

A Comparative Study of Amtolmetin Guacil and Diclofenac Sodium in Patients with Knee Osteoarthritis

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Abstract

Introduction: Management of pain in patients with knee osteoarthritis remains a challenge due to patients' age, comorbidities, necessity of medicines such as Nonsteroidal Anti-Inflammatory Agents (NSAIDs) should be taken for a long period, and this raises the requirements for well-tolerated medicinal product such as amtolmetin guacil whose gastro sparing action is mediated through increasing of Nitric Oxide-synthesis.

Patients and methodology: Fifty patients aged 50-69 years with knee osteoarthritis of stage II- III by Kellgren & Lawrence scale, were enrolled in the study. Patients were divided into 2 groups. Group I (30 patients) was assigned for amtolmetin guacil (AMG) tablets, 600 mg twice daily (Niselat, produced by Dr Reddys Laboratories Ltd) and group II (20 patients) was assigned for diclofenac sodium (DS) tablets, 50 mg twice daily. Duration of treatment was 1 month. Patients were assessed by WOMAC questionnaire, Lequesne Index, functional movement assessment. All adverse events reported were documented during the study period.

Results: The efficacy of treatments, as assessed by pain intensity (WOMAC) showed that AMG was associated with a significant reduction in pain intensity as compared to diclofenac by 30 days, 55% and 30% respectively. The improvement in functional abilities was significantly better with AMG as compared with DS by day 20 (35% and 24% respectively), and day 30, (50% and 30% respectively). AMG was well tolerated and was not associated with gastrointestinal adverse effects and hepatic function. In patient who completed 30 days of treatment, AMG was more frequently assessed as having "improvement" or "substantial improvement" as compared to DS.

Conclusions: Amtolmetin guacil is an effective treatment for knee osteoarthritis and provides better reduction in pain and improvement in functional abilities of patients. The better safety profile of AMG makes it a choice of treatment for the older patients and patients with high risk of gastrointestinal complications. Good patient tolerance to the treatment and high level of patient assessment of treatment efficacy should positively impact compliance and treatment efficacy.

Introduction

Osteoarthritis (OA) is one of the most prevalent types of arthritis and chronic joint disorders, which could lead to severe pain and chronic disability particularly in the knee OA [1]. Despite the availability of many analgesics, treatment of pain in knee osteoarthritis remains a complex problem as majority of knee osteoarthritis patients are aged, have comorbid conditions, and require medication for a long duration of time [2,3]. Hence, safety profile of these therapeutic agents is of key importance. The most frequently occurring adverse events (AEs) of non-steroidal anti-inflammatory drugs (NSAIDs) for OA are gastrointestinal AEs [4,5]. Risk factors for the NSAID-induced peptic ulcers, one of the most serious features of gastropathies, are: history of complicated peptic ulcer, 2 and more NSAIDs use, NSAIDs combination with aspirin, NSAIDs in high doses, combined use of NSAIDs and anticoagulants, anamnesis of non-complicated peptic ulcer, age more than 70 years, and combined use of NSAIDs and glucocorticoids [6,7]. Patients with knee osteoarthritis often have one or more risk factors listed above: old age, aspirin prophylaxis, anticoagulants use and uptake of a few NSAIDs due to absence of expected effect from single drug. Hence, these patients fall in high risk category for development of gastropathies.

A few approaches for decreasing risk of development of gastrointestinal complications associated with NSAIDs are in practice. Drugs such as proton pump inhibitors, H2 blockers, synthetic prostaglandins analogues, *Helicobacter pylori* eradication treatment may be used to prevent the occurrence of NSAIDs induced GI side effects [8]. Also, using enteric coated tablets, selective COX inhibitors, and increasing of NO-synthesis in gastric mucosa are few options available [8-13]. NSAID which effectively alleviate pain and have gastroprotective properties are the drug of choice for the patients with knee osteoarthritis. This further benefits by limiting the pill burden used to control the GI adverse effects. This is of special importance for the elderly patients on medications for the treatment of comorbidities.

