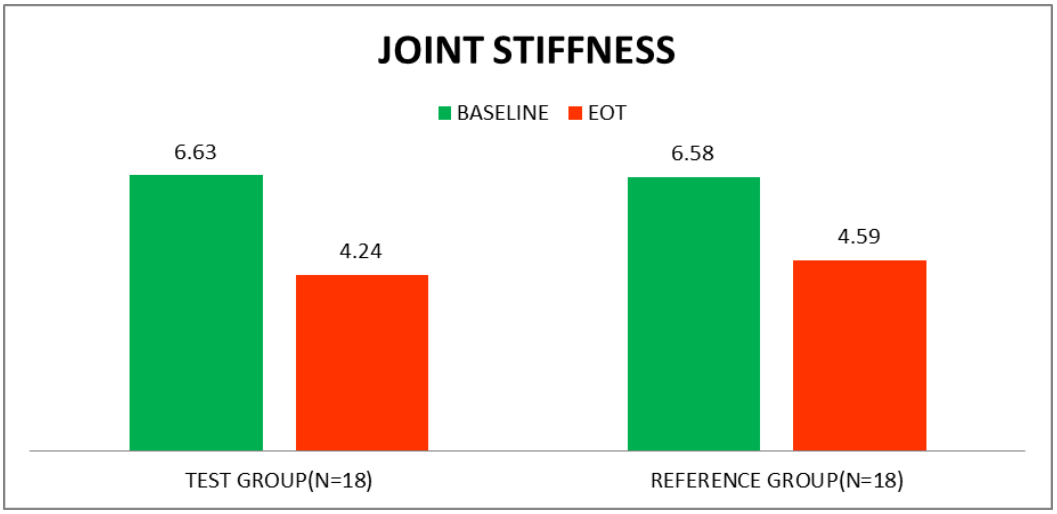
1. Joint Stiffness
2. Pain
3. Physical functioning
4. Overall



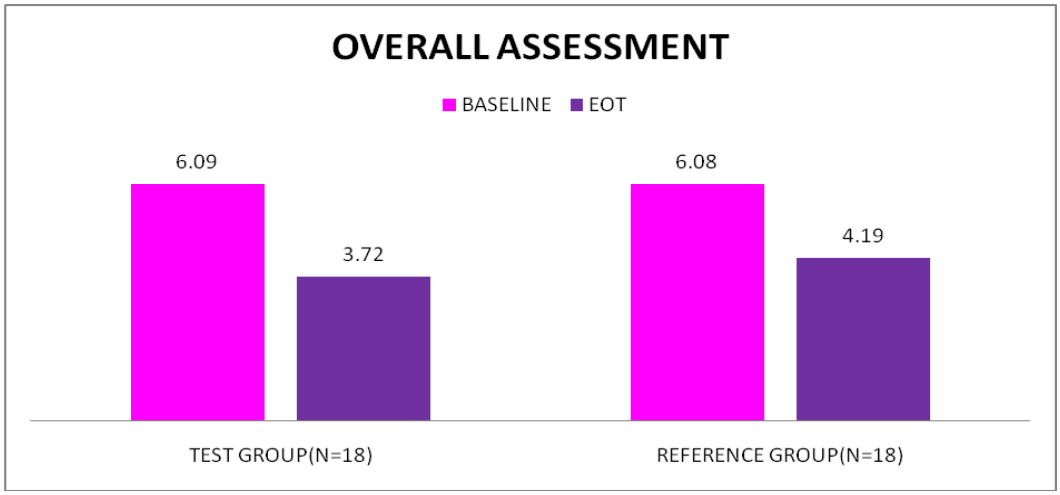
Graph No 10: Change In Pain



Graph No 11: Physical Function Assessment



Graph No 12: Joint Stiffness

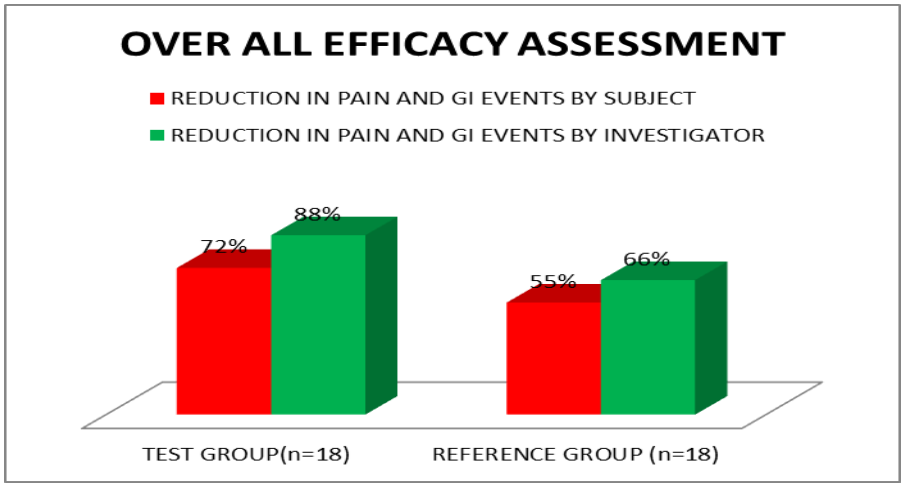


Graph no 13- Overall assessment.

