Double blind clinical trial comparing the safety and efficacy of nimesulide (100mg) and diclofenac in osteoarthrosis of the hip and knee joints.

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Summary

Background: **Osteoarthritis of the hip or knees is a very disabling condition in both Caucasians and Africans. A lot of medical drugs have been in use with their corresponding side effects, hence the search for newer drugs with fewer side effects.**

Study design: **A double blind clinical trial comparing the safety and efficacy of nimesulide and diclofenac was carried out in the University College Hospital Ibadan. All patients referred to the outpatients department of the orthopaedic division with osteoarthritis of the hips and knees who met the criteria for inclusion in the study were used for the study.**

Results: **There were a total number of sixty-seven (67) patients.**

70.6% of the nimesulide patients had only mild pain in the involved joint on completion of the eight weeks trial compared to 50% of the diclofenac group.

A significant proportion of the patients in the diclofenac group (50% vs 17.6%) had break through pain that warranted the use of at least two tablets of 500mg of paracetamol per week in contrast to the nimesulide group.

There was a statistically significant difference in the frequency of side effects between the patients in the diclofenac group and the nimesulide group ($p<0.05$).

Conclusion: **Nimesulide was found to be more effective in relieving pain in osteoarthritis of the hip and knees and with less side effects than diclofenac.**

Key-words: ***Nimesulide, Diclofenac, Osteoarthritis, Knee, Hip.***

Résumé

Introduction: L'ostéoarthrites de la hanche et des genoux est une maladie qui peut rendre personne invalide chez les Africains et les Blans les deux. Beaucoup de médicaments ont été utilisés avec leur effet secondaire correspondant donc l'enquête pour des nouveaux médicaments avec peu d'effet secondaire.

Plan d'étude: Un aveugle double épreuve clinque qui fait une comparaison du sans danger et l'efficacité du nimesulide et et diclofenaque a été effectué au centre hospitalier universitaire, Ibadan. Tous les patients envoyés au service des consultation externes de la section d'orthopédique avec l'ostéarthrites de hanche et genoux qui ont satisfait le critère acceptable dans cette étude ont été utilisé pour cette étude.

Résultats: Dans l'ensemble, il y a un nombre total de soixante sept (67) patients. 70,6% des patients nimesulide avaient un douleur legère seulement dans l'articulation impliquée après la fin du huitième semaine d'épreuve par rapport au 50% au groupe de diclofenaque. Une proportion importante des patients dans le groupe de diclofenac (50% Vs 17,6%) avaient une douleur percée ce qui a provoqué l'utilisation d'au moins deux comprimés de 500mg de paracetamol chaque semaine par rapport au groupe de nimesulide. Il y avait une différence statistiquement sensible dans la fréquence de réactions supplimentaire entre les patients dans le groupe de diclofenaque et du groupe nimesulide ($P<0,05$)

Conclusion: Nimesulide est noté d'être plus éfficace pour douleur lancinante dans l'ostéoarthrites de la hanche et genoux et avec une baisse dans les réactions supplementaire plus que l'utilisation de diclofenac.

Introduction

Osteoarthrosis is a chronic illness for which there is no known curative medical treatment. Unfortunately, this disease affects people in their early forties when they are supposed to be active. The review of literature suggests a high prevalence among Caucasians [1].Fifteen percent (15%) of the population in the United States of America was estimated in 1995 to have some form of arthritis and this was projected to be 18% by the year 2020. [2] Recent experiences in the University College Hospital, Ibadan, Nigeria have revealed that this condition may not be uncommon in the Nigerian environment. At the moment, the only available cure for this disease is surgery; however, this may not be readily available, affordable and accessible to majority of Nigerians afflicted with the disease. Therefore, the present search for an effective medical treatment, if found, will go a long way to alleviate the problems associated with this disease.