Benefit-risk of selective COX inhibitors in patients with cardiovascular disease is still a topic of debate [9]. Majority of older patients with knee osteoarthritis have cardiovascular and gastrointestinal high risks. Amlolmetin guacyl (AMG) was shown to alleviate pain and inflammation, and have a favourable GI tolerability profile as compared to traditional NSAIDs [10-14]. Efficacy of AMG was similar to the other NSAIDs compared in the trials [10-13]. Studies have shown significantly high endoscopy score with other NSAIDs' group (27.6%) compared to AMG (21.4%) and the number of patients with severe gastric and/or duodenal ulcer after treatment was significantly more in other NSAIDs' group (14.2%) compared to AMG (4.3%) [13]. AMG increases nitric oxide (NO) which causes the gastric sparing effect. This is mediated by of the presence of vanillic moiety in the AMG, which stimulates capsaicin receptors and releases Calcitonin Gene Related Peptide (CGRP) and consequently increases NO, hence counter balancing the deleterious effects of prostaglandin depletion due to COX inhibition and providing mucosal protection [14]. Despite their favourable characteristics, NO-donors have not adequately been studied for comorbid and polypharmacy conditions. There is limited data available comparing the efficacy and safety aspects of AMG with diclofenac in older knee osteoarthritis patients. We conducted this study to compare the efficacy and safety of AMG with diclofenac sodium in patients with knee osteoarthritis aged 50-69 years.

Material and Methodology

This was an open label, controlled, randomized, parallel groups study. Randomization of patients was done 3:2 at study site to receive oral AMG or diclofenac sodium. The objective was to study the efficacy and safety of AMG in patients with knee osteoarthritis of stage II-III Kellgren & Lawrence scale [15], in comparison with treatment with diclofenac sodium. The study was conducted during the period November 2014 - April 2015, in accordance to the Declaration of Helsinki, and Good Clinical Practice (GCP). The study protocol and any amendments to the same were approved by the Institutional Review Board (IRB) of the respective study centre. After obtaining detailed information, patients signed Informed Consent form for participation in the study.

Patients of both sexes aged 50-69 years with knee osteoarthritis stage II-III by Kellgren & Lawrence scale [15] (to maintain homogeneity of the disease condition), with pain syndrome intensity more than 40 mm by Visual Analogue Scale (VAS), were enrolled in the study. Diagnosis of knee osteoarthritis was based on clinical and X-ray evaluation. Patients who didn't take any NSAIDs prior 7 days and corticosteroids prior 4 weeks were eligible for the study. Patients with known hypersensitivity to AMG, its metabolites, and any component of drug formulation, and allergic reactions to any NSAIDs, acute peptic ulcer, gastrointestinal bleeding or perforation,

heart failure, hepatic or renal impairment, were excluded from the study. Patients did not receive any other form of therapy such as exercise therapy, physical therapy as per Unified Clinical Protocol for primary, secondary and tertiary medical care and medical rehabilitation "Osteoarthritis" of Ministry of Health of Ukraine; 2016 [19]. Study was conducted at State Institution D. F. Chebotariov Institute of Gerontology of National Academy Medical Sciences of Ukraine, Ukrainian Scientific-Medical Center for the Problems of Osteoporosis.

Patients were randomized 3:2 by random choice by the doctor in to 2 groups; 30 Patients in group I received therapy with oral AMG (Dr Reddys Laboratories, India) 600 mg twice daily, and 20 patients in group II received diclofenac sodium tablets, 50 mg twice daily, with food intake; for 30 days duration.

Study methods

Clinical evaluation for pain, joint stiffness and laboratory tests (full blood count, ESR, ALT, AST, cholesterol, glucose) were performed at the beginning and at the end of the Study. Dynamics of intensity of pain syndrome and functional ability of knee joints were evaluated by Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) scale and Lequesne Index at the beginning of the study and every 10 days, till end of the study duration of 30 days [16,17]. The evaluation of the treatment efficacy was done by Likert scale; significant improvement, improvement, absence of treatment effect and reported worsening [16,17]. All adverse events reported were documented during the study period and the risk of emerging of gastrointestinal AEs were estimated.

