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# THE COMBINED EFFECT OF ALBENDAZOLE AND IVERMECTIN IN THE TREATMENT OF LYMPHATIC FILARIASIS: A CASE STUDY OF FOUR RURAL COMMUNITIES OF OBUBRA L.G.A. OF CROSS RIVER STATE, NIGERIA

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## ABSTRACT

The efficacy of the combination of albendazole (400mg/kg) and ivermectin (3mg/kg) over single doses of ivermectin (3mg/kg) and albendazole (400mg/kg) in the treatment of lymphatic filariasis (LF) was assessed between August 2003 and July 2004 in four filariasis endemic rural communities of Ofumbongha, in Obubra LGA of Cross River State, Nigeria. One thousand and six hundred males and females aged 16years and above were listed for the study, out of which 880 who were microfilaria positive were eventually used for the study. The microfilaria positive subjects were randomized into 3 groups for different treatment regimen. A group was treated with albendazole alone, another group with ivermectin alone, while the third were treated with a combination of albendazole and ivermectin. Treated individuals were monitored for seven days to record any adverse reaction and the effect of treatment on the microfilariaemiae was followed up for one year. Treatment efficacy was eventually analyzed for only 801 microfilaria positive individuals who had >or =100mf/ml of blood and who were present for re-examination up to 12 months. All the three groups showed significant ($P< 0.05$) reduction of the microfilarial load at the follow up examinations. The combination therapy of albendazole and ivermectin was significantly ($P< 0.05$) more effective in clearing microfilaria in night blood (90.4%) within one year than any of the other regimens (ivermectin alone, 70.7%; and albendazole alone, 59.5%). The three regimens were well tolerated and clinically safe although few cases of mild side-reactions were observed in all the treated groups. The study showed that the combination of albendazole and ivermectin was most effective for the suppression of microfilariaemiae in human blood stream and is therefore recommended for mass distribution, which could be made community-based and community-directed.

**KEY WORDS:** Combined effect, Ivermectin, Albendazole, Treatment, Filariasis, Nigeria.

## INTRODUCTION

Lymphatic filariasis, resulting from infection with the lymphatic-dwelling roundworms, *Wuchereria bancrofti* and *Brugia malayi* is one of the major vector - borne diseases in tropical Africa (Meyrowitsch, et al., 1996). The ubiquitous mosquito is the vector of this disease, affecting over 120 million people in over 80 countries within the tropical and sub-tropical regions (WHO, 2001). Thus, more than one third of the affected individuals, are in the West African sub-region (Michael et al., 1997). A prevalence of up to 50% has been documented in the humid, swampy, farming rural communities of Nigeria. Reports of urban filariasis in Nigeria are mainly unconfirmed (Jinadu, 2002.).

Lymphatic filariasis is rarely fatal, but its recurrent acute febrile attacks of adenolymphangitis, debilitating and disfiguring chronic manifestations of lymphoedema, elephantiasis and hydrocoele are scourges and a tragedy to

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the affected individuals and communities as a whole (WHO, 2003). Other disabling and discomforting chronic manifestations of filariasis in endemic areas include skin damages leading to secondary bacterial infection as well as haematuria, chyuria and chylocele (Jinadu, 2002). These awful impacts of the disease made the World Health Organizations at its fiftieth assembly, in 1997 to call for the elimination of *Lymphatic filariasis* globally as a public health problem.

There is no vaccine for prevention of filariasis. Prevention and control centers on mass treatment with anti-filarial drugs to prevent ingestion of larvae by mosquitoes (WHO, 2000). Diethylcarbarnazine Citrate (Banocide) was formally the drug of choice for the treatment of lymphatic filariasis but later dropped because of its serious side effects and not being so effective in clearing the worms. Furthermore, it cannot be an area co-endemic with *Onchocerca volvulus* and *Loa loa* infections (Ottesen, 1994, Ottesen et al., 1995, WHO, 1995).