Nimulid is a known non-steroidal anti-inflammatory drug (NSAID) whose efficacy and effectiveness have been reported positively in India [3]. NSAIDS exert their anti-inflammatory action through their inhibition of synthesis of prostaglandin; however, the action of nimesulide appears to be different from most conventional NSAIDS

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in this respect. Nimesulide selectively inhibits the formation of pro inflammatory prostaglandin with significant less effect on the prostaglandins that have gastroprotective action [4]. Consequently, Nimesulide is better tolerated by the gastro-intestinal tract than other NSAIDS. Orally administered Nimesulide is rapidly and extensively absorbed with mean peak plasma concentrations achieved within 1.22 to 3.88 hours of administration and the presence of food does not reduce either the rate or extent of absorption [5], Nimesulide is rapidly distributed principally throughout the extracellular fluid compartment and is extensively bound to plasma proteins. Excretion of unchanged drug in urine and faeces is negligible and it is primarily eliminated by metabolic transformation with the principal metabolite as 4' hydroxyl derivative.[5] In order to introduce this drug to the public, it is important to further assess the effectiveness of the drug in Nigeria. Therefore, the manufacturing company decided to carry out a phase 3 clinical trial of the drug. The effectiveness of Nimulid as an anti-inflammatory and analgesic agent examined in a phase 3 drug trial at the University College Hospital is reported in this paper.

Materials and methods

Study population

All patients coming for treatment of osteoarthrosis in UCH that satisfy the inclusion and exclusion criteria participated in this study. These patients normally come to UCH, either through the General outpatient (GOP) or Orthopaedic Clinic and special emphasis was placed on Osteoarthrosis of the hips and knees.

Inclusion criteria

1. Patients with symptoms severe enough to require long term NSAID therapy.
2. Patients in the age group 35-80 years.
3. Patients who could attend the clinic at two weeks interval for at least 2 months.
4. Patients wishing to provide informed consent.

Exclusion criteria

(i) Patient with non-degenerative disease.
(ii) Treatment with intra-articular injection of corticosteroid within one month of proceeding enrolment.
(iii) History of severe renal/hepatic or hematopoietic disease.
(iv) Presence of active peptic ulcer.
(v) Patients allergic to NSAIDS.
(vi) Pregnant or lactating women
(vii) Patients with generalized degenerative joint disease.
(viii) Moribund patients or patients requiring intensive care therapy.
(ix) Patients on hydantoin or anticoagulants.
(x) Patients who had participated in a new NSAID drug trial program in the preceding four weeks.

Study design

A double blind randomized parallel design of Nimulid drug trial using Diclofenac as the 2nd arm of treatment (control group) was carried out. All patients willing to take part in the study had a thorough explanation of the research protocol including the possible side effects. They were later requested to sign consent of their willingness to take part in the presence of a nurse practitioner in the clinics. They were randomized using sealed envelopes to either the Nimulid group or the Diclofenac group

All patients took a placebo for one week before commencement of NSAID to annul the effect of any other prior analgesic or NSAID drug. Patients were randomly allocated to receive either Nimulid or Diclofenac. Neither the doctor nor the patient was aware of the drug received.
(a) The study lasted 16 months and each patient was followed up for a minimum period of 8 weeks.
(b) A new patient was recruited when a patient dropped out of the study due to any reason.

Drug dispensation

Patients were given 100MG of Nimesulide tablet twice daily after meals for 2 weeks after an initial period of a placebo being given for one week to wash out the system before commencing the Nimesulide.
The Nimesulide was continued every fortnight for a period of six weeks. The other group of patients also had a placebo for seven days and Diclofenac 50MG tablets twice daily after meals for a total period of six weeks. Patients who were lost for reasons other than lack of effective drug therapy were replaced by another patient. So also, immediate contact phone number and address of the principal investigator was given to all patients in case of any serious side effects both during and after office hours. Patients who completed the trial protocol of seven weeks were considered for final evaluation.

Assessment procedures

The eligible patients were enrolled after a complete physical examination and the following tests were carried out before and after the drug trial:

- Full Blood Count (FBC)
- Liver Function Test (LFT)
- Renal Function Test (RFT)
- Electrocardiogram (ECG)

At the end of eight weeks, the physician was required to make an overall judgment on the outcome of the therapy on a 4 point scale of Excellent, Good, Fair or Poor.