A total of 50 patients were planned for the study; 30 patients on AMG and 20 patients on diclofenac sodium, considering the better tolerability of AMG from previous studies [10-14]. Treatment outcomes between groups were compared by Student's t-criteria and descriptive statistics was used for other parameters. Results of the study were analysed by Statistika 10.0, Copyright StarSoft Inc.,1984-2011. Critical level of reliability during checking of statistical hypotheses was $p < 0.05$.

Results

A total of 50 patients were enrolled in the study; 30 patients on AMG and 20 patients on diclofenac sodium. The baseline characteristics of patients at the beginning of the study in both groups were similar in terms of age, anthropometrics and pain syndrome intensity (Table 1).

The efficacy as assessed by pain intensity (WOMAC) showed that AMG was associated with a significant reduction in pain intensity as compared to diclofenac by day 30 (55.1% and 29.9%, respectively) (Figure 1).

Table 1: Baseline characteristics.

Groups	Age, years	Weight, kg	Height, cm	Pain intensity (VAS, mm)
Group I (AMG) Mean±SD	60.8±8.7	86.7±13.3	166±7.8	5.7±1.5
Group II (Diclofenac) Mean±SD	63.1±7.9	87.1±17.5	165±8.4	5.9±1.8
P value	0.34	0.65	0.74	0.36

Stiffness, as assessed by WOMAC, showed an early significant reduction for AMG vs diclofenac by day 20, 31% vs 18%. By day 30, a trend towards better reduction was observed with AMG as compared to diclofenac (Figure 2).

Functional abilities of the patients improved in both groups. The improvement was significantly better with AMG as compared with diclofenac by day 20 and 30, 35% and 24%, and 54% and 30% respectively (Figure 3).

With the reduction in pain, the functional joint condition also improved significantly in patients on AMG. By day 30, as compared to baseline, the reduction in Lequesne Index, 3- and 15-meter test, and timed up and go test were significantly better with AMG, similar benefit was not observed with diclofenac (Figure 4).