- Table 4 presents the overall efficacy assessment given by the subject and doctor. It is the total efficacy response measured in terms of the reduction in vas score by subjects in test group is 72% and by investigator 88% , where as in reference group by subjects it is 55% and by investigator 66%. Graph 5 represents the percentage of pain relief in both groups.

Table no 5- over all assessment score

OVER ALL EFFICACY ASSESSMENT	TEST GROUP (N=18)%	REFERENCE GROUP (N=18)%
Reduction in pain and gi events by subject	13 (72%)	10 (55%)
Reduction in pain and gi events by investigator	16 (88%)	12(66%)



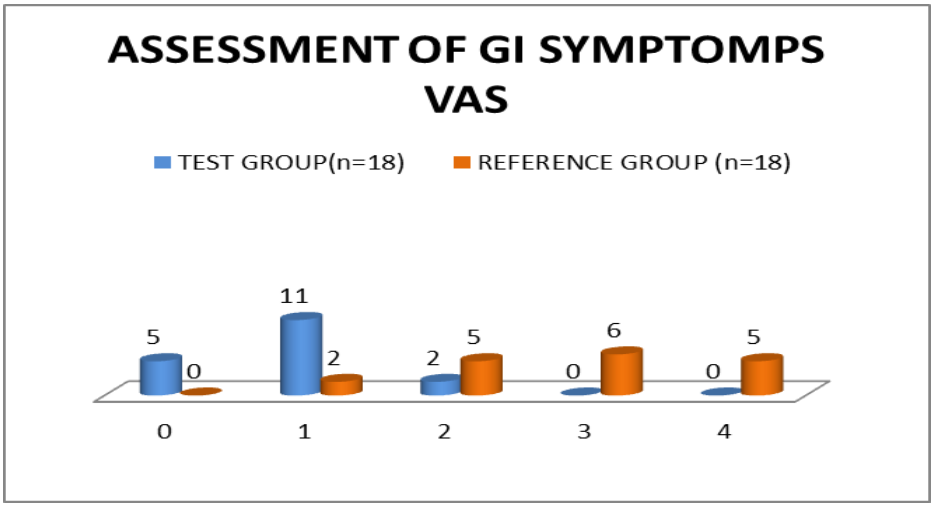
Graph no 14: Overall assessment score

- Table 5 represents gi vas score, the gi vas score gives the grades of symptoms of gi , due to NSAIDS effect. There are 0,1,2,3,4 grades according to gi vas depending on the symptoms or severity the subject would be asked to choose the grade.
- The GI score for both the groups were collected, in test group there were 5 subjects in 0 grade, and 11 in grade 1, 2 in 2nd grade and o subjects in 3rd and 4th grade were reported, where as in the reference group 5 subjects in 4th grade were reported. 6 in 3rd, 5 in 2nd, 2 in 1grades and 0 in 0 grades were reported.

Table no 6: Assessment of gi vas score

GI SYMPTOMS SEVERITY GRADES	TEST GROUP (N=18)	REFERENCE GROUP (N=18)
O	5	0
1	11	2

2	2	5
3	0	6
4	0	5



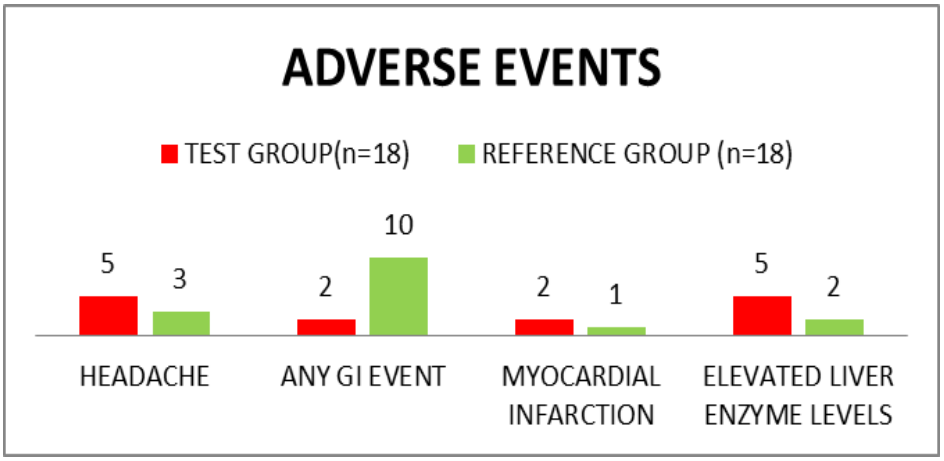
Graph no 15: Assessment of GI vas score

- There was significant difference in gi vas score, it is presented graphically in 6th graph.
- The safety assessment was done on the basis of number of adverse events reported by the subjects. There were no serious adverse reaction in any subject, the adverse events reported are presented in graph no 7.They are headache, MI, elevated liver enzyme levels, gi disturbances were reported. There is a significant difference in the both groups.
- The test group subjects showed better efficacy in terms of pain management and gastric tolerability when compared to the reference group.