The new drugs, ivermectin and albendazole are guaranteed to be safe and effective in the elimination of microfilariaemia in over 98% of the population (Jinadu, 2002). This unique profile makes them well tolerated for annual large-scale mass treatment programmes in areas co-endemic for onchocerciasis (WHO, 2000) Some scanty researches have been made on the efficacy and safety of a combination therapy of ivermectin and albendazole (Adiss et al., 1997; Dunyo et al., 2000) in some parts of Africa. However, this work was carried out in Cross River State of Nigeria where such combination therapy has neither been tried nor commenced but where the endemicity of lymphatic filariasis is very high (Braide et al., 2003). The result obtained will be of immense benefit to the on going lymphatic filariasis control progamme in Cross River State of Nigeria.

## MATERIALS AND METHOD

### The Study Area

The study was carried out in four rural communities of Ofumbongha, comprising; Ofumbongha 1, Ofumbongha 2, Ofumbongha 3 and Ofumbongha 4, all in Obubra Local Government Area of Cross River State, Nigeria. Ofumbongha communities are located within the Cross River State virgin forest zone. The area is hilly, with undulating plains. The communities belong to the same ecological zone. Rainfall in these communities is high, mostly between the months of July - September.

The people are predominantly farmers while few are hunters or fishermen and some deal on timber. These activities predispose them to high rate of mosquito bites, which account for high prevalence of lymphatic filariasis in these communities. They have nucleated settlement. Most of the houses have mud walls and thatched roofs. The waste water from the households creates the main breeding sites for the mosquito vector that transmits lymphatic filariasis. They depended on Primary Health Care Centers (P.H.C) or private practitioners in nearby towns for health care.

### Subjects

The estimated total population of the communities is about 2400 out of which 1600 were examined. Every household was visited to enumerate its members. The criteria for selection included;
(1) Those that have lived in the communities for one year and above;
(2) Those that were 16 years old and above.
The subjects examined voluntarily gave their consent. The work was carried out under the close supervision of 3 medical doctors working with the Onchocerciasis Control Unit, Calabar. The Control Unit, Calabar, also obtained clinical ethical clearance for the study. The Unit supplied the drugs used in treating the subjects.

### Advocacy

Letters were sent to the clan head of each of the four communities one-week before sampling. The letters vividly explained the aims and objectives of the research work, and the date of sampling. The letters were sent through contact persons who were well known in the community. On the day of sampling, the people were made to gather in their village squares during the day.

**Clinical Examinations**
The subjects were physically examined for the presence of lymphoedema, hydrocoele and elephantiasis in males as well as enlarged breasts in females. Private apartments were made available where the examinations took place. A female doctor was used to examine female subjects to avoid misunderstanding that may arise from the subjects and for optimum co-operation. Lactating and pregnant mothers were not included.

**Parasitological Examinations / Microscopy**
Between 22.00hrs and 24.00hrs of the same day, 20µl (0.02ml) of pre-treatment capillary blood was collected from the thumb of each subject, after sterilizing with cotton wool soaked with methylated spirit. Giemsa Staining Technique was used as described by Cheesbrough (2002). The entire preparation was examined microscopically for the presence of microfilaria using x10 objective, with the condenser iris closed sufficiently to give a good contrast. For clearer view of the sheaths of the pathogenic microfilaria, x40 objective was used. The number of microfilariae in the entire smear were counted and multiplied by 50 to give an approximate number of microfilariae per milliliter of blood (Cheesbrough, 2002).

**Treatment**
Selected subjects were divided into 3 groups in each community. One group was given albendazole (400mg / kg) alone, another group was treated with ivermectin (3 mg / kg) alone and the last group was given a combination of albendazole and ivermectin (400mg / kg and 3mg/kg) respectively. The total number of those treated with albendazole alone was 255 likewise those treated with ivermectin alone, while 370 were treated with a combination of ivermectin and albendazole. The village heads provided buckets of water with cups at the village squares. The people were made to queue up and the drugs were given to them. The drugs were taken immediately under the full view of the investigator. The people were closely monitored for 7 days to find out if there was any adverse effect from the treatment. The health centers in the communities were made ready to receive subjects with any severe adverse drug-related effect(s). After three months, the people treated were re-examined and again after six months and lastly after a year to determine their microfilarial load. The subjects were instructed not to take any other drug for filariasis.