Evaluation parameters

Initial evaluation using the same criteria was carried out for each patient before the commencement of the drug and final evaluation after the completion of the drug
The initial evaluation was made using the following criteria:
Functional disability with the pain index graded thus:
Grades 0, 1, 2, 3, 4 were used for Pain after normal day

activities, Pain on strenuous activity or walking distance, Pain after walking short distance and Pain at rest respectively. After the complete physical examination, the following criteria were used to make the final evaluation: Relief of presenting symptoms (mainly) pain at the time of enrolment and on subsequent visits, Outcome based on doctor's assessment, Presence or Absence of side effects, Weekly intake of additional analgesic medication e.g. (Paracetamol).

At the last visit, grades 0, 1, 2, 3 and 4 were used for the patients' assessment of the symptoms as Worse than before, Same as before, Slightly better than before, Much better and Very much better (symptoms abated) respectively.

The frequency of escape medication was also assessed as patients who were given either Nimesulide or Diclofenac were advised to take Paracetamol 500mg in case of any increase in pain. The information regarding the amount of Paracetamol per week was recorded in the data sheet.

Side effects

Drowsiness, Dyspepsia, Anorexia, Dry mouth, Heart burn, Nausea, Vomiting/Diarrhoea were the side effects recorded with other non-steroidal anti inflammatory drugs listed in the data sheet and enquired from the patients at the fortnight visits:
The grades 0, 1, 2, 3, and 4 were used to record the Severity as Absent, Mild, Moderate but drug continued and Severe or intolerable - drug withdrawn respectively.

Results

There were sixty –seven (67) patients that took part in the study with thirty -two patients given Diclofenac while thirty-five patients had Nimesulide. However two of the patients in the Diclofenac group discontinued the drug because of the side effects while one of the Nimesulide group did the same. Four patients in the Diclofenac group confessed at the last visit that they did not complete the last week dose of the drug. Thus 60 patients, 34 in the Nimesulide group and 26 in the Diclofenac group fulfilled all the criteria for the study and had complete data for statistical analysis. There was no occult stool test on the three patients that discontinued the drugs because of heartburn.

There was a female preponderance as only 16.7% were males. The age, sex and other patients characteristics are shown in Table 1. Patients in the Nimesulide group were older (mean age of 59.6 years) than those in the Diclofenac group with a mean age of 51.6 years.

The mean duration of diseases of patients in the Diclofenac group was longer than those in the Nimesulide group(17.6 months Vs 13.14 months).
A statistically significant proportion of the patients in the Diclofenac group (50% vs 17.6%) had break through pain that warranted the use of at least two tablets of 500 mg of Paracetamol per week in contrast to the Nimesulide group (χ_2=11.322 P<0.05). The frequency was also higher in the Diclofenac group where 23.1% used more than ten tablets per week as against none in the Nimesulide group. The most common side effect was heart burn and nausea and this was severe in 3.6% of the patients in the Diclofenac group as compared to 1.6% of the Nimesulide group, while 15% of the Diclofenac group had moderate heart burn but still continued with the drug as compared with 1.6% of patients in the Nimesulide group. There was a statistically significant difference in the frequency of side effects between patients in the Diclofenac group and the Nimesulide group (P<0.05).

The results of the outcome of trial presented in Table 2 showed that none of the patients in the Diclofenac group reported no pain at the end of the trial period whereas 5.9% of patients in Nimesulide reported no pain. Also, a higher proportion (70.6%) of patients in the

Table 1 The demographic and other characteristics of the study patients

Demographic characteristics		Nimesulide	Diclofenac	Test statistics	P-Value
1.	**Age (Years)**				
	Mean	59.6	51.1	-2.345	.022
	SD	12.07	14.38		
	N	34	26		
2.	**Sex**				
	Male	4 (11.7)	6 (23.1)	χ^2= 1.357	0.207
	Female	30 (88.3)	20 (76.9)		
	Total	34 (56.7)	26 (43.3)		
3.	**Joint involvement**				
	Unilateral	17 (50)	16 (61.5)	χ^2 =.793	0.265
	Bilateral	17 (50)	10 (38.5%)		
4.	**Duration of disease**				
	Mean	13.14	17.6	Mann-Whitney U	0.001
	Median	12.0	15.5	=229.000	
	SD	7.99	7.12		
	N	34	26		