SAFETY ASSESSMENT

Table no 7: Adverse events reported:

ADVERSE EVENTS	TEST GROUP	REFERENCE GROUP
HEADACHE	5	3
ANY GI EVENT	2	10
MYOCARDIAL INFARCTION	2	1
ELEVATED LIVER ENZYME LEVELS	5	2



Graph no. 16: Adverse events reported:

DISCUSSION

Non steroidal anti-inflammatory drugs (NSAIDs).[8] are effective anti-inflammatory and analgesic agents and are among the most commonly used classes of medications worldwide. However, their use has been associated with potentially serious dose-dependent gastrointestinal (GI) complications such as upper GI bleeding.

Although most studies involve the perioperative setting, similar results have been obtained in other acute pain states, such as acute musculoskeletal pain, migraine, etc. Non-steroidal anti-inflammatory drug (NSAID) toxicity in the upper gastrointestinal tract is the most common serious drug-induced toxicity reported to drug regulatory authorities.

Although gastroprotective therapies are available, they are underused, and patient and physician awareness and recognition of some of the factors influencing the development of NSAID-related upper GI complications are limited. Proton pump inhibitors are the co-medication of choice as they effectively reduce gastrointestinal adverse events of NSAIDs.[9] and are safe even in long-term use. Co-medication with vitamin C has only been little studied in the prevention of NSAID-induced gastropathy.

The combination of Paracetamol, Aceclofenac and Rabrprazole may show improved efficacy in reduction of pain and also the gastric intolerability is maintained when compared with combination of only NSAIDS in patients suffering with acute pain.[10] The study was conducted at OMNI hospitals, Hyderabad.

The results from the study suggest that the IP showed greater efficacy in reduction of pain (VAS, WOMAC) and in maintaining the gastric intolerability.[11]

Further long term studies should be done on the combination of drugs to check the safety and efficacy and gastric intolerability.

CONCLUSION

- The study was conducted in OMNI HOSPITALS, HYDERABAD. This comparative study was not done on Indian patients as per the literature review. Beneficial effects of combination therapy can be accounted for only by a temporary restoration. Scores similar results were observed for VAS scores but the gastric tolerability is reduced in subjects with arthritic condition.
- Although both the treatments measured by WOMAC & VAS score, test group was found to be more effective. The study suggests that the combination therapy is safe in patients suffering with pain and take NSAIDS every day. Use of Rabeprazole found to be safe in the test group.[12]
- The test group results were found to be safe and effective than the reference group.

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REFERENCES

1. Brater DC: Renal effects of cyclooxygyenase-2-selective inhibitors. J Pain Symptom Manage., 2002; 4: S15-20; discussion S21-3.
2. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs Meta-analysis of randomised trials. BMJ., 2006; 332(7553): 1302-8.
3. Solomon DH, Avorn J, Sturmer T, Glynn RJ, Mogun H, Schneeweiss S. New users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk. Arthritis Rheum., 2006; 54(5): 1378-89.
4. FitzGerald GA, Patrono C: The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med., 2001; 9; 345(6):433-42.
5. Graham DJ: COX-2 inhibitors, other NSAIDs, and cardiovascular diseases: the seduction of common sense. JAMA., 2006, 4; 296(13): 1653-6.

6. Role of paracetamol in the acute pain management.Kehlet H[1], Werner MU.Département de Chirurgie Digestive 435 et Centre Anti-douleur, Départementd'Anesthésie, HôpitalUniversitaire de Hvidovre, Hvidovre, Danemark. henrik.kehlet@hh.hosp.dk
7. Jan C Becker, Wolfram Domschke, and Thorsten Pohle. Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond Br J Clin Pharmacol., 2004; 58(6): 587–600.
8. Hawkey CJ. Non-steroidal anti-inflammatory drug gastropathy: causes and treatment. Gastroenterology., 2000; 119: 521-535
9. Graham DY. Helicobacter pylori and nonsteroidal anti-inflammatory drugs: interaction with proton pump inhibitor therapy for prevention of nonsteroidal anti-inflammatory drug ulcers and ulcer complications--future research needs. Am J Med., 2001; 110(1A): 58S-61S.
10. Lahoti G, Navjeevan. To evaluate efficacy and safety of fixed dose combination of aceclofenac + paracetamol + thiocolchicoside (acenac-MR) in the treatment of acute low back pain. J Indian Med Assoc., 2012; 110(1): 56-8.
11. Lee JH, Lee YC, Jeon SW, Kim JW, Lee SW. Guidelines of prevention and treatment for NSAID-related peptic ulcers. Korean J Gastroenterol., 2009; 54(5): 309-17
12. Hawkey CJ, Atherton JC, Treichel HC, Thjodleifsson B, Ravic M. Safety and efficacy of 7-day rabeprazole- and omeprazole-based triple therapy regimens for the eradication of Helicobacter pylori in patients with documented peptic ulcer disease. Aliment Pharmacol Ther., 2003; 17(8): 1065-74.