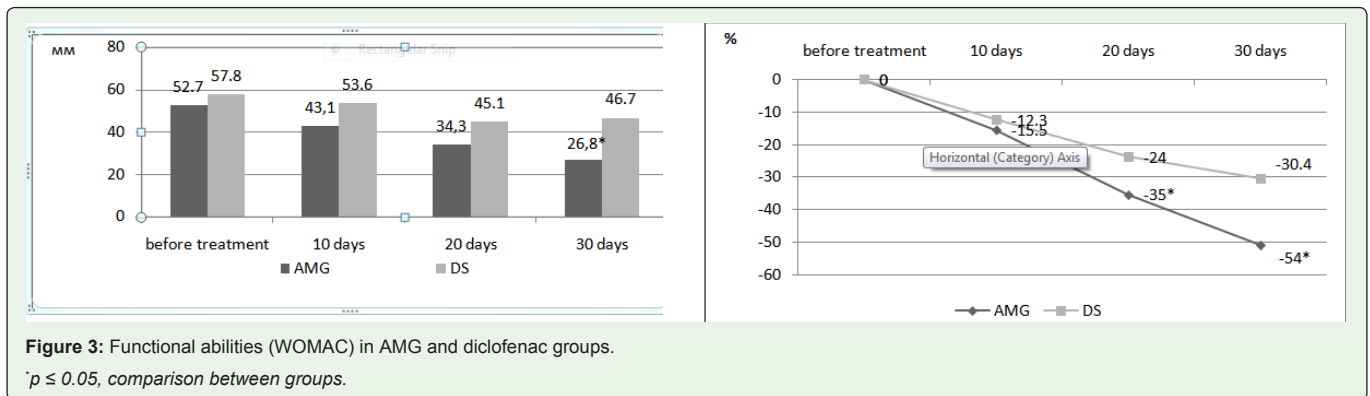
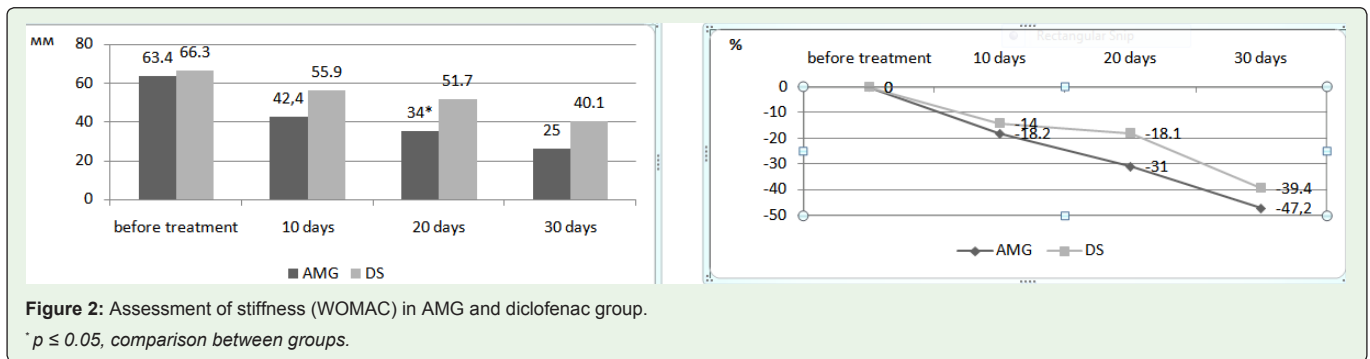
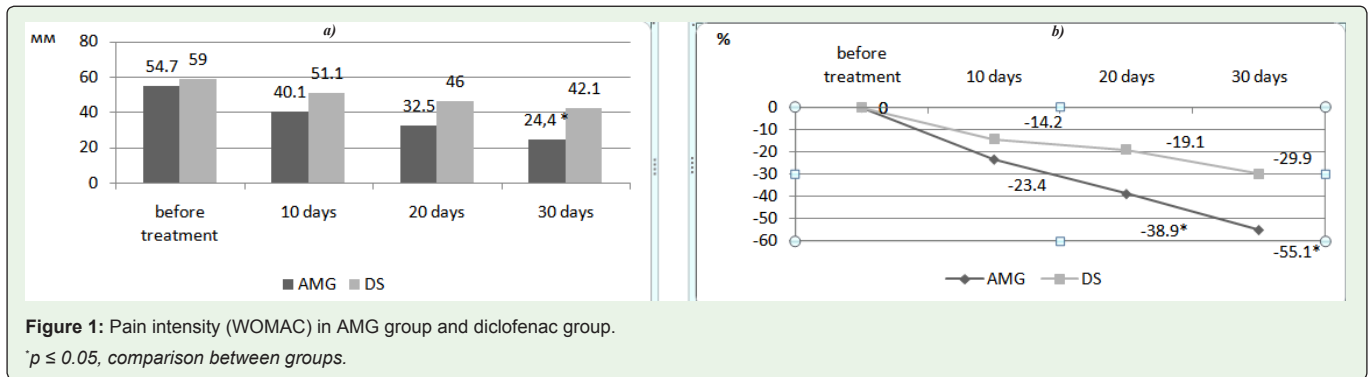
Patients who took AMG gave better evaluation on Likert scale for the treatment course efficacy. Fourteen (50%) patients from the