Table 2 The outcome measures of patients on Nimesulide and Diclofenac group

Outcome measures	Nimesulide n = 34	Diclofenac n = 26	Test statistics	P-Value
1. **Av. No.of Paracetamol / wk**				
None	28 (82.4)	13 (50)	χ^2 =11.322	0.010
< 4 Tablets	3 (8.8)	2 (7.7)		
4 – 10 Tablets	3 (8.8)	5 (19.2)		
> 10 Tablets	0 (0)	6 (23.1)		
2. **Severity of symptoms before treatment**				
Mild	5 (14.7)	0 (0)	χ^2 = 7.725	.021
Moderate	23 (67.6)	25 (96.2)		
Severe	6 (17.6)	1 (3.8)		
3. **Severity of symptoms after treatment**				
No Pain	2 (5.9)	0 (0)	χ^2 = 5.977	0.113
Mild	24 (70.6)	13 (50)		
Moderate	5 (14.7)	10 (38.5)		
Severe	3 (8.8)	3 (11.5)		
4. **Frequency of side effect**				
None	25 (73.6)	6 (23.2)	χ^2 =17.880	0.000
Mild	7 (20.6)	9 (34.6)		
Moderate(heat burn)	1 (2.9)	9 (34.6)		
Severe	1 (2.9)	2 (7.6)		
5. **Overall assessment**				
Excellent/Good	24 (70.6)	9 (34.6)	χ^2= 8.978	0.011
Fair/Satisfactory	7 (20.6)	8 (30.8)		
Poor	3 (8.8)	9 (34.6)		

Nimesulide group had only mild pain in the involved joint on completion of the 8 weeks trial compared to 50% of the Diclofenac group. Likewise 14.7% of the patients in the Nimesulide group had moderate pain as compared to 38.5% of the Diclofenac group while 2.1% of patients in the Nimesulide group reported severe pain after the completion of the trial compared to 18.4% of patients in the Diclofenac group. A low frequency (3.8%) of patients in the Diclofenac group had severe symptoms before treatment and this increased to 11.5%. On the contrary, for the patients in the Nimesulide group, 17.6% had severe symptoms before treatment and this reduced to 8.8% after the trial. However, there was no statistically significant difference in the severity of symptoms before and after trial, for the Diclofenac group (Chi square value=1.664, P>0.05). But for the Nimesulide group there was a highly significant difference in the severity of symptoms before and after the treatment (Chi square value 37.696, P<0.05).

There were no statistical significant differences in the pre and post enrolment hematological and biochemical parameters in both the Diclofenac and the Nimesulide group. However, majority of the patients in the Nimesulide group complained of yellowish discolouration of the urine which reverted back to normal two to three weeks after the trial. The result presented in panel 5 of table 2 showed a statistically significant difference between the overall judgment on therapeutic

Table 3 Severity of symptoms after therapy against duration of disease in both Nimesulide and Diclofenac Groups.

		Duration of illness			Test statistics	P- value
Group	**Severity of symptoms**	< 1 yr	1 – 2 yrs	> 2 yrs	χ^2 =5.240	0.264
Diclofenac N = 26	**Mild**	5 (19.2)	6 (23.1)	2 (7.7)		
	Moderate	2 (7.7)	8 (30.8)	0 (0)		
	Severe	0 (0)	3 (11.5)	0 (0)		
Nimesulide N = 34	**No pain**	2 (5.9)	0 (0)	0 (0)	χ^2 = 24.933	0.000
	Mild	17 (50.0)	7 (20.6)	0 (0)		
	Moderate	5 (14.7)	0 (0)	0 (0)		
	Severe	1 (2.9)	0 (0)	2 (5.9)		

Table 4 2 way Anova analysis of response of subjects with longer duration of diseases to therapy in Nimesulide and Diclofenac groups.