**Analysis of Data**
The significant reduction of microfilariae (Mf) from the people was calculated using SPSS Microsoft computer model, which involves the analysis of variance (ANOVA). Differences between proportions were computed with chi-square.

## RESULTS

**Overall Prevalence and Microfilarial load for each Community before selection of subjects for treatment**
Of the 1600 persons examined, 880 (51.8%) were positive for microfilariae in their blood field. Ofumbongha 3 had the highest prevalent (58.3%), followed by Ofumbongha 4 (54.5%), while Ofumbongha 1 had the least (40.0%)(Table 1). The males were slightly more infected (52.5%) than females (50.7%). The total microfilarial load for the four communities was very high (93,550), Ofumbongha 3 had the highest (35,400), followed by Ofumbongha 4 (30,850), while Ofumbongha 2 had the least (12,950)(Table 1).

**Table 1**: Overall Prevalence and Microfilarial Load of Each Community Before Selection of Subjects for Treatment

| | No. Examined | | | No. Positive (%) | | | Community Mf Load/mm |
|---|---|---|---|---|---|---|---|
| Community | M | F | T | M | F | T | |
| Ofumbongha 1 | 170 | 130 | 300 | 75 (44.1) | 45 (34.6) | 120 (40.0) | 14, 350 |
| Ofumbongha 2 | 150 | 100 | 250 | 67 (44.7) | 43 (43.0) | 110(44.0) | 12, 950 |
| Ofumbongha 3 | 370 | 230 | 600 | 200 (54.1) | 150 (65.2) | 350(58.3) | 35, 400 |
| Ofumbongha 4 | 300 | 250 | 550 | 178 (59,3) | 122 (48.8) | 300 (54.5) | 30, 850 |
| Total | 990 | 710 | 1700 | 520 (52.5) | 360 (50.7) | 880 (51.8) | 93, 550 |

**NB. Mf= Microfilarial; M = Males; F= females; T = Total**

Number of microfilarial load is calculated by multiplying average number of microfilaria in the field by 50 (Chesbough, 2002)

**Result of Treatments on community microfilarial load for the Four Communities**: The effectiveness of the drugs in reducing the microfilarial load six months and one year after treatment is shown in Table 2. Only 801 (91.0%) of the initial population treated came for re-examination at the sixth and twelfth month after treatment. There was significant ($P< 0.01$) reduction in the overall community microfilarial load from 83,826 at time of treatment to 24,950 and 20,360, six months and one year after treatment respectively (Table 2). Ofumbongha 3, still recorded the highest community microfilarial load (8,250), followed by Ofumbongha I (4,310) while Ofumbongha 2 had the least (.3,550)(Table 2).

**Table 2**: Microfilarial Load of 801 Treated Subjects by Community and Different Treatment Regimen Before and After Treatment

| Community | CMFL Before Treatment | | | Community MFL Six Months After Treatment | | | Community MFL 1yr After Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment Regimen | Alb. | Iver. | Alb + Iver | Alb. | Iver. | Alb + Iver. | Alb. | Iver. | Alb+ Iver. |
| Ofumgha 1 | 3900 | 3980 | 5090 | 2250 | 1700 | 760 | 2230 | 1550 | 530 |
| Ofumgha 2 | 3290 | 3280 | 4644 | 1700 | 1400 | 740 | 1660 | 1350 | 540 |
| Ofumgha 3 | 9271 | 9261 | 13330 | 5050 | 2600 | 2000 | 4750 | 2200 | 1300 |
| Ofumgha 4 | 8390 | 8440 | 10950 | 3650 | 1700 | 1400 | 1600 | 1550 | 1000 |
| Total | 24,851 | 24,961 | 34,014 | 12650 | 7400 | 4900 | 10240 | 6650 | 3470 |
| Sub-Totals: CMFL of 801 Before Treatment =83, 826 | | | | CMFL 6months after Treatment =24,950 | | | CMFL 1yr after Treatment =20,360 | | |