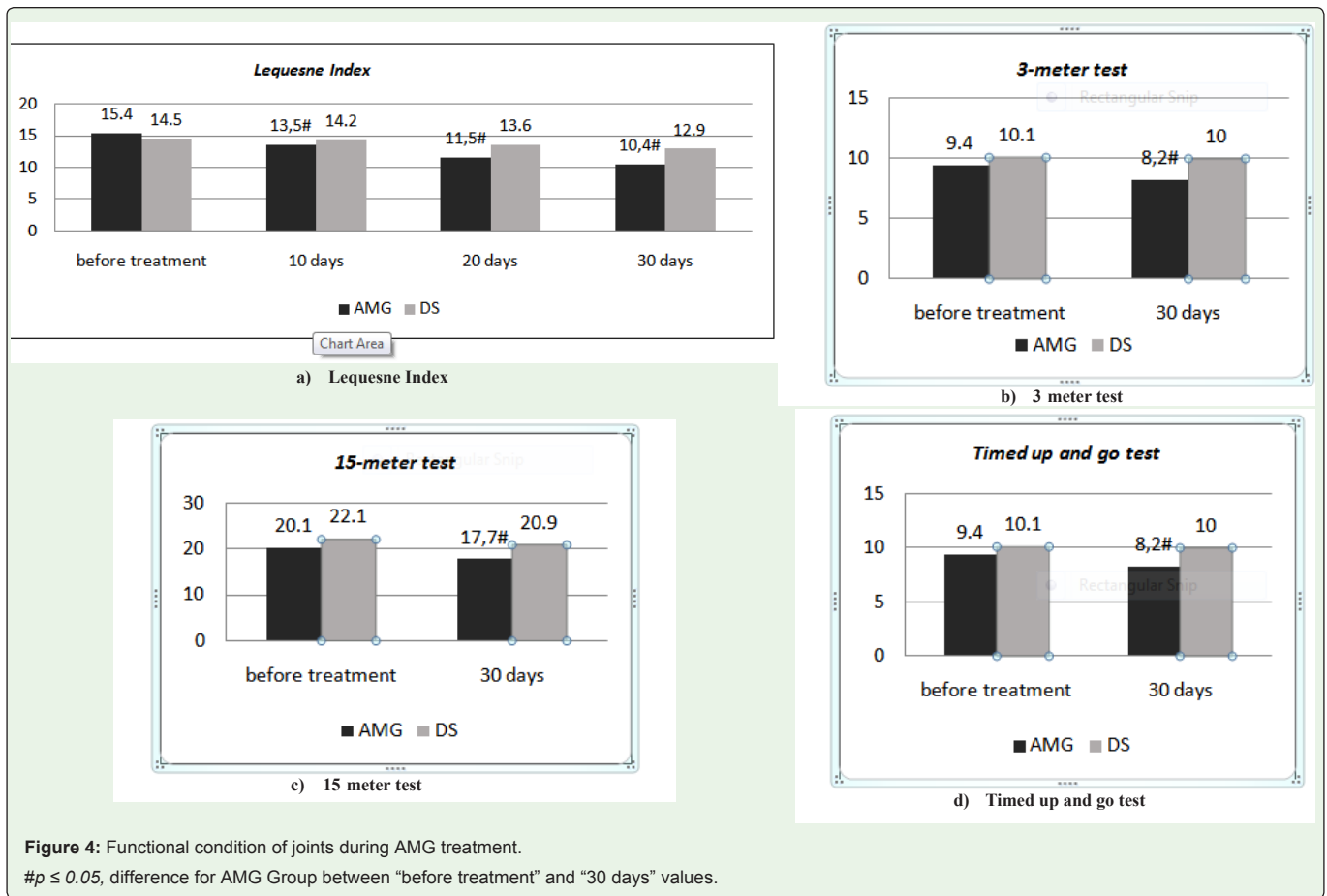
Group I and 3 (18.8%) patients from the Group II reported significant improvement, (4.3, $p < 0.05$). Ten (35%) patients from the Group I and 6 (37.5%) patients from the Group II reported improvement, 1 (7.5%) patient and 5 (31.2%) patients respectively reported absence of treatment effect, 2 (7.5%) patients and 2 (12.5%) patients respectively reported worsening.

In general, more patients in the AMG group were satisfied with the treatment (24, 85%) versus 9 (56%) patients in diclofenac sodium group (4.6, $p < 0.05$).