Test of between subject effects

Dependent variable: Duration of Illness

Source	Type III Sum of Squares	df	Mean square	F	Sig
Corrected Model	**1339.763**	6	223.279	5.086	.000
Intercept	**5928.489**	1	5928.486	135.043	.000
Group	**24.073**	1	24.073	.548	.462
Severity of symptoms after	**588969**	3	196.323	4.472	.007
Severity of symptoms after* Group	**599.490**	2	299.745	6.828	.002
Error	**2326.734**	53	43.901		
Total	**17304.760**	60			
Corrected Total	**3666.407**	59			

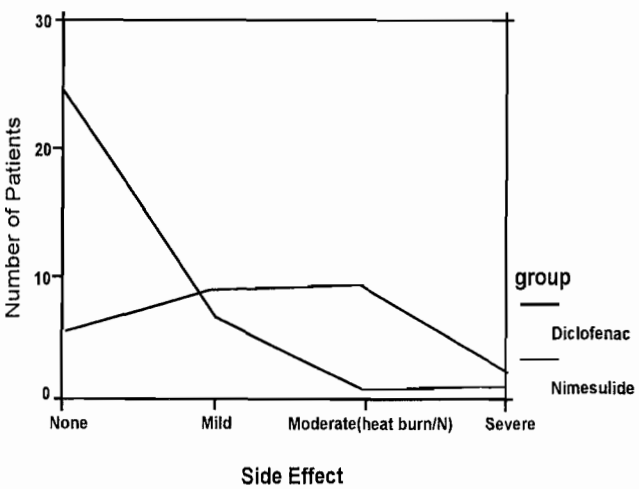

Fig. 1 ***Frequency of side effect in the Nimesulide and Diclofenac groups***

intervention in the two treatment groups (Chi square value 8.976, P <0.05). A higher proportion of the patients on Nimesulide were rated as excellent/good (70.6% Vs 34.6%) while the proportion with poor assessment was higher in the Diclofenac group (8.8% Vs 34.6%). The results presented in tables 3 and 4 showed a statistically significant difference in pain relieve in patients who have had the disease for a longer period of one year and above in the Nimesulide group as compared with the Diclofenac group.

Discussion

The anti-inflammatory activity of most NSAID is said to depend on their inhibition of the synthesis of prostaglandins as shown in human monocytes in vitro[6]. Afterwards, it has been found that some drugs are able to inhibit a distinct isoform of cyclooxygenase cox-2 but will not inhibit cox-1 and thus will not harm the stomach[7]. The present study has shown that the use of Nimesulide (Nimulid) which spares the cox-1 has minimal effect on the stomach.

It has been found that Diclofenac as well as some NSAIDS like aspirin and ibuprofen has a high cox1/cox2 activity ratio for example ratio of 166 for aspirin and 0.7 for Diclofenac [8]. Compounds with decreasing activity ratios have decreasing side effects and less irritant action on the stomach, hence aspirin would not be the drug of choice for arthritis because of its potent inhibitory action on cox-1 but remains the drug of choice in reducing the number of primary and secondary heart attacks and strokes [9].

Nimesulide (Nimulid) is one of the new drugs with selective inhibition of cox-2 without the severe side effects of damaging the stomach or the kidney [10,11]. Like other NSAIDS, cox-2 inhibitors can cause salt and water retention, leading to edema and worsening hypertension [12], however this was not borne out by our study probably because it was for a short period.

Nimesulide may reduce the breakdown of osteoarthritic human cartilage; however the effects of this drug on the natural course of osteoarthritis needs to be established in further clinical studies.

Conclusions

The finding in this study that patients on Nimesulide required less than 5 tablets of Paracetamol and no patient required more than 10 tablets of Paracetamol per week as compared to 24% in the Diclofenac group, showed the improved efficacy of Nimesulide in relieving pain than Diclofenac sodium. It was also shown from the study that Nimesulide was more effective than Diclofenac in

patients who have had the osteoathritis of the hip or knees for a longer period of time in excess of eight months.

Although the urine was coloured deep yellow by Nimesulide in almost all patients this reverted to normal after the drug was stopped. There were no biochemical, hematological or electrocardiograph changes before and after the trials.

In conclusion, the safety and efficacy of Nimesulide in the management of osteoarthrosis of the knee and hip joints is twice as superior to those of Diclofenac in the patients studied at the University College Hospital, Ibadan, Nigeria.

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