**NB; Alb.and Alb = Albendazole, Iver.= Ivermectin; T. = Total; MFL= Microfilarial Load; CMFL = Community microfilarial Load; Ofumgha = Ofumbongha**

**NB: Computed result is for the 801-microfilaria positive subjects who were present for re-examination exercises up to 12 months.**

**Result of Treatments on community prevalence rate for the Four Communities:**
The treatment had significant ($P<0.01$) reduction effect on both the overall prevalence and that of each community (Tables 3). Of the 801 treated subjects who came for re-examination after one year 188 (23.5%) were still microfilaria-positive. Ofumbongha 1 had the highest prevalence of 33.3% followed by Ofumbongha 2 (26.7%) while Ofumbongha 4 had the least (19.0%). With regards to the different drug regimens, those treated with ivermectin and albendazole combination therapy had significantly ($P< 0.05$) lower prevalence (4.4%) than those treated with ivermectin alone (6.7%) and those treated with albendazole alone (12.4%) (Table 3).

Table 3: Effect of the Different Drug Regimens on the Community and overall Prevalence of Filariasis one Year after Treatment by Communities and Sex

| Parameters: | COMMUNITIES Ofumbongha 1 | Ofumbongha 2 | Ofumbongha 3 | Ofumbongha 4 | Total |
|---|---|---|---|---|---|
| **Total prevalence of the 801 treated subjects who came for re-examination after one Year** | | | | | |
| Males | 60 | 59 | 180 | 168 | 467 |
| Females | 42 | 42 | 144 | 106 | 334 |
| Total | 102 | 101 | 324 | 274 | 801 |
| No. Positive (%) | 34 (33.3) | 27 (26.7) | 75 (23.1) | 52 (19.0) | 188(23.5) |
| **No of those treated with Albendazole alone that were still positive after one year** | | | | | |
| Males | 10 | 7 | 25 | 18 | 60 |
| Females | 7 | 5 | 15 | 12 | 39 |
| Total (%) | 17 (16.7) | 12 (11.9) | 40 (12.3) | 30 (14.9) | 99 (12.4) |
| **No of those treated with ivermectin alone that were still positive after one year** | | | | | |
| Males | 8 | 6 | 13 | 7 | 33 |
| Females | 4 | 4 | 8 | 7 | 21 |
| Total (%) | 12 (11.8) | 10 (9.9) | 20 (6.2) | 12 (4.4) | 54 (6.7) |
| **No of those treated with Albendazole & Ivermectin that were still positive after one year** | | | | | |
| Males | 3 | 3 | 9 | 6 | 21 |
| Females | 2 | 2 | 6 | 4 | 14 |
| Total (%) | 5 (4.9) | 5 (5.0) | 15 (4.6) | 10 (3.6) | 35 (4.4) |

**Comparison of the Average Percentage Effectiveness of Combined Therapy (Albendazole and Ivermectin) over Single Doses of Albendazole or Ivermectin**
Computation of the average percentage effectiveness (reduction effect of each drug on community microfilarial load) of the three different drug regimens on the treated subjects showed that the percentage effectiveness of the single dose regimen of albendazole was 59.5% and that of ivermectin was 74.8% while the combination of albendazole and ivermectin regimen stood at 90.4% (Fig. 1)