Safety and tolerability

Among the patients who received AMG, all the patients completed 10 days of treatment and 2 patients refused to participate further in the study: one patient due to complete relief from pain thereby requiring no further treatment, and the other patient refused due to episode of increased arterial pressure, which in patient’s opinion





was associated with treatment drug. All other patients completed 30 days of treatment with no AEs reported. During active questioning of patients, there were no adverse effects related to NSAID-gastrophathy (epigastric pain, heartburn, nausea, vomiting).

Among the patients who took diclofenac sodium, AEs were reported in 3 patients which were epigastric pain and nausea. Of these, one patient discontinued from the study after 10 days, second was prescribed additional omeprazole 20 mg in fasting state but discontinued from the study after 20 days due to aggravation of AE symptoms. Third patient was prescribed omeprazole 20 mg in fasting conditions in addition to diclofenac after 20 days of therapy. Six patients discontinued participation in the study without reporting of AEs, 4 from them during first 10 days refused to take diclofenac sodium more due to anticipated emergence of AEs. One patient discontinued after 10 days for the same reasons. One patient refused to come to the last visit. Overall 12 patients completed the study among the patients who took diclofenac sodium. The probable risk of emerging of gastrointestinal AEs in the AMG group was lesser than in diclofenac group, however difference did not reach significance level (Relative Risk [RR]= 0.078, p = 0.08). There were no differences observed in transaminases (ALT, AST) levels during the treatment in both the groups.

Discussion

Osteoarthritis is a common musculoskeletal disorder and knee

osteoarthritis is particularly associated with chronic disability [1]. The mainstay of management of symptoms is with analgesics, but the gastrointestinal tolerability is an issue [2,3]. Amtolmetin guacyl (AMG) was shown to alleviate pain and inflammation, and have a favourable GI tolerability profile as compared to traditional NSAIDs mediated through its unique nitric oxide (NO) increasing mechanism which causes the gastric sparing effect [10-14]. Ours is perhaps the first study to compare the efficacy and safety of AMG and diclofenac in patients with knee osteoarthritis. The study data shows that AMG significantly decreases intensity of pain in patients with knee osteoarthritis. Though the outcomes were similar during the first 10 days of treatment, the outcomes were superior with AMG as compared to diclofenac during the 20 and 30 days of treatment. AMG showed similar clinical benefit in the clinical features of OA; pain, stiffness and disorders of functional abilities. The better outcomes with AMG were accompanied with near absence of AEs. Similar published studies comparing AMG and diclofenac sodium in OA were not available. The majority of available publications dealt with the protective influence of AMG on gastric mucosa [13]. Study by F. Montrone et al, compared AMG to piroxicam in patients with OA [11]. The study data showed similar efficacy for AMG and piroxicam, but the tolerability with AMG was better as observed in our study. Although the proportion of AEs reported were similar for both treatment groups in the study by F. Montrone et al, the severity of AEs reported were of low grade in the AMG group vs piroxicam [11].

During evaluation of influence of AMG and diclofenac sodium in patients with rheumatoid arthritis, AMG had a similar efficacy to diclofenac sodium [18]. Incidence of severe gastric and/or duodenal ulcer after treatment was significantly lower with AMG, 1 (3%) as compared to diclofenac, 8(25%) after 30 day treatment [18]. Comparing the effect AMG and celecoxib in patients with rheumatoid arthritis during 24 weeks, AMG efficacy was proven, along with lesser AEs and significantly better endoscopic results after 4 weeks [19].

The open label design of the study and small sample size is a limitation, and larger doubled blinded studies could provide further information.

Conclusions

Amtolmetin guacil is an effective treatment option for knee osteoarthritis that significantly decreases pain, starting constraint, and limitation of functional abilities of the patients. Being well tolerated, AMG allows considering it as drug of choice for the older patients and patients with high risk of gastrointestinal complications. Good tolerability of treatment and effectiveness of treatment will contribute to improving compliance and treatment outcomes.

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