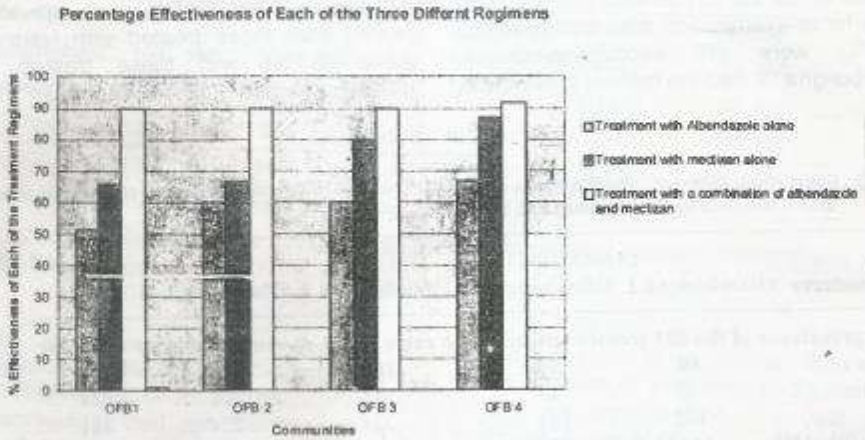


Fig. 1: Average percentage effectiveness of each of the Three Drug Regimens

**NB: Ofb = Ofumbougha**

Combination of albendazole and ivermectin regimen was shown to be most effective followed by single ivermectin regimen, and lastly by single albendazole regimen. Chi-square analysis showed that the percentage effectiveness was significant ($P < 0.05$) in all the treatments, but highly significant ($P<0.01$) in the combination of both albendazole and ivermectin regimen

## DISCUSSION

The result obtained indicates that lymphatic filariasis is endemic in Ofumbongha communities of Obubra Local Government Area of Cross River State, Nigeria. Braide *et al* (Braide et al., 2003) made the same observation in some other areas of Cross River State, Nigeria. Result obtained from oral interaction with the people showed that they were aware of the existence of lymphoedema in their communities. It was discovered that lymphoedema existed in Ofumbongha communities since 1950's and the local name given to the disease is "Abighe", meaning "swollen legs". The presence of the disease was attributed to so many things such as; witchcraft, evil spirits or evil men in the society (native doctors) who were believed to use spiritual powers to invoke it on people.

Analysis of the efficacy of the drugs showed that all the three regimens had reductive effect on the microfilariamiae in the treated subjects. However, the combination of albendazole and ivermectin regimen was significantly ($P<0.05$) more effective and more efficacious in reducing microfilarial load among the subjects, than any of the single dose regimens of either albendazole or ivermectin alone. Baseline information from some researchers (WHO, 1995, Adiss et al., 1997, Ottesen, et al., 1997; Dunyo et al., 2000) made the same observations from their different works. The very low microfilarial load in most of the treated subjects as well as the lower prevalence rate obtained after the first twelve months of treatment confirms the effectiveness of the drugs in the control of the disease.

The study as well confirmed that single dose regimen of either albendazole or ivermectin or a combination of albendazole and ivermectin were well tolerated and efficacious. There was no serious adverse effect on the people treated with any of the

drug regimens. However, some mild side effects were recorded, such as vomiting, nausea and stomach discomfort as earlier observed by Das *et al*, (2001).

It was World Health Organization that recommended the use of a combination of albendazole and ivermectin for the first time in 1995 for treating lymphatic filariasis because of its safety, high efficacy, fewer side effects and the quality of being used effectively where omchocerciasis and *Loiasis* are co-endemic with lymphatic filariasis. Since Merck and Sharp group is donating ivermectin free to endemic regions for treating onchocerciasis and lymphatic filariasis, and SmithKline Beecham has also pledged to donate albendazole free for treating lymphatic filariasis, a lymphatic filariasis elimination programme could be formed in endemic arrears of Cross River State of Nigeria (and indeed other parts of the country). Such treatment campaign could be integrated into the on-going community-directed ivermectin distribution programme used hitherto for the control of river blindness in endemic areas. This will facilitate the long desired goal of eliminating lymphatic filariasis in Nigeria and other parts of Africa by the year 2020 as targeted by WHO (1997